INVITED COMMENTARY

Model-Based Versus Patient-Specific Dosimetry: Blurring the Lines

Internal radionuclide radiation dosimetry continues to evolve, in some respects, along 2 seemingly separate paths: model-based and patient-specific dosimetry. However, as models become increasingly anthropomorphic and the associated formulae become more flexible, the distinction between model-based and patient-specific dosimetry is being blurred. The elegant article by Jönsson et al. (*1*) in this issue of *The Journal of Nuclear Medicine* serves to further blur this distinction.

The archetype of the model-based approach is the "MIRD schema" (*2–5*). Developed by the MIRD Committee of the Society of Nuclear Medicine, the MIRD schema is perhaps the most widely used methodology for internal dose calculations in medicine. (The International Commission on Radiological Protection has developed a similar methodology (*6*).) As applied to risk assessment for diagnostic radiopharmaceuticals, its traditional application, the MIRD schema implicitly assumes that activity and cumulated activity are uniformly distributed within source regions and that radiation energy is uniformly deposited within target regions. Moreover, dosimetry for diagnostic radiopharmaceuticals is generally based on average time–activity data in animal models or small cohorts of human subjects and average human anatomy.

The analysis by Jönsson et al. (*1*) includes several notable refinements, specifically for the gastrointestinal tract, of the MIRD schema. First, the small intestine is modeled as a hexagonal tube system and the previously ignored cross-dose contribution from nearby loops of intestine is thereby included. Second, Jönsson et al. use a detailed model of the pertinent small-scale anatomy, with villi of height 500 μm, crypt cells (identified as the radiosensitive target cells) of height 150 μm, and an overlying mucus layer of thicknesses 5–200 μm. Several recent dosimetric analyses have likewise used models of the gastrointestinal tract's small-scale anatomy (*7,8*), but the current model appears to be the most detailed and realistic. Third, as in several other recent analyses of walled-organs radionuclide dosimetry, the separate dose contributions from activity in the intestinal wall as well as the luminal contents are considered. In earlier walled-organ dosimetry models, activity was either assumed to be only in the luminal contents or uniformly distributed in a combined "contents-wall" region (*7,8*). However, even with today's high-resolution modalities, discrimination of, for example, luminal and wall activities is beyond the capability of nuclear medicine imaging. Jönsson et al. thus suggest that autoradiograms of tissue specimens from experimental animals, or perhaps of surgical specimens from patients, might well complement imaging-based time–activity studies (*9*). Measured activities could then be realistically partitioned among small-scale source regions.

The MIRD schema and other model-based approaches to internal dosimetry have proven invaluable for dosimetric risk assessment in diagnostic nuclear medicine. However, to the extent that specific patients deviate kinetically and anatomically from the respective kinetic and anatomic models, tissue dose estimates may be inaccurate. Loevinger (*3*) has stated that ". . . there is in principle no way of attaching a numerical uncertainty to the profound mismatch between the patient and the model (the totality of all assumptions that enter into the dose calculation). The extent to which the model represents in some meaningful way a patient, or a class of patients, is always open to question. . . ." Although any such inaccuracies are probably unimportant for diagnostic radiopharmaceuticals, the risk–benefit ratios are dramatically smaller and therefore the tolerances for inaccuracies in dose estimation are greatly reduced in radionuclide therapy. With the growth of radionuclide therapy, various techniques beyond the traditional MIRD schema—techniques for patient-specific radiation dosimetry—are being developed to improve the accuracy of dose estimates (*10,11*).

A general patient-specific treatment-planning paradigm is as follows (*11–16*). A tracer (diagnostic) activity of the therapeutic radiopharmaceutical is administered to the patient. Serial time–activity measurements are performed for the critical normal organs or the total body and, in some instances, tumor or other target tissue. These kinetic data are integrated to determine the corresponding cumulated activities (or residence times), and the absorbed doses per unit administered activity are calculated. The actual therapeutic administered activity is then either the maximum tolerated activity—that is, the activity projected to deliver maximum tolerated doses to one or more critical normal tissues—or, less commonly, a minimum effective dose to tumor or other target tissue.

Most commonly, myelosuppression has proven to be the therapy-limiting toxicity in radionuclide therapy. For

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^{131}I-iodide treatment of metastatic thyroid cancer, for example, the therapeutic administered activity is that calculated to deliver no more than 2 Gy (200 rad) to blood (as a surrogate for bone marrow) (*11*,*15*,*17–20*). In radioimmunotherapy of non-Hodgkin's B-cell lymphoma with ^{131}I-labeled anti-B1 (anti-CD20) monoclonal antibody, on the other hand, the therapeutic administered activity is that delivering a dose of 0.75 Gy (75 rad) to the total body (again as a surrogate for bone marrow) (*21–24*). However, therapy-limiting "second-organ" toxicities (i.e., toxicity among organs other than the bone marrow) may occur and are, in fact, beginning to be observed for certain radionuclide therapies. For example, in radiopeptide therapy with β-ray–emitting radiometals such as ^{90}Y and ^{177}Lu, renal thrombotic microangiopathy and resulting kidney failure have been observed (*25–27*). As described by Boerman et al. (*25*), for example, low-molecular-weight peptides such as DOTA-D-Phe^1-Tyr^3-octreotide are filtered by the glomeruli and subsequently reabsorbed in the proximal renal tubule. Once internalized, the radiopeptides are metabolically degraded, with the radiometal–chelate–amino acid complex trapped in the proximal tubule cells, rather than transferred back to the blood. The high uptake and long retention of the radiometal in the proximal tubules and the short range of the emitted β-rays then result in a highly localized absorbed dose to the proximal tubule cells. Once maximum tolerated renal doses are established, an anatomically realistic, small-scale dosimetric model of the kidney (i.e., including the proximal renal tubule cells), combined with measured patient-specific kinetics, should yield reliable estimates of maximum tolerated activities for planning radiopeptide therapy in individual patients.

The work of Jönsson et al. (*1*) is an elegant example of the type of anatomically detailed dosimetric model that may be used with patient-specific time–activity data to estimate the dose to a critical (i.e., therapy-limiting) small-scale target region and to thereby more reliably implement a maximum-tolerated-activity treatment-planning algorithm.

