

# Is Routine Dosimetry Really Happening?

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**O**ne important aspect of radiopharmaceutical therapy (RPT) that sets it apart from virtually all other oncologic therapeutic approaches is the ability to noninvasively image and verify the existence of the molecular therapeutic target before therapy. But perhaps the most powerful aspect of RPT has not yet been realized. That is the ability to quantitatively measure the relative expression of the molecular target and to quantitatively calculate the absorbed radiation dose to both tumors and normal tissue in RPT applications. Armed with this knowledge, physicians would have the ability to tailor patient-specific administered activities designed to achieve the highest therapeutic effect while staying below toxic radiation doses to normal organs.

Running parallel to the explosive growth of clinical RPT is the availability of both publicly available and commercial dosimetry software and an increasing literature base targeting methods for more reproducible and accurate image-based dosimetry measurements. Despite these advances, significant barriers to widespread adoption of clinical dosimetry in RPT are impeding implementation of personalized therapy, and a significant amount of rigorous science needs to be completed before this future can be realized. In the meantime, there are currently niche opportunities for clinical dosimetry applications to aid in the management of patients. The question is whether facilities are actually performing routine clinical dosimetry in RPT.

## RPT DOSIMETRY BARRIERS TO ADOPTION

For purposes of this commentary, *clinical dosimetry* refers to using the results of quantitative nuclear image-based dosimetric calculations to potentially modify patient treatment. Standing directly in the path of adoption and practice of clinical dosimetry are several substantial barriers. The first is a significant lack of controlled clinical trial evidence to support the use of dosimetry to positively impact safety and efficacy. The positive potential is clear and compelling, but evidence is scant. The lack of radiopharmaceutical-specific dose-effect relationships for different critical organs and tumor types currently cripples our ability to predict treatment response or toxicity with reasonable certainty, even if absorbed doses were accurately measured.

Economic and reimbursement issues are another critical barrier to adoption of clinical dosimetry; these fall into 2 separate categories. It is within a physician's purview to use dosimetric information to increase or decrease the injected activity of either  $^{177}\text{Lu}$ -vipivotide

tetraxetan (Pluvicto; Novartis) or  $^{177}\text{Lu}$ -DOTATATE (Lutathera; Novartis) (the two most used RPT agents) to the patient under the practice of medicine. Although decreasing the injected dose for safety purposes has no economic ramifications, increasing the dose for enhanced efficacy would require ordering a second 7.4-GBq vial that would carry a crippling nonreimbursable expense. This is the first reimbursement hurdle. Second, the uncertain and evolving reimbursement situation for the additional SPECT imaging and physicist time associated with the dosimetry calculations make it challenging to justify the use of dosimetry in the busy clinic. There are current coding options for reimbursement for single and serial SPECT imaging that should allow for imaging data collection. However, reimbursement codes specific to RPT dosimetry calculations do not exist, with the closest codes being conventionally used for external-beam radiotherapy dosimetry. It is difficult to envision clinical dosimetry entering the mainstream workflow and realizing its clinical potential if the coding issue is not remedied.

Logistic challenges represent a third significant barrier category. Even dosimetry-capable sites resist asking patients to come in for multiple SPECT/CT imaging sessions, particularly patients who travel several hours for treatment. Asking patients for their time, effort, and expense for dosimetry imaging is likely unjustified and unethical unless they are likely to derive direct benefit from the dosimetry. Single-time-point imaging for dosimetry is a logistically more reasonable request, but the accuracy of the absorbed dose estimate is compromised, which may impact patient care. This is an evolving space.

Fourth, absorbed dose estimate calculations are currently variable. Most of this stems from a lack of standardization of methodologies (1). This limitation is being addressed by professional societies through a series of best-practices manuscripts under development.

## THE CASE FOR CLINICAL DOSIMETRY

The technical infrastructure for clinical dosimetry exists. Reliable commercial and public domain dosimetry software is available, and results have been demonstrated to be comparable (2). An increasing number of well-trained physicists is available to perform the calculations reliably. Accurate quantitative SPECT/CT images on which dosimetry is based are finally becoming a reality. Significant advancements in SPECT calibration, calibration verification, and standardization are being driven by cooperative efforts from international professional societies and manufacturers (3–5).

In some situations, additional imaging and associated dosimetry are clinically justifiable even given the barriers. Although it is true that dose-response curves for most organs—even for currently

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approved radiopharmaceuticals—are incomplete, we do have baseline knowledge of higher-dose-rate external-beam radiation therapy-generated dose-response curves for the kidney (23 Gy) and bone marrow (2 Gy) that can be used as a conservative guideline in circumstances that warrant it. Many are of the opinion that the 23-Gy threshold is inappropriate for our low-dose-rate RPT application, and mounting clinical evidence in the literature suggests that the threshold for kidney injury for currently approved  $^{177}\text{Lu}$  radiopharmaceuticals is substantially higher (6,7). Regardless of the threshold used, there is an opportunity for clinical use of kidney dosimetry in patients who might be more susceptible to kidney injury. In these cases, administered activity can be lowered on the basis of dosimetry, as necessary, to remain below prescribed limits determined by the physician. Existing reimbursement can be used for both imaging and dosimetry, although this reimbursement may not be sufficient to cover costs (8).

