Feasibility of single-time-point dosimetry for radiopharmaceutical therapies

Authors: Xinchou Hou¹, Julia Brosch², Carlos Uribe^{1,3}, Alessandro Desy^{4,5}, Guido Böning², Jean-Mathieu Beaugard^{4,5}, Anna Celler¹, Arman Rahmim^{1,3,6}

Affiliations: ¹Department of Radiology, University of British Columbia, Vancouver, Canada; ²Department of Nuclear Medicine, University Hospital, Ludwig-Maximilians-Universität, Munich, Germany; ³Functional Imaging, BC Cancer, Vancouver, BC, Canada; ⁴Cancer Research Centre and Department of Radiology and Nuclear Medicine, Université Laval, Quebec City, Canada; ⁵Department of Medical Imaging and Oncology Division of Research Centre, CHU de Québec – Université Laval, Quebec City, Canada; ⁶Department of Integrative Oncology, BC Cancer Research Institute, Vancouver, Canada

Corresponding Authors: Xinchou Hou, PhD; BC Cancer Research Institute; 675 West 10th Ave Office 6-112 Vancouver, BC, V5Z 1L3; email: xchou@mail.ubc.ca; Arman Rahmim, PhD; BC Cancer Research Institute; 675 West 10th Ave Office 6-112 Vancouver, BC, V5Z 1L3; email: arman.rahmim@ubc.ca.

Conflicts of Interest: None of the authors report any conflict of interest.

Grant support: This work was supported by the National Institutes of Health (NIH) / Canadian Institutes of Health Research (CIHR) Quantitative Imaging Network (QIN) Grant number 137993; the German Research Foundation (DFG) within the research training group GRK2274; Clinical Research Scholarship from the Fonds de recherche du Québec – Santé, and CIHR operating grant MOP-142233.

Word Count (abstract): 253

Word Count (total): 4632

Key words: Dosimetry; Quantitation; radiopharmaceutical therapy; SPECT; Single-time-point

Short title: Single-time-point dosimetry

ABSTRACT

Due to challenges in performing routine personalized dosimetry in radiopharmaceutical therapies, interest in single-time-point (STP) dosimetry, particularly utilizing only one SPECT scan, is on the rise. Meanwhile, there are questions about reliability of STP dosimetry, with limited independent validations. In the present work, we analyze two STP dosimetry methods and evaluate dose errors for a number of radiopharmaceuticals based on effective half-life distributions.

Method: We first challenged the common assumption that radiopharmaceutical effective half-lives across the population are Gaussian (normal) distributed. Then, dose accuracy was estimated based on two STP dosimetry methods for a wide range of potential scan-times post-injection (p.i.), for different radiopharmaceuticals applied to neuroendocrine tumors and prostate cancer. The accuracy and limitations of using each of the STP methods were discussed.

Results: Log-normal distribution was shown as more appropriate to capture effective half-life distributions. The STP framework was shown as promising for dosimetry of ^{177}Lu -DOTATATE, and for kidney dosimetry of different radiopharmaceuticals (errors<30%). Meanwhile, for some radiopharmaceuticals, STP accuracy is compromised (e.g. in bone marrow and tumors for ^{177}Lu -PSMA therapies). Optimal SPECT scanning time for ^{177}Lu -DOTATATE is at ~72 h p.i., while 48 h p.i. would be better for ^{177}Lu -PSMA compounds.

Conclusion: Our results demonstrate that simplified STP dosimetry methods may compromise the accuracy of dose estimates, with some exceptions such as for ^{177}Lu -DOTATATE and for kidney dosimetry in different radiopharmaceuticals. Simplified personalized dosimetry in the clinic continues to be a challenging task. Based on these results, we make suggestions and recommendations for improved personalized dosimetry using simplified imaging schemes.

INTRODUCTION

Image-based personalized dosimetry, as applied to radiopharmaceutical therapies, allows physicians to limit critical organ toxicities, and to potentially predict response to treatment and enable personalized therapy decisions (1). In order to perform dosimetry with acceptable accuracy, it is often assumed necessary to perform multiple quantitative scans (e.g. SPECT) to assess distribution of the therapeutic compound over time and quantify its biokinetics in organs and tumors. Nevertheless, this task is challenging in a clinical environment as it requires performing a series of scans over multiple days for each therapy cycle in each patient, followed by complex and time-consuming data processing and calculations (2).

To address this challenge, with the aim of enabling routine dosimetry in the clinic, a number of simplified approaches have been proposed. One approach is to perform dosimetry estimation using only a single SPECT scan (single-time-point (STP) dosimetry) (3–7); in particular, see the recent discussion by Hänscheid and Lassmann (8).

Two STP methods were proposed by Hänscheid *et al* (3) and Madsen *et al* (4). Both methods assume that the radiopharmaceutical clearance in a patient's region of interest (ROI) follows a mono-exponential decay behavior with an effective half-life of T_{eff} , in which case the time-integrated activity $\tilde{A}$ in the ROI can be calculated using the following formula:

$$\tilde{A} = \frac{1}{\ln 2} \cdot A(T_{sc}) \cdot 2^{\frac{T_{sc}}{T_{eff}}} \cdot T_{eff} , \quad (1)$$

where T_{sc} is the SPECT scan time point, and $A(T_{sc})$ represents activity in the ROI measured at time T_{sc} . This activity can be determined from the quantitatively reconstructed SPECT image. However, T_{eff} may be difficult to measure, requiring performance of a series of SPECT scans with subsequent data fitting for

the ROIs. Furthermore, the effective half-life could vary significantly between different individual patients, and/or between therapy cycles.

The STP method of Hänscheid *et al* (3) proposes that the last component of Eq (1), i.e. $2^{\frac{T_{sc}}{T_{eff}}} \cdot T_{eff}$, can be approximated by $2T_{sc}$. Their theoretical calculations indicated that if T_{sc} remains within 0.75-2.5 times the patient-specific effective half-life T_{eff} , errors in dose estimates would be below 10%. Then, an analysis of 29 ^{177}Lu -DOTATATE/DOTATOC patient studies was performed as an example to confirm this theoretical finding (3).

On the other hand, the work published by Madsen *et al* (4), based on ^{90}Y -DOTATOC data from a clinical trial, considered the concept of using population mean effective half-life (T_{p-eff}) and demonstrated that the accuracy of STP dosimetry for kidneys would be improved by setting the scan time (T_{sc}) close to or slightly larger than T_{p-eff} (4). This STP dosimetry framework was verified to have good accuracy by Amato *et al* in treatment of hyperthyroidism with ^{131}I radioiodine (9). Both formulations used by Hänscheid *et al* and Madsen *et al* are listed in Table 1.

Inspired by these works, we recently investigated accuracy of STP dosimetry for kidneys using different scan time points (4h, 24h and 72h post activity injection): data from 53 ^{177}Lu -DOTATATE neuroendocrine tumors in radioligand therapy of 39 patients were used (6). The impact of the deviation of the particular patient's T_{eff} from T_{p-eff} on the accuracy of kidney doses was estimated. The most favorable scan time point T_{sc} , i.e. the scan which would result in dosimetry errors for the kidneys below 10%, was suggested to be set at times between 1 to 1.5 T_{p-eff} . However, our previous study was solely focused on kidney doses and on one specific compound, namely ^{177}Lu -DOTATATE.

For a given patient, the effective half-lives for radiopharmaceutical clearance from tumors vs. organs-at-risk (OARs) are usually different. In order to achieve acceptable accuracy of dose estimates when using

STP method, a compromise has to be made, as the optimal scan time point may be different for tumors vs. OARs. These time points would also be different for different radiopharmaceutical compounds.

In the present work, we compare the accuracy of dose estimates using the two STP methods listed in Table 1, for different common compounds used in radiopharmaceutical therapies. Meanwhile, we challenge the common default assumption that effective half-life distributions across the population are Gaussian (normal) distributed. Subsequently, based on our results, we provide recommendations for dosimetry workflows.

MATERIALS AND METHODS

Since organ-based absorbed mean dose could be considered nearly proportional to the time-integrated activity, the dose error (DE) can be estimated from the time-integrated activities (as estimated using either method M1 or M2) as follows:

$$\text{DE (\%)} = \left(\frac{\tilde{A}_{Mx}}{\tilde{A}} - 1 \right) \times 100\%, \quad (2)$$

where $\tilde{A}_{Mx}$ represents either $\tilde{A}_{M1}$ or $\tilde{A}_{M2}$ (Table 1), and reference $\tilde{A}$ is calculated using Eq (1). We investigated scan time points ranging from 24 h to 144 h (day 1 to day 6) following activity injection.