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REFERENCES

1. Jönsson L, Liu X, Jönsson B-A, et al. A dosimetry model for the small intestine incorporating intestinal wall activity and cross-doses. *J Nucl Med.* 2002;43:1657-1664.
2. Watson EE. Foreward. *J Nucl Med.* 1999; 40(suppl):1S–2S.
3. Loevinger R. The MIRD perspective. In: Adelstein S, Kassis A, Burt R, eds. *Dosimetry of Administered Radio*nuclides. Washington, DC: American College of Nuclear Physicians/Department of Energy; 1989:29–43.
4. Loevinger R, Budinger TF, Watson EE. *MIRD Primer for Absorbed Dose Calculations*. Revised. New York, NY: Society of Nuclear Medicine; 1991.
5. Howell RW, Wessels BW, Loevinger R, in collaboration with the MIRD Committee. The MIRD perspective 1999. *J Nucl Med.* 1999;40(suppl):3S–10S.
6. International Commission on Radiological Protection. *Radiation Dose to Patients from Radiopharmaceuticals*. ICRP Publication 53. New York, NY: Pergamon Press; 1988.
7. Poston JW Jr, Kodimer KA, Bolch WE, Poston JW Sr. A revised model for the calculation of absorbed energy in the gastrointestinal tract. *Health Phys.* 1996;71:307–314.
8. Stubbs JB, Evans JF, Stabin MG. Radiation absorbed doses to the walls of hollow organs. *J Nucl Med.* 1998;39:1989–1995.
9. Jönsson B-A, Strand SE, Larsson BS. A quantitative autoradiographic study of the heterogeneous activity distribution of different indium-111-labeled radiopharmaceuticals in rat tissues. *J Nucl Med.* 1992;33:1825–1833.
10. Thomas SR. Options for radionuclide therapy: from fixed activity to patient-specific treatment planning. *Cancer Biother Radiopharm.* 2002;17: 71–82.
11. Zanzonico PB. Internal radionuclide radiation dosimetry: a review of basic concepts and recent developments. *J Nucl Med.* 2000;41:297–308.
12. DeNardo SJ, DeNardo GL, O'Grady LF, et al. Treatment of a patient with B cell lymphoma by I-131 LYM-1 monoclonal antibodies. *Int J Biol Markers.* 1987;2:49–53.
13. DeNardo DA, DeNardo GL, Yuan A, et al. Prediction of radiation doses from therapy using tracer studies with iodine-131-labeled antibodies. *J Nucl Med.* 1996;37:1970–1975.
14. Sgouros G, Barest G, Thekkumthala J, et al. Treatment planning for internal radionuclide therapy: three-dimensional dosimetry for nonuniformly distributed radionuclides. *J Nucl Med.* 1990;31:1884–1891.
15. Zanzonico P, Edwards C, Sgouros G, et al. Practical dosimetry: quantitative imaging in radionuclide therapy. In: Adelstein S, Kassis A, Burt R, eds. *Dosimetry of Administered Radionuclides.* Washington, DC: American College of Nuclear Physicians/Department of Energy; 1989:275–294.
16. Erdi AK, Erdi YE, Yorke ED, Wessels BW. Treatment planning for radio-immunotherapy. *Phys Med Biol.* 1996;41:2009–2026.
17. Zanzonico PB, Bigler RE, Sgouros G, Strauss A. Quantitative SPECT in radiation dosimetry. *Semin Nucl Med.* 1989;19:47–61.
18. Zanzonico P, Brill A, Becker D. Radiation dosimetry. In: Wagner H, Szabo Z, Buchanan J, eds. *Principles of Nuclear Medicine*. 2nd ed. Philadelphia, PA: W.B. Saunders; 1995:106–134.
19. Benua R, Cicale N, Sonenberg M. The relation of radioiodine dosimetry to results and complications in the treatment of metastatic thyroid cancer. *AJR.* 1962;87:171–182.
20. Furhang EE, Larson SM, Buranapong P, Humm JL. Thyroid cancer dosimetry using clearance fitting. *J Nucl Med.* 1999;40:131–136.
21. Kaminski MS, Zasadny KR, Francis IR, et al. Radioimmunotherapy of B-cell lymphoma with [^{131}I]anti-B1 (anti-CD20) antibody. *N Engl J Med.* 1993;329:459–465.
22. Kaminski MS, Zasadny KR, Francis IR, et al. Iodine-131-anti-B1 radioimmunotherapy for B-cell lymphoma. *J Clin Oncol.* 1996;14:1974–1981.
23. Wahl RL, Zasadny KR, MacFarlane D, et al. Iodine-131 anti-B1 antibody for B-cell lymphoma: an update on the Michigan phase I experience. *J Nucl Med.* 1998;39(suppl):21S–27S.
24. Zasadny KR, Gates VL, Fisher SJ, Kaminski MS, Wahl RL. Correlation of dosimetric parameters with hematological toxicity after radioimmunotherapy of non-Hodgkin's lymphoma with I-131 anti-B1: utility of a new parameter—"total body dose-lean" [abstract]. *J Nucl Med.* 1995;36(suppl): 214P.
25. Boerman OC, Oyen WJ, Corstens FH. Between the Scylla and Charybdis of peptide radionuclide therapy: hitting the tumor and saving the kidney. *Eur J Nucl Med.* 2001;28:1447–1449.
26. Cohen EP, Moulder JE, Robbins ME. Radiation nephropathy caused by yttrium 90. *Lancet.* 2001; 358:1102–1103.
27. Otte A, Weiner SM, Cybulla M. Is radiation nephropathy caused by yttrium-90? *Lancet.* 2002; 359:979.