# POINT/COUNTERPOINT

*Suggestions for topics suitable for these Point/Counterpoint debates should be addressed to Habib Zaidi, Geneva University Hospital, Geneva, Switzerland: habib.zaidi@hcuge.ch; Jing Cai, The Hong Kong Polytechnic University, Hong Kong: jing.cai@polyu.edu.hk; and/or Gerald White, Colorado Associates in Medical Physics: gerald.white@mindspring.com. Persons participating in Point/Counterpoint discussions are selected for their knowledge and communicative skill. Their positions for or against a proposition may or may not reflect their personal opinions or the positions of their employers.*

# Personalized dosimetry is a must for appropriate molecular radiotherapy

Michael G. Stabin, Ph.D.
*NV5/Dade Moeller, 1835 Terminal Drive, Richland 99352 WA, USA*
*(Tel: 509-376-5605; E-mail: stabinmg17@gmail.com)*

Mark T. Madsen, Ph.D.
*Department of Radiology, University of Iowa, Iowa City 52242 IA, USA*
*(Tel: 319-356-3373; E-mail: mark-madsen@uiowa.edu)*

Habib Zaidi, Ph.D., Moderator

(Received 26 August 2019; accepted for publication 2 September 2019; published 4 October 2019)

[https://doi.org/10.1002/mp.13820]

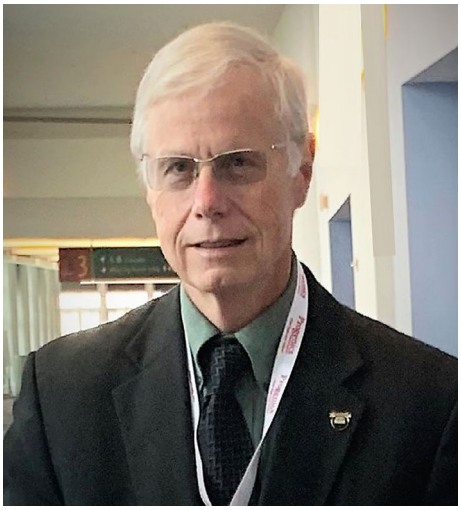
## OVERVIEW

This is an exciting time for targeted molecular radiotherapy. Recent advances in the field of theranostics are enabling the implementation of innovative approaches for the treatment of a plethora of systemic malignancies. Theranostics introduced a paradigm shift in medicine by offering the advantage of combining specific targeted therapy based on specific targeted diagnostic tests. In the era of precision medicine, it is time to revive the debate on standardized versus personalized or patient-individualized dosimetry. It is gratifying to see in perspective the progress made in internal dosimetry, from conventional fixed amounts administered to all patients to patient-specific dosimetry based on actual patient data and molecular imaging tools, advanced computational modeling of the human body, and sophisticated Monte Carlo-based calculation techniques enabling accurate patient-specific estimates of the delivered radiation dose. It is becoming widely accepted that personalized dosimetry enables a more rigorous approach for treatment planning aiming at improved understanding of the dose–response relationship.

While some think that personalized dosimetry is a must for appropriate molecular radiotherapy, others think that the approach is too complex, difficult to implement from a logistics standpoint, and requires too many resources and competences not necessarily available in clinical facilities. All these drawbacks are still hampering its implementation in the clinic. This is the topic addressed in this month's Point/Counterpoint debate.

Arguing for the proposition is Michael G. Stabin, PhD. Dr. Stabin is a certified physicist working for NV5. Previously he was an associate professor in the Department of Radiology and Radiological Sciences at Vanderbilt University, in Nashville, TN. Before that he was a visiting professor at the Universidade Federal de Pernambuco in Recife, Brasil for 2 yr, and was a scientist at the Radiation Internal Dose Information Center of Oak Ridge Institute for Science and Education for 15 yr. He has a Bachelor of Science and a Master of Engineering degree in Environmental Engineering (Health Physics emphasis) from the University of Florida and received his PhD in Nuclear Engineering (Health Physics emphasis) from the University of Tennessee. He is a Certified Health Physicist (1988, and recertified since then). He is a member of the Health Physics Society and the Society of Nuclear Medicine. He has over 225 publications in the open literature, most in the area of internal dosimetry for nuclear medicine applications, including complete textbooks on health physics and internal dose assessment. He has served as member and chair of the American Board of Health Physics Certification Examination Panel (Part I and II), and as an associate editor of the Health Physics Journal from 1992 until now. He also serves on task groups of the Society of Nuclear Medicine (the RAdiation Dose Assessment Resource,



RADAR), American Association of Physicists in Medicine (AAPM), and the International Commission on Radiological Protection (ICRP). He has developed several models, methods, and tools that have become widely used in the nuclear medicine community, including the MIRDOSE and OLINDA/EXM personal computer software codes for internal dose calculations.