Image-based marrow dosimetry is more challenging to justify, but its role as a potential predictive safety biomarker warrants investigation. Blood biomarkers do a good job of measuring in-treatment hematopoietic toxicity, and these data are easy and inexpensive to collect. Referring physicians are comfortable managing patients who manifest marrow toxicities, so this is familiar and comfortable territory. Imaging the marrow with SPECT systems has challenges associated with the relatively small size of the marrow space and the limited resolution of modern SPECT systems, as well as being confounded by inaccurate scatter correction. However, image-based marrow dosimetry has the potential to be a predictive biomarker for high-grade hematopoietic toxicity from short courses of therapy (cumulative activity given over only 1 or 2 administrations), which would be of significant clinical value.

#### THE CURRENT CLINICAL DOSIMETRY SITUATION IN NORTH AMERICA

As is the case with virtually all technologic developments, there is always a subset of early adopters who seek to take advantage of new technologies and capabilities. The current question is whether institutions are routinely performing clinical dosimetry. To generate primary data to answer this question, a survey was sent to a subgroup of U.S. and Canadian institutions deemed most likely to be performing routine dosimetry: the 36 Society of Nuclear Medicine and Molecular Imaging–designated comprehensive therapy centers of excellence. By requirement, all of these centers must have the necessary personnel and infrastructure to perform personalized dosimetry. All sites listed a physicist, and each was asked to respond to 4 questions:

1. Are you and your institution performing any clinical RPT dosimetry at your site?
2. If you are performing clinical dosimetry, are you billing for SPECT imaging? Are you billing for the dosimetry work?
3. If you are performing clinical dosimetry, is this on all patients or only a subset, and if only a subset, can you briefly describe that subpopulation?
4. (Optional) Are you routinely performing RPT dosimetry but only for clinical trials (you may specify internal or external clinical trials).

One additional site known to perform clinical dosimetry was surveyed. Of the total of 37 sites, 20 responses were received. Results are summarized in Table 1 and below.

For the first question, regarding whether the institution was performing any clinical RPT dosimetry, 11 of the 20 responded in the affirmative—that they were performing some clinical dosimetry. However, it is important to note that a small subset of these performed dosimetry on  $^{131}\text{I}$ ,  $^{90}\text{Y}$ , and  $^{131}\text{I}$ -iobenguane (Azedra; Lantheus) but explicitly excluded  $^{177}\text{Lu}$ -DOTATATE and  $^{177}\text{Lu}$ -vivotide tetraxetan.

For the second question, of the 11 that responded positively to the clinical dosimetry question, 9 responded that they were billing for the nuclear medicine imaging. Only 3 of the 11 sites stated that they are billing for dosimetry calculations. Three of the 11 sites explicitly stated that their institutions were looking into codes to bill for dosimetry services but had not yet billed. The remaining 5 sites were either explicitly not billing for dosimetry or were silent because of lack of knowledge of internal billing policies. In related activity, 3 sites reported that although not performing clinical dosimetry, they nonetheless performed posttherapy SPECT imaging for baseline imaging and response to therapy, and they billed for it.

For the third question, the patient subpopulations identified to receive dosimetry were a mixed bag and included  $^{177}\text{Lu}$ -DOTATATE,  $^{177}\text{Lu}$ -vivotide tetraxetan,  $^{131}\text{I}$ -iobenguane,  $^{90}\text{Y}$  radioembolization, and  $^{131}\text{I}$  therapies. Two sites reported performing  $^{90}\text{Y}$  dosimetry for radioembolization procedures. Others did not report this population as one that received dosimetry, perhaps because of the ambiguity of the question, which explicitly refers to RPT dosimetry, from which radioembolization might be excluded by survey responders.

$^{131}\text{I}$  dosimetry was reported by 4 sites. The subpopulations and methods varied. The reported subpopulations were those with lung metastases or with critical organ risk factors associated with the procedure based on the locations of the metastases.

For 8 sites that explicitly reported performing dosimetry for  $^{177}\text{Lu}$ -DOTATATE and  $^{177}\text{Lu}$ -vivotide tetraxetan patients, all but one reported that only a limited number were being performed. The clinical indications were mostly on a case-by-case basis. A ninth site is prospectively collecting dosimetry data on virtually all patients who can tolerate the treatment, although the site is primarily targeting its own safety database for dose response. For the 8 other responding sites, 2 common clinical situations reported by several sites included patients with potential renal susceptibility and those returning for retreatment.

For the fourth question, which was optional, 10 sites reported that they were performing on-site dosimetry for their own internal clinical trials. Additionally, all these sites are engaged in externally sponsored trials for which they supply multiple-time-point imaging data but do not perform the dosimetry for the trial. Two sites reported performing dosimetry calculations for both internal and external clinical trials. Interestingly, 3 physicists independently practice their dosimetry skills on these outside clinical trials when permitted.

It is critical to reiterate that this sampling of sites is from a consortium of institutions in the United States and Canada most likely to be performing clinical and research dosimetry and by no means is meant to be representative of the community at large. It is also important that these data explicitly exclude sites from the European Union, where some form of dosimetry is required by community directive 2013/59/Euratom article 56 (9). Although this directive is not strictly followed, RPT dosimetry is more common in the European community (10).

**TABLE 1**  
Survey Results

Site	Clinical dosimetry?	Billing for SPECT? Dosimetry?	Dosimetry of all clinical patients or subset?	Optional: RPT dosimetry for clinical trials
1	No	Yes (SPECT)	Subset (unspecified)	Yes (internal and external trials)
2	Yes	Yes (SPECT)	Subset (single/compromised kidney function, significant bone mets/lung mets, retreatment)	No response
3	Yes	No	Subset (those who agree to multiple imaging)	No response
4	Yes	Yes (SPECT)	Subset (reduced kidney function, