Rethinking Dosimetry: The Perils of Extrapolated External-Beam Radiotherapy Constraints to Radionuclide Therapy

Jonathan Strosberg[1], Michael S. Hofman[2,3], Taymeyah Al-Toubah[1], and Thomas A. Hope[4]

[1]Department of Gastrointestinal Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida; [2]Prostate Cancer Theranostics and Imaging Centre of Excellence, Molecular Imaging and Therapeutic Nuclear Medicine, Cancer Imaging, Peter MacCallum Centre, Melbourne, Victoria, Australia; [3]Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Victoria, Australia; and [4]Department of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, California

Ongoing discussion within the nuclear medicine community suggests that all radionuclide therapies (RNTs) should include posttreatment quantitative dosimetry as part of standard clinical care. The hypothesis is that fixed administered activities limit the potential efficacy of RNT and increase the risk of side effects; therefore, patient-specific dosimetry should be leveraged to improve patient outcomes. Furthermore, the development of new radionuclides is often constrained by dosimetry-defined limits to normal organs extrapolated from external-beam radiation therapy (EBRT).

At the same time, with few exceptions, nonradioactive oncologic therapies are administered as fixed or calculated doses based on patient weight or body surface area. Although personalized dosing schemes based on tumor burden, pharmacokinetics, and pharmacodynamics can potentially improve the therapeutic index of cancer treatments, very few such regimens have been adopted in clinical practice (1–3). Large, randomized clinical trials are required to validate personalized treatment regimens compared with conventional ones, and few such trials have been conducted.

RNTs differ from nonradioactive systemic cancer treatments, as absorbed doses to tumors and normal organs can be quantified directly. Many experts argue that the similarities between RNT and EBRT mandate dosimetry: no radiation oncologist would conceive of treating a patient without a precise dose calculation to target tumor and surrounding tissues. Once a threshold of radioactivity administered to a field is exceeded, toxicity can be irreversible. By analogy, no systemic RNT should be administered without analyzing the absorbed dose to at-risk organs and tumors (4,5).

However, in many other ways, this comparison fails. EBRT is administered in a prescriptive fashion to a specific region. Effective dose ranges (typically measured in grays) for particular cancers have been well established, and the radiation sensitivities of surrounding tissues are known. Precise radiation doses to tumors and adjacent organs can be calibrated using increasingly sophisticated techniques to maximize response and minimize toxicity (6).

None of these features of EBRT can be translated to systemically administered RNT. Instead, RNT dosimetry estimates absorbed dose to tumors and organs using imaging after the administration of the therapy. Additionally, absorbed doses and their biologic effects vary substantially on the basis of radionuclide properties, including pathlength and linear energy transfer (7).

In EBRT, dosimetry is calculated for tissues within a radiation field. With RNT, the usual organs of concern are typically the kidneys (for renally excreted radiopharmaceuticals) and the bone marrow, the organ most sensitive to the effects of systemic radiation. Renal doses are more straightforward to estimate than marrow doses, and therefore, the kidneys are commonly treated as the target organ. Traditionally, a threshold absorbed dose of 23 Gy to the kidneys has been considered a maximum tolerable dose, guided by the International Commission on Radiological Protection recommendations or QUANTEC (Quantitative Analyses of Normal Tissue Effects in the Clinic) (7–9). However, there are obvious pitfalls when trying to correlate the biologic effects of EBRT on the entire kidney with the effects of radionuclides excreted through renal tubules. Even among β-emitting radionuclides, the differences in nephrotoxicity between ^{90}Y (12-mm pathlength) and ^{177}Lu (2-mm pathlength) are substantial when administered at a similar estimated absorbed dose to the kidney (10).

Let us assume that we could accurately measure normal-organ–absorbed doses. With respect to kidney-based dosing, it is increasingly apparent that the kidney is not a dose-limiting organ. Although single-arm studies have suggested that ^{177}Lu-DOTATATE causes a modest annual decrease in glomerular filtration rate, the randomized phase III NETTER 1 trial showed no difference in creatinine clearance over time between the ^{177}Lu-DOTATATE and control arms (11). Studies that calibrate administered activity on the basis of absorbed renal doses nearly uniformly lead to an increase in total administered activity (12). However, if the kidney is not a dose-limiting organ, administration up to an artificial renal dose threshold should not be considered a personalized form of treatment but rather a simple dose escalation.