Arguing against the Proposition is Mark T. Madsen, PhD. Dr. Madsen is an Emeritus Professor of Radiology at the University of Iowa. In addition to his work on personalized dosimetry with $Y^{90}$ DOTATOC radionuclide therapy which received the SNMMI Henry Wagner Award in 2016, his research interests include nuclear medicine quality assurance, image processing, emission computed tomography, and abnormality manipulation of tomographic images for image perception research and he has more than 80 peer-reviewed publications. He has been an active member in many professional societies and is a fellow of the American College of Radiology, the American Association of Physicists in Medicine, and the Society of Nuclear Medicine and Molecular Imaging.

## FOR THE PROPOSITION: Michael G. Stabin, Ph.D

### Opening Statement

I wrote "The case for patient-specific dosimetry in radionuclide therapy" in 2008.[1] My main point was that "Treating all nuclear medicine patients with a single, uniform method of activity administration amounts to *consciously choosing that these patients be treated with a lower standard of care* than patients who receive radiation externally for cancer treatments." Some have objected to this statement, but it is simply undeniable. I just returned from the 2019 SNMMI annual meeting, where the focus of the dosimetry session was how dosimetry is an invaluable aid in planning and executing $^{177}$Lu Lutathera therapies, among others.

In "The Case" I refuted all of the arguments against performing patient-individualized therapy in nuclear medicine:

- *Methods are not standardized for performing dose calculations.*

Obtaining quantitative planar and/or tomographic data for dosimetry is well-described in the literature[2,3]; reliable software is available for calculating standardized dose estimates, with adjustment of dose estimates for individual patient organ masses.[4]

- *Performing such calculations is too difficult and expensive.*

Cancer patients have been subjected to many difficult procedures; lying on an imaging table for a couple of extra scans is not a huge difficulty. Cost estimates are much less than conventional external beam therapy, or at the outside, quite comparable.[5]

- *Dose calculations have had poor success in predicting tissue response.*

Not if good dosimetry methods are used. In "The Case," several studies were cited in which good quality dosimetry predicted biological response quite well.[6–9] We have also learned how to modify dose numbers to account for the effects such as dose rate (Biologically Effective Dose)[10] and dose nonuniformity (Equivalent Uniform Dose).[11]

- *There must be some objective evidence that the use of radiation dose calculations provides positive benefit that justifies extra effort and cost.*

Our colleagues in external beam therapy have always used individualized dosimetry as a key element in radiation therapy. Current clinical trials now underway in Europe are clearly showing the benefit of patient-individualized dose calculations in nuclear medicine therapy.

### Conclusions

Patient-individualized medicine is improving patient care in almost every area of medical practice currently, EXCEPT in nuclear medicine therapy. We estimate and record dose estimates for patients obtaining *diagnostic* CT exams, for airline crews obtaining much lower doses of radiation, all radiation workers, etc. The ONLY group on this planet for which we allow significant radiation exposures without estimation of radiation dose is nuclear medicine therapy patients. This has several important negative consequences:

1. The patients are not receiving optimal radiation therapy that can give them the best chance of overcoming their disease.
2. Many years after a given radiation therapy, physicians may wish to know what radiation doses have been received by a patient previously, to carefully plan appropriate levels that may be tolerated. We cannot

give these physicians any valid numbers to work with, as we simply have no idea what they are.

3. We have several decades of experience relating doses received from external beam therapy to observed radiation effects, to manage normal tissue complication probabilities and tumor control probabilities. We NEED dosimetry data for radiopharmaceutical therapy, in order to obtain meaningful dose/effect correlations. We can never correlate any doses with any observed effects, if we never calculate any doses!

Calculating patient-individualized dosimetry for nuclear medicine therapy patients is simply a moral imperative. These patients deserve the highest standards of care available. Arguments for perpetuating this culture of "one size fits all" therapy simply must end.

## AGAINST THE PROPOSITION: Mark T. Madsen, Ph.D

### Opening Statement

It would seem silly to make the argument against personalized dosimetry for radionuclide therapy. It is well known that there are significant individual differences in the magnitude of radiation dose delivered to critical organs from standardized administered activities,[12] and this potentially leads to either the undertreatment of targeted disease or the exceeding of radiation dose limits to the critical organs resulting in radiotoxic effects.[13] However, personalized dosimetry requires an accurate estimate of the number of decays (time integrated activity) that occur in the critical organ and in the case of radionuclides with a substantial gamma ray component, in all the source organs that have a significant dose contribution to the critical organ.[2,14] To obtain this information, image-based measurements (planar, SPECT or PET) must be acquired at multiple time points often spanning 72 or more hours[2,15,16] after the administration of the either the radionuclide therapeutic agent itself (which can be done when several cycles of therapy will be given)[1] or the administration of a pretreatment surrogate radiotracer.[17] In both situations, there are challenging demands placed on clinic resources which include the imaging system time and availability and technologist time. In addition, there is a time required for processing and analyzing the imaging studies which may require a medical physicist or other individual who has the specific training and experience to perform internal radiation dosimetry.[18,19] While sufficient resources may be available at some academic institutions, they are not at many other clinics and these issues will become even more challenging as the number of patients receiving radionuclide therapies increases. Another consideration with the collection of these studies is the burden that it places on the patients who must remain in the proximity of the clinic at their own expense until the image-based studies are completed.

Along with the technical challenges discussed above, there is the concern about the applicability of current dosimetric approaches. For example, recent papers comparing observed marrow toxicity as a function of measured red marrow radiation dose show a disappointing correlation.[20] This could suggest that the conventional methodology for estimating red marrow doses is not adequate for these radiotherapeutic agents.

In an ideal world with unlimited economic and technical support resources, it would be impossible to defend the claim that personalized dosimetry was not desirable. However, the world is not ideal and both economic and technical support resources are limited to the extent that the practical implementation of radionuclide therapy will be a luxury available to only well-funded academic clinics.

### Rebuttal: Michael G. Stabin, Ph.D

My esteemed colleague makes many outstanding points in his opening statement. As I am passionate about this story, I shall only try to respectfully rebut two points:

Dr Madsen argues that *While sufficient resources may be available at some academic institutions, they are not at many other clinics and these issues will become even more challenging as the number of patients receiving radionuclide therapies increases.* It is far past time that sufficient resources be allotted to allow these struggling patients to get the care that they deserve, as do external beam therapy patients every single day of every single week.

He also asserts: *Recent papers comparing observed marrow toxicity as a function of measured red marrow radiation dose show a disappointing correlation*." As I noted in my opening, WELL-DONE dosimetry correlates doses with effects. We have been developing marrow dose models since the days of Spiers, and we have very adequate models. If we never even try to calculate marrow doses, with any model, we can never expect to get reasonable dose/effect correlations. We must try, it's for the sake of the patients!

### Rebuttal: Mark T. Madsen, Ph.D

Dr. Stabin makes a very strong case in support of the proposition and it is difficult to refute his rationale about the need for personalized dosimetry in molecular radiotherapy. In my opening statement, I chose to focus on the challenges that are associated with personalized internal dosimetry; and while Dr. Stabin has addressed most of these concerns in his opening statement, I think it is important to explore these issues further. Dr. Stabin noted that the focus of the dosimetry session at the recent SNMMI Annual Meeting was on the importance of personalized dosimetry in planning and executing $^{177}$Lu Lutathera treatments. However, it should be realized that $^{177}$Lu Lutathera was approved with a standard administration dosage (7.4 GBq every 8 weeks for a total of 4 administrations[21]) without any requirements for personalized dosimetry.

Dr. Stabin notes that obtaining the required quantitative data for internal dosimetry is well-described in the literature. That is certainly true and Dr. Stabin and his colleagues at Vanderbilt University have been among the leaders in

developing dosimetric procedures as well as dose calculation software to facilitate accurate dose estimates.[4] Even so, it takes a lot of training and experience in performing these studies to reach the level of expertise required to reliably provide patient dose estimates. Dr. Stabin notes in his opening statement that the perceived lack of success in predicting tissue response from dose estimates is the result of poor methodology. The number of clinics and individuals with sufficient training is, at this time, insufficient for the nationwide demands posed by radionuclide treatments.

Dr. Stabin notes that cancer patients have to put up with many difficult clinical procedures and that lying on an imaging table for extra scans is not much of a burden. However, it is not the imaging time of the scan that is the issue, but the requirement of multiple imaging sessions over many days (up to a week in some cases). For meaningful personalized dosimetry, multiple imaging sessions ought to be acquired with each treatment cycle since there can be substantial changes in the critical organ dose as treatment progresses.

In closing, I want to reemphasize that I am only focusing on the challenges that are associated with the proposition. I agree with Dr. Stabin that the additional resources required to provide accurate dosimetric treatment planning for external beam therapy are not only well-accepted but are also required. It seems reasonable that similar resources should be made available for molecular radiotherapy. However, until they are, the practical implementation of radionuclide therapy may be a luxury available to only well-funded academic clinics.

## CONFLICT OF INTEREST

Dr. Stabin and Dr. Madsen have no relevant conflict of interest.

## REFERENCES


1. Stabin MG. Update: the case for patient-specific dosimetry in radionuclide therapy. *Cancer Biother Radiopharm*. 2008;23:273–284.
2. Siegel JA, Thomas SR, Stubbs JB, et al. Pamphlet No. 16: techniques for quantitative radiopharmaceutical biodistribution data acquisition and analysis for use in human radiation dose estimates. *J Nucl Med*. 1999;40:37S–61S.
3. Dewaraja YK, Wilderman SJ, Ljungberg M, Koral KF, Zasadny K, Kaminiski MS. Accurate dosimetry in 131I radionuclide therapy using patient-specific, 3-dimensional methods for SPECT reconstruction and absorbed dose calculation. *J Nucl Med*. 2005;46:840–849.
4. Stabin MG, Sparks RB, Crowe E. OLINDA/EXM: the second-generation personal computer software for internal dose assessment in nuclear medicine. *J Nucl Med*. 2005;46:1023–1027.
5. Cost estimates in this section from personal communication. G Flux. UK: Royal Marsden Hospital; 2006.
6. Kobe C, Eschner W, Sudbrock F, et al. Graves' disease and radioiodine therapy. Is success of ablation dependent on the achieved dose above 200 Gy? *Nuklearmedizin*. 2008;47:13–17.
7. Shen S, Meredith RF, Duan J, et al. Improved prediction of myelotoxicity using a patient-specific imaging dose estimate for non-marrow-targeting (90)Y-antibody therapy. *J Nucl Med*. 2002;43:1245–1253.
8. Siegel JA, Yeldell D, Goldenberg DM, et al. Red marrow radiation dose adjustment using plasma FLT3-L cytokine levels: improved correlations between hematologic toxicity and bone marrow dose for radioimmunotherapy patients. *J Nucl Med*. 2003;44:67–76.
9. Pauwels S, Barone R, Walrand S, et al. Practical dosimetry of peptide receptor radionuclide therapy with (90)Y-labeled somatostatin analogs. *J Nucl Med*. 2005;46:92S–98S.
10. Bodey RK, Flux GD, Evans PM. Combining dosimetry for targeted radionuclide and external beam therapies using the biologically effective dose. *Cancer Biother Radiopharm*. 2003;18:89–97.
11. Henriquez FC, Castrillon SV. A quality index for equivalent uniform dose. *J Med Phys*. 2011;36:126–132.
12. 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.
13. Chiesa C, Castellani R, Mira M, Lorenzoni A, Flux GD. Dosimetry in 131I-mIBG therapy: moving toward personalized medicine. *Q J Nucl Med Mol Imaging*. 2013;57:161–170.
14. Boucek JA, Turner JH. Personalized dosimetry of 131I-rituximab radioimmunotherapy of non-hodgkin lymphoma defined by pharmacokinetics in bone marrow and blood. *Cancer Biother Radiopharm*. 2014;29:18–25.
15. Marin G, Vanderlinden B, Karfis I, et al. A dosimetry procedure for organs-at-risk in (177)Lu peptide receptor radionuclide therapy of patients with neuroendocrine tumours. *Phys Med*. 2018;56:41–49.
16. Huizing DMV, de Wit-van der Veen BJ, Verheij M, Stokkel MPM. Dosimetry methods and clinical applications in peptide receptor radionuclide therapy for neuroendocrine tumours: a literature review. *EJNMMI Res*. 2018;8:89.
17. Huang SY, Bolch WE, Lee C, et al. Patient-specific dosimetry using pretherapy [(1)(2)(4)I]m-iodobenzylguanidine ([(1)(2)(4)I]mIBG) dynamic PET/CT imaging before [(1)(3)(1)I]mIBG targeted radionuclide therapy for neuroblastoma. *Mol Imaging Biol*. 2015;17:284–294.
18. Dewaraja YK, Frey EC, Sgouros G, et al. MIRD pamphlet No. 23: quantitative SPECT for patient-specific 3-dimensional dosimetry in internal radionuclide therapy. *J Nucl Med*. 2012;53:1310–1325.
19. Medical IAEA.Physics Staffing Needs in Diagnostic Imaging and Radionuclide Therapy: An Activity Based Approach. IAEA Human Health Series Publications Report No. 15. Vienna, Austria: IAEA; 2018.
20. Svensson J, Ryden T, Hagmarker L, Hemmingsson J, Wangberg B, Bernhardt P. A novel planar image-based method for bone marrow dosimetry in (177)Lu-DOTATATE treatment correlates with haematological toxicity. *EJNMMI Phys*. 2016;3:21.
21. LUTATHERA® [prescribing information]. Advanced Accelerator Applications USA. Millburn, NJ: Inc.; July; 2018.