In this study, by using these scan time points, we estimated DEs for “generic” patient-specific T_{eff} ranging from 0 h to 200 h. While M1 does not depend on T_{eff} , for M2 the values of the population-based mean T_{p-eff} were set to be between 10 h to 120 h, to capture a wide range of possibilities. Subsequently, for both, tumors and OARs, DEs were investigated by using these two STP methods for four commonly used radiopharmaceuticals, namely ^{177}Lu -DOTATATE and ^{90}Y -DOTATOC as used in treatments of neuroendocrine tumors, and ^{177}Lu -labeled prostate-specific membrane antigen (PSMA) compounds (including ^{177}Lu -PSMA-617 and ^{177}Lu -PSMA-I&T) as used for prostate cancer.

In order to investigate the accuracy of STP dosimetry, we aimed to first obtain 95% confidence intervals (CI) for the distributions of effective half-lives for a given radiopharmaceutical and organ/target of interest. Table 2 summarizes effective half-lives for different radiopharmaceuticals as available in the literature or from our own data. For most datasets, limited information, e.g. mean (m), standard deviation (SD) and range values for half-lives could be found, with the exception of five datasets from our own clinical studies (marked with “†” in Table 2, where the individual T_{eff} values for patients were available; i.e. Studies 1, 4 and 8). For Studies 1 and 4, patient data were from the radiopharmaceutical therapy trial NCT02754297, approved by the CHU de Québec - Université Laval institutional Ethics Committee, and all patients provided a written consent to participate. Study 8 was based on retrospective and anonymized data, acquired for routine clinical dosimetry, as approved by the Ethics Committee of LMU Munich 20-520, including waiver of consent.

Based on a common and default assumption that effective half-lives follow a normal distribution, 95% CI would be set at $m \pm 1.96SD$. By contrast, our analysis in this work shows that a log-normal distribution is a more proper assumption. For each of our five full datasets with complete listing of effective half-lives (from Studies 1, 4 and 8 in Table 2), the Kolmogorov-Smirnov (K-S) test was performed to check the null hypothesis that our data and/or its corresponding log-transformation were normally distributed. Furthermore, distribution fittings were performed, and analytic 95% CI for the effective half-lives per ROI were calculated, and compared with the true range of 95% data, as calculated using the quantile function. Having found that log-normal distribution is a more appropriate model, we mapped the reported m and SD values from different studies to log-normal distributions with exponent parameters μ and σ (i.e. mean and standard deviations of the natural logarithm) as given by:

$$\mu = \log \left(\frac{m^2}{\sqrt{m^2 + SD^2}} \right) \quad (3)$$

$$\sigma = \sqrt{\log(1 + SD^2/m^2)} \quad (4)$$

Subsequently, from the mapped log-normal distributions, 95% CI ranges were computed. Finally, DE values for the computed ranges (spreads) of effective half-lives were estimated using both methods: M1 and M2.

RESULTS

The results of calculated DE values from methods M1 and M2 are presented in Figure 1 for a wide range of T_{p-eff} and T_{eff} values. The DEs within $\pm 10\%$ are highlighted in green. Overall, it is seen that for both STP methods, the accuracy of dose estimates highly depends on the spread of patient T_{eff} values and the scan time selected by the users (further elaborated in the discussion section).

The distributions of effective half-lives were then investigated based on the five datasets with complete listing of effective half-lives for ^{177}Lu -DOTATATE and ^{177}Lu -PSMA-I&T (marked with “†” in Table 2, Studies 1,4 and 8). Supplemental Table 1 lists the results of K-S test with p-values, demonstrating that most effective half-lives data follow log-normal distribution. In addition, the corresponding histograms with probability density function (PDF) curves of log-normal distribution fittings are shown in Supplemental Figure 1 in the supplemental material. The true and analytically-estimated 95% CI ranges based on normal and log-normal distribution assumptions are also shown in Supplemental Figure 1. Furthermore, Supplemental Figure 2 shows the DE values from these three different types of ranges (i.e. computed based on true 95% CI vs. normal and log-normal assumption), confirming that doses computed based on log-normal distribution were more similar to those from the true 95% range, further strengthening the log-normal assumption.

Subsequently, in Table 2, we computed 95% CI ranges based on log-normal distribution assumption, from reported mean and SD values in the literature, as described in the methods section. In fact, had we assumed a normal distribution, computed 95% CI values of half-lives would extend below 0 for some

studies. Based on these, the DE values for the investigated radiopharmaceuticals are presented in Figure 2 and 3 for kidney and bone marrow, respectively, which are OARs in the particular radiopharmaceutical therapies investigated, and Figure 4 for tumors. We see that for ^{177}Lu -DOTATATE, estimated dose errors are relatively low, while for some other radiotracers, large errors can be obtained for both STP dosimetry methods. Additionally, the comparison of DE values for the published range listed in Table 2 with those obtained from estimated 95% CI is shown in Supplemental Figure 3 in supplemental material.

DISCUSSION

As shown in Figure 1, when scan time point T_{sc} is in the range $0.8-1.6 T_{p-eff}$, the dose error (DE) values from both Methods 1 and 2 were found to be similar (differences $< 7\%$). Small DE ($< 10\%$) could be observed when T_{sc} is set within $0.75-2.5 T_{eff}$ for Method 1, which is consistent with prior reporting (3). However, for Method 2, the accuracy of absorbed dose depends not only on the T_{sc} , but also on the deviation of patient-specific effective half-life T_{eff} from population-based mean T_{p-eff} . Overall, T_{sc} should be preferably set in the range $1-1.5 T_{p-eff}$, in order to achieve lower DE but allowing larger deviations between T_{eff} and T_{p-eff} . This agrees with Figure 4 published by Wei *et al* (6). For example, if $T_{p-eff}=47$ h (the kidney's mean T_{p-eff} for ^{177}Lu -DOTATATE in Study 1, Table 2), lower than 10% DE could be observed when the deviation between T_{p-eff} and T_{eff} are within $[-38\%, 43\%]$, if T_{sc} is set to 72h. However, when T_{sc} is set to 24h p.i., the deviation between T_{p-eff} and T_{eff} is only allowed within $[-10\%, 10\%]$ in order to have $DE < 10\%$.

Figure 2-4 summarize potential DE values based on the analysis of our own or published effective half-lives for commonly used radiopharmaceuticals. In general, our results suggest that there is a high possibility of dose underestimation when using STP framework. The extent of this would depend on the radiopharmaceutical and considered ROI. In particular:

1. For kidneys, similar DEs are obtained from both, Method 1 and Method 2, when T_{sc} is set to 48-96 h (i.e. day 2-day 4 p.i.) as shown in Figure 2. However, large differences between Method 1 and Method 2 are observed for either early (24 h p.i.) or late (>96 h p.i.) scan time points. For most of the investigated radiopharmaceuticals, smallest DEs could be achieved when T_{sc} is set to 48 h p.i.. However, for ^{177}Lu -DOTATATE, scan time point as 72 h p.i. is slightly better than 48 h p.i. with $\text{DE} < 10\%$. For ^{177}Lu -PSMA-compound therapies, even at “optimized” scan time points, DE could be larger than 20%.

2. For bone marrow dosimetry (Figure 3), smallest DE values (<30%) could be obtained when T_{sc} is set to 72-96 h p.i. for ^{177}Lu -DOTATATE. However, for ^{177}Lu -PSMA-617, STP method should be used only with great caution as in the majority of our investigated scenarios, it largely underestimated the dose, especially when using Method 1.

3. For neuroendocrine tumor lesions treated with ^{177}Lu -DOTATATE (Figure 4), similar to bone marrow dosimetry, scan time points T_{sc} of 72-120 h p.i. results in $\text{DE} < 30\%$, while for prostate cancer lesions treated with ^{177}Lu -PSMA-I&T, the lowest DE (<30%) can be achieved for scans at 48 h p.i., as displayed in Figure 4.

Additionally, differences of DEs for the same radiopharmaceutical and ROI could also be observed between different studies. This is mainly due to the different methods used for estimating effective half-lives from different groups, including segmentation methods, imaging type and scan time points, as well as fitting models. For example, analysis in Study 1 is based on small-volume kidney dosimetry, using a 4ml small region within the kidney for dose estimation; while for Study 2, data from whole kidney segmentation is listed. As another example, study 8 used three SPECT/CT scans, while five hybrid planar/SPECT scans were employed in Study 9. At the same time, these differences did not influence our main findings in this work.

In summary, the STP dosimetry framework is mostly suitable for dosimetry of ^{177}Lu -DOTATATE and kidney dosimetry for different radiopharmaceuticals. Less reliable results were obtained in our analysis for bone marrow and lesions in ^{177}Lu -PSMA compounds. Combining the results of kidneys, bone marrow and tumors for ^{177}Lu -DOTATATE, SPECT scanning at 72 h p.i. should be considered as optimal, while early time points, such as 48 h p.i., would be better for ^{177}Lu -PSMA therapies, in agreement with findings from studies published by Wei *et al* and Jackson *et al* (6,7). Equally accurate results could be achieved when using Method 1 and Method 2 when the suggested scan time are employed.

At the same time, our analyses based on the limited data currently available suggest that, due to potentially large discrepancies in pharmaceutical clearance rate between patients, the errors obtained when using STP methods could be 30% or more in some therapeutic compounds and targets. More studies and/or potential modifications of the STP dosimetry methods would be required. For example, Jackson *et al* (7) employed the STP method to predict doses from ^{177}Lu -PSMA-617 therapy using a population of normalized pharmacokinetic curves. However, the accuracy of this method has not been confirmed and the mean absolute error was employed to represent the accuracy, which could be smaller than the dose error format we reported here (8). In addition, individual clinical data may be used to narrow range of effective half-lives, around which STP scans could be performed. As an example, we suggest that variations in the estimated glomerular filtration rate (eGFR) may indicate varying kidney function, in turn impacting effective half-life. In fact, in Supplemental Figure 4, we investigate and show a significant correlation between these two factors. Similar correlation between the kidney dose and eGFR were also found in Del Prete *et al* 2017 (10). Thus, a potential improved STP framework would utilize modified estimated half-life values based on such clinical parameters.

In general, our results show that accuracy of STP framework is highly dependent on patient-specific radiopharmaceutical clearance times, and the large discrepancies between patients suggest STP methods may not be appropriate to use in all therapies/radiopharmaceuticals. In such cases where STP may be

problematic, an alternative practical approach for patient-specific dosimetry may be to use at least two time points for imaging and subsequent effective half-life calculation for the first cycle of treatment to estimate patient-specific pharmaceutical kinetics, specifically patient- and organ-specific T_{eff} values. However, the choice of scan time point for the two scans is crucial and it should be avoided to set them during the early radiopharmaceutical uptake phase. Afterwards, this information could be incorporated into the more generalized form (Eq (1)), to estimate effective half-life for the following cycles. The accuracy of such an approach was investigated by Del Prete *et al* (11) who observed dose errors of -0.5%, 15.7% and -5.6% for kidney, bone marrow and tumour, respectively, for ^{177}Lu -DOTATATE.

CONCLUSION

We have analyzed the accuracy of two STP dosimetry methods for a number of radiopharmaceutical therapy agents. Our results indicate that using these simplified STP dosimetry methods may, in some therapeutic compounds and targets, largely compromise the accuracy of dose estimates. A prominent exception to this is ^{177}Lu -DOTATATE, wherein reasonably small (<30%) dose errors can be achieved when using the STP framework scanning at ~72 h p.i. (3 days p.i.), and kidney dosimetry in general for radiopharmaceuticals investigated in this work. As an alternative for improved dosimetry in STP dosimetry, we suggest that patient-specific biokinetics be determined using two or ideally more scans during the first treatment cycle, while using the STP framework for the following cycles. At the same time, this approach needs to be validated, since the effective half-lives could potentially change over multiple treatment cycles. Alternatives to existing STP methods also include improved estimation of patient-specific effective half-lives from clinical data, e.g. evidence provided in this work for the kidney using eGFR values. Enabling routine personalized dosimetry in the clinic remains a challenging task given the complex data processing and calculations for high accuracy on the one hand, and interest in more feasible methods.

DISCLOSURE

The authors have no conflicts of interests.

KEY POINTS

QUESTION: Is single-time-point dosimetry feasible in current clinical studies for all radiopharmaceutical therapies?

PERTINENT FINDINGS: We compared and assessed feasibility of STP dosimetry methods. Patient effective half-life distributions for different radiopharmaceuticals and organs/targets were evaluated. STP dose estimation accuracy was seen as compromised in some radiopharmaceuticals, e.g. for bone marrow and bone lesions in ^{177}Lu -PSMA compounds.

IMPLICATIONS FOR PATIENT CARE: We provide caution and guidance for the use of simplified dosimetry protocols in clinical radiopharmaceutical therapy.

REFERENCES

1. Stabin MG, Madsen MT, Zaidi H. Personalized dosimetry is a must for appropriate molecular radiotherapy. *Med Phys*. 2019;46:4713-4716.
2. Ljungberg M, Gleisner KS. Personalized dosimetry for radionuclide therapy using molecular imaging tools. *Biomedicines*. 2016;4:1-21.
3. Hänscheid H, Lapa C, Buck AK, Lassmann M, Werner RA. Dose mapping after endoradiotherapy with ^{177}Lu -DOTATATE/DOTATOC by a single measurement after 4 days. *J Nucl Med*. 2018;59:75-81.
4. Madsen MT, Menda Y, O'Dorisio TM, O'Dorisio MS. Technical Note: Single time point dose estimate for exponential clearance. *Med Phys*. 2018;45:2318-2324.
5. Willowson KP, Eslick E, Ryu H, Poon A, Bernard EJ, Bailey DL. Feasibility and accuracy of single time point imaging for renal dosimetry following ^{177}Lu -DOTATATE ('Lutate') therapy. *EJNMMI Phys*. 2018;5:33
6. Zhao W, Esquinas PL, Frezza A, Hou X, Beauregard JM, Celler A. Accuracy of kidney dosimetry performed using simplified time activity curve modelling methods: A ^{177}Lu -DOTATATE patient study. *Phys Med Biol*. 2019;64:175006
7. Jackson PA, Hofman MS, Hicks RJ, Scalzo M, Violet J. Radiation Dosimetry in ^{177}Lu -PSMA-617 Therapy Using a Single Posttreatment SPECT/CT Scan: A Novel Methodology to Generate Time- and Tissue-Specific Dose Factors. *J Nucl Med*. 2020;61:1030-1036.
8. Hänscheid H, Lassmann M. Will SPECT/CT Cameras soon be able to display Absorbed Doses? Dosimetry from Single Activity Concentration Measurements. *J Nucl Med*. 2020;61:1028-1029

9. Amato E, Campennì A, Ruggeri RM, Auditore L, Baldari S. Comment on: "Technical note: Single time point dose estimate for exponential clearance" [Med. Phys. 45(5), 2318-2324 (2018)]. *Med Phys.* 2019;46:2776-2779.
10. Del Prete M, Buteau FA, Beauregard JM. Personalized ^{177}Lu -octreotate peptide receptor radionuclide therapy of neuroendocrine tumours: a simulation study. *Eur J Nucl Med Mol Imaging.* 2017;44:1490-1500.
11. Del Prete M, Arsenault F, Saighi N, et al. Accuracy and reproducibility of simplified QSPECT dosimetry for personalized ^{177}Lu -octreotate PRRT. *EJNMMI Phys.* 2018;5:25.
12. Hou X, Zhao W, Beauregard JM, Celler A. Personalized kidney dosimetry in ^{177}Lu -octreotate treatment of neuroendocrine tumours: A comparison of kidney dosimetry estimates based on a whole organ and small volume segmentations. *Phys Med Biol.* 2019;64:175004.
13. Heikkonen J, Mäenpää H, Hippeläinen E, Reijonen V, Tenhunen M. Effect of calculation method on kidney dosimetry in ^{177}Lu -octreotate treatment. *Acta Oncol (Madr).* 2016;55:1069-1076.
14. Desy A, Bouvet GF, Frezza A, Després P, Beauregard JM. Impact of dead time on quantitative ^{177}Lu -SPECT (QSPECT) and kidney dosimetry during PRRT. *EJNMMI Phys.* 2020;7:32.
15. Menda Y, Madsen MT, O'Dorisio TM, et al. ^{90}Y -DOTATOC dosimetry-based personalized peptide receptor radionuclide therapy. *J Nucl Med.* 2018;59:1692-1698.
16. Kurth J, Krause BJ, Schwarzenböck SM, Stegger L, Schäfers M, Rahbar K. External radiation exposure, excretion, and effective half-life in ^{177}Lu -PSMA-targeted therapies. *EJNMMI Res.* 2018;8:32.
17. Sarnelli A, Belli ML, Di Iorio V, et al. Dosimetry of ^{177}Lu -PSMA-617 after mannitol infusion and glutamate tablet administration: Preliminary results of EUDRACT/RSO 2016-002732-32 IRST

protocol. *Molecules*. 2019;24:621.

18. Baum RP, Kulkarni HR, Schuchardt C, et al. ^{177}Lu -labeled prostate-specific membrane antigen radioligand therapy of metastatic castration-resistant prostate cancer: Safety and efficacy. *J Nucl Med*. 2016;57:1006-1013.
19. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol*. 2005;5:1-10.

Figure 1. Dose errors (%) resulting from using Method 1 (marked in black dotted line) and Method 2 (with population based mean T_{p-eff} ranging from 10-120 h, marked in colored lines) relative to the true effective half-life of radiopharmaceutical washout. The dose errors within $\pm 10\%$ were highlighted in green.

Figure 2. The dose errors (%) of kidney doses estimated using STP dosimetry methods (Method 1 in blue and Method 2 in red) for situations when patient effective half-lives are within simulated 95% CI range listed in Table 2. The green and magenta dashed lines indicate $\pm 10\%$ and $\pm 30\%$ of DE values, respectively. Four sets of results shown in the ^{177}Lu -DOTATATE column correspond to the effective half-life data from four different publications listed in Table 2 (Studies 1-4).

Figure 3. The dose errors (%) of bone marrow doses estimated using STP dosimetry methods (Method 1 in blue and Method 2 in red) for situations when patient effective half-lives are within simulated 95% CI range from Table 2. The green and magenta dashed lines indicate $\pm 10\%$ and $\pm 30\%$ of DE values, respectively. Two sets of results correspond to the data from Study 4 and 7.

Figure 4. The dose errors (%) of tumour doses estimated using STP dosimetry methods (Method 1 in blue and Method 2 in red) for situations when patient effective half-lives are within 95% CI range from Table 2. The green and magenta dashed lines indicate $\pm 10\%$ and $\pm 30\%$ of DE values, respectively. The two sets of lines shown in the $^{177}\text{Lu-DOTATATE}$ column corresponds to the data from Study 3 and 4; While, the three sets of lines shown in the column of $^{177}\text{Lu-PSMA-I\&T}$ represent the results for bone metastases and lymph node metastases from Study 8 and 9.

Table 1. STP dosimetry application methods

Methods	Approximation	Conclusion
Method 1 (M1) (3)	$\tilde{A}_{M1} = \frac{1}{\ln 2} \cdot A(T_{sc}) \cdot 2 T_{sc}$	Error < 10% if $T_{sc} \in [0.75T_{eff}, 2.5T_{eff}]$
Method 2 (M2) (4,7)	$\tilde{A}_{M2} = \frac{1}{\ln 2} \cdot A(T_{sc}) \cdot 2^{\frac{T_{sc}}{T_{p-eff}}} \cdot T_{p-eff}$	Smallest errors can be observed if $T_{sc} \in [T_{p-eff}, 1.5T_{p-eff}]$

Table 2. The mean effective half-lives and standard deviation (SD), as well as computed 95% confidence interval (CI), of organs and lesions for commonly used radiopharmaceuticals which were used in this investigation.