The bone marrow is a dose-limiting organ for many patients, and an absorbed dose of 2 Gy to the red marrow is considered a maximum threshold, extrapolated from ^{131}I therapy (13). However, marrow dosimetric calculations are imprecise. Uptake on

posttherapy imaging may be reduced because of partial-volume effects or may be overestimated because of background noise. Even with the addition of plasma sampling, calculated marrow doses may vary depending on the technique, and different radionuclides can produce substantial variations in marrow toxicity [14]. Moreover, patient-specific factors (age, genomic predisposition, prior treatments, etc.) influence sensitivity to radiation (as is the case with chemotherapy) [15–17]. Some studies have shown no correlation between bone marrow dose and cytopenias; others have shown weak correlations [10,18,19]. However, a more straightforward method of assessing bone marrow toxicity and adjusting administered activity is the complete blood count. There is no evidence that dosimetric calculations are superior to a simple complete blood count for personalizing treatment. Additionally, there is no evidence that dosimetry can predict the most catastrophic long-term complications of treatment: myelodysplastic syndrome or acute leukemia [20,21].

Dosimetry can also be used to calculate absorbed tumor doses. Although dose–response relationships are expected, our understanding of tumor dosimetry in RNT lags far behind our knowledge of optimal dosing in EBRT. Traditional approaches using several manually identified index tumor lesions, typically with the highest activity, fail to correlate with survival outcomes or lead to actionable changes in management [22]. This is not surprising given tumor heterogeneity and the varying doses delivered to sites within an individual. Newer approaches using whole-body tumor dosimetry may be superior. For example, among 11 patients who received less than a 10-Gy median whole-body tumor dose after ^{177}Lu-PSMA-617 treatment, only one achieved a prostate-specific antigen response [23]. However, it is not yet clear how tumor dosimetry data can be leveraged to improve patient outcomes. For example, should a low absorbed tumor dose prompt additional cycles of treatment or early discontinuation for futility?

Dosimetry has evolved enormously in the last decade. There has been a transition from planar imaging to quantitative SPECT/CT imaging. This has enabled a shift from dosimetry modeling based on a standard human with assumed organ masses and shapes to direct measurements using voxel-based techniques [24]. New PET-like ring-designed SPECT/CT devices using solid-state detectors enable more accurate dose estimates with better resolution and speed. Contouring of normal organs has moved from a manual process at multiple time points to semiautomated techniques using defined thresholds or fully automated techniques using deep learning algorithms assisted by the CT [25]. The number of time points required for accurate dosimetry is decreasing, with even single time points feasible, using either patient-specific parameters from cycle 1 or population-based databases [26].

Dosimetry sits at a crossroads. It is time to move away from extrapolating external-beam–defined normal-organ constraints to RNT. Direct observation of adverse effects is simpler and superior. We must still monitor for longer-term adverse effects, especially within organs of interest. Advances in quantitative SPECT/CT and software open new opportunities to redefine the use of dosimetry to improve patient outcomes. Undoubtedly, there are superior personalized administration schedules that modulate the amount and frequency of the administered activity. However, only well-designed randomized clinical trials with long-term follow-up can accurately evaluate whether novel dosimetry-based prescriptions are superior to fixed schedules. As with any other oncologic therapy, the burden of proof is on us to demonstrate that these strategies yield superior efficacy or safety outcomes. We hope that improved evidence-based strategies will be developed to improve patient care.

DISCLOSURE

REFERENCES

1. Masson E, Zamboni WC. Pharmacokinetic optimisation of cancer chemotherapy. Effect on outcomes. *Clin Pharmacokinet.* 1997;32:324–343.
2. Larson RA, Druker BJ, Guilhot F, et al. Imatinib pharmacokinetics and its correlation with response and safety in chronic-phase chronic myeloid leukemia: a subanalysis of the IRIS study. *Blood.* 2008;111:4022–4028.
3. Lau DK, Fong C, Arouri F, et al. Impact of pharmacogenomic DPYD variant guided dosing on toxicity in patients receiving fluoropyrimidines for gastrointestinal cancers in a high-volume tertiary centre. *BMC Cancer.* 2023;23:380.
4. Stabin MG. Update: the case for patient-specific dosimetry in radionuclide therapy. *Cancer Biother Radiopharm.* 2008;23:273–284.
5. Wahl RL, Sunderland J. Radiopharmaceutical dosimetry for cancer therapy: from theory to practice. *J Nucl Med.* 2021;62(suppl 3):1S–2S.
6. Jaffray DA. Image-guided radiotherapy: from current concept to future perspectives. *Nat Rev Clin Oncol.* 2012;9:688–699.
7. Wahl RL, Sgouros G, Iravani A, et al. Normal-tissue tolerance to radiopharmaceutical therapies, the knowns and the unknowns. *J Nucl Med.* 2021;62(suppl 3):23S–35S.
8. Wessels BW, Konijnenberg MW, Dale RG, et al. MIRD pamphlet no. 20: the effect of model assumptions on kidney dosimetry and response—implications for radionuclide therapy. *J Nucl Med.* 2008;49:1884–1899.
9. Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys.* 1991;21:109–122.
10. Bodei L, Kidd M, Paganelli G, et al. Long-term tolerability of PRRT in 807 patients with neuroendocrine tumours: the value and limitations of clinical factors. *Eur J Nucl Med Mol Imaging.* 2015;42:5–19.
11. Strosberg JR, Caplin ME, Kunz PL, et al. ^{177}Lu-Dotatate plus long-acting octreotide versus high-dose long-acting octreotide in patients with midgut neuroendocrine tumours (NETTER-1): final overall survival and long-term safety results from an open-label, randomised, controlled, phase 3 trial. *Lancet Oncol.* 2021;22:1752–1763.
12. Del Prete M, Buteau FA, Arsenault F, et al. Personalized ^{177}Lu-octreotate peptide receptor radionuclide therapy of neuroendocrine tumours: initial results from the P-PRRT trial. *Eur J Nucl Med Mol Imaging.* 2019;46:728–742.
13. Benua RS, Cicale NR, Sonenberg M, Rawson RW. The relation of radioiodine dosimetry to results and complications in the treatment of metastatic thyroid cancer. *AJR.* 1962;87:171–182.
14. Reidy-Lagunes D, Pandit-Taskar N, O'Donoghue JA, et al. Phase I trial of well-differentiated neuroendocrine tumors (NETs) with radiolabeled somatostatin antagonist ^{177}Lu-satoreotide tetraxetan. *Clin Cancer Res.* 2019;25:6939–6947.
15. Huang RX, Zhou PK. DNA damage response signaling pathways and targets for radiotherapy sensitization in cancer. *Signal Transduct Target Ther.* 2020;5:60.

16. Asadollahi R, Britschgi C, Joset P, et al. Severe reaction to radiotherapy provoked by hypomorphic germline mutations in ATM (ataxia-telangiectasia mutated gene). *Mol Genet Genomic Med.* 2020;8:e1409.

17. Mylavarapu S, Das A, Roy M. Role of BRCA mutations in the modulation of response to platinum therapy. *Front Oncol.* 2018;8:16.

18. Bergsma H, Konijnenberg MW, Kam BL, et al. Subacute haematotoxicity after PRRT with ^{177}Lu-DOTA-octreotate: prognostic factors, incidence and course. *Eur J Nucl Med Mol Imaging.* 2016;43:453–463.

19. Garske-Román U, Sandström M, Fröss Baron K, et al. Prospective observational study of ^{177}Lu-DOTA-octreotate therapy in 200 patients with advanced metastasized neuroendocrine tumours (NETs): feasibility and impact of a dosimetry-guided study protocol on outcome and toxicity. *Eur J Nucl Med Mol Imaging.* 2018;45:970–988.

20. Bergsma H, van Lom K, Raaijmakers MHGP, et al. Persistent hematologic dysfunction after peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE: incidence, course, and predicting factors in patients with gastroenteropancreatic neuroendocrine tumors. *J Nucl Med.* 2018;59:452–458.

21. Goncalves I, Burbury K, Michael M, et al. Characteristics and outcomes of therapy-related myeloid neoplasms after peptide receptor radionuclide/chemoradionuclide therapy (PRRT/PRCRT) for metastatic neuroendocrine neoplasia: a single-institution series. *Eur J Nucl Med Mol Imaging.* 2019;46:1902–1910.

22. Alipour R, Jackson P, Bressel M, et al. The relationship between tumour dosimetry, response, and overall survival in patients with unresectable neuroendocrine neoplasms (NEN) treated with ^{177}Lu DOTATATE (LuTate). *Eur J Nucl Med Mol Imaging.* 2023;50:2997–3010.

23. Violet J, Jackson P, Ferdinandus J, et al. Dosimetry of ^{177}Lu-PSMA-617 in metastatic castration-resistant prostate cancer: correlations between pretherapeutic imaging and whole-body tumor dosimetry with treatment outcomes. *J Nucl Med.* 2019;60:517–523.

24. Jackson PA, Beauregard JM, Hofman MS, Kron T, Hogg A, Hicks RJ. An automated voxelized dosimetry tool for radionuclide therapy based on serial quantitative SPECT/CT imaging. *Med Phys.* 2013;40:112503.

25. Jackson P, Hardcastle N, Dawe N, Kron T, Hofman MS, Hicks RJ. Deep learning renal segmentation for fully automated radiation dose estimation in unsealed source therapy. *Front Oncol.* 2018;8:215.

26. 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.