Radio-pharmaceutical	Study	Reference	# of Patients (# of data)	Organ/Target	Median (range)	T_{p-eff} mean (h)	T_{p-eff} SD (h)	95% CI (h) [†]
¹⁷⁷ Lu-DOTATATE	1	Hou <i>et al</i> 2019 (12)	30 (87)	Kidney [‡]	46 (30-82)	47.0	11.6	28.5-73.6
	2	Heikkonen <i>et al</i> 2016 (13)	24 (24)	Kidney	N/A (36-59)	45.3	5.9	34.8-57.4
	3	Hänscheid <i>et al</i> 2018 (3) [§]	27 (54)	Kidney*	51 (40-68)	51.0	7.0	38.8-66.0
			25 (25)	Liver*	67 (55-117)	76.5	15.5	51.4-110.7
			27 (27)	Spleen*	68 (52-99)	68.0	11.8	49.5-91.6
			22 (22)	Tumour*	77 (56-130)	85.4	18.5	56.0-125.8
	4	Del Prete <i>et al</i> 2018 (11) Desy <i>et al</i> 2020 (14)	158 (1117)	Kidney* [‡]	47 (23-159)	50.8	16.9	25.6-91.0
			158 (474)	Bone marrow* [‡]	70 (29-160)	76.4	27.6	36.2-142.8
			158 (2166)	Tumour* [‡]	84 (16-161)	87.8	30.5	42.8-160.6
⁹⁰ Y-DOTATOC	5	Menda <i>et al</i> 2018 (15)	25 (69)	Kidney	N/A (25-92)	37.5	12.5	19.4-67.2
¹⁷⁷ Lu-PSMA-617	6	Kurth <i>et al</i> 2018 (16)	25 (25)	Whole-body	N/A (22-86)	40.5	15.8	18.8-79.1
	7	Sarnelli <i>et al</i> 2019 (17)	9 (9)	Parotid gland	33 (26-61)	35.4	10.6	22.2-53.2
			9 (9)	Kidney	31 (12-81)	39.2	20.9	17.2-76.2
			9 (9)	Red marrow	8 (3-15)	8.0	4.7	3.2-16.3
			9 (9)	Liver	25 (13-63)	33.5	20.0	13.4-69.1
			9 (9)	Whole-body	40 (32-80)	52.4	22.2	27.2-90.5
¹⁷⁷ Lu-PSMA-I&T	8	Written communications	15 (290)	Bone metastases [‡]	38 (13-191)	42.6	19.1	16.9-90.0
	9	Baum <i>et al</i> 2016 (18)	30 (N/A)	Bone metastases*	52 (14-149)	52.0	30.0	16.2-132.6
			30 (N/A)	Lymph node metastases*	43 (25-160)	43.0	32.0	9.9-132.7
			30 (N/A)	Kidney*	33 (19-83)	33.0	14.0	14.8-64.9
			30 (N/A)	Parotid gland*	25 (20-43)	25.0	5.0	16.7-36.1

*The data of effective half-lives were published in the format of median and range only. For Studies 3 and 9, their corresponding values of mean and SD were then calculated based on method by Hozo *et al* 2005 (19). For Study 4, we had access to complete listing of effective half-lives. [†]The 95% CI of range was estimated assuming log-normal statistics, as described in the text.

[‡] T_{eff} of each individual ROI (organ or lesion) was available (i.e. complete listing of effective half-lives for all patients).

[§]This overall dataset (29 patients) consisted primarily of ¹⁷⁷Lu-DOTATATE (22 patients) but also included some ¹⁷⁷Lu-DOTATOC (7 patients).

Graphical Abstract:

Supplemental Material

Table 1: Results of the Kolmogorov-Smirnov (K-S) test along with p-values, on five full datasets with complete listing of half-lives for all patients, as listed in Table 2. P-values larger than 0.05 indicate match with the null hypothesis (e.g. that data distribution is normal, top, or log-normal, bottom)

	¹⁷⁷ Lu-DOTATATE Kidney (Study 1)	¹⁷⁷ Lu-DOTATATE Kidney (Study 4)	¹⁷⁷ Lu-DOTATATE BM (Study 4)	¹⁷⁷ Lu-DOTATATE Tumour (Study 4)	¹⁷⁷ Lu-PSMA-I&T Tumour (Study 8)
Normal	Yes	No	No	No	No
p-value	0.08	5.40E-17	1.74E-04	8.49E-08	0.001
Log-Normal	Yes	No	Yes	No	Yes
p-value	0.47	5.86E-06	0.60	0.0010	0.71

Figure 1: Distribution fitting and 95% confidential interval (range) comparison of effective half-lives for the five full datasets mentioned in Table S1, involving ¹⁷⁷Lu-Dotatate and ¹⁷⁷Lu-PSMA-I&T.

Figure 2: Dose errors (DE, %) comparisons for ranges of half-lives computed based on (i) normal and (ii) log-normal distributions, as well as (iii) the true range of half-life values covering 95% of the data, for the five full datasets from Study 1, 4 and 8 with complete list of half-lives.

Figure 3: DE(%) comparisons for ranges of half-lives computed based on (i) 95% CI range from estimated log-normal distributions and (ii) the true range of half-life values from published data. The upper plots represent the DE values for Method 1, while the lower plots represent the DE values for Method 2.

Figure 4: The relationship between eGFR and patient specific half-life from Study 1 of Table 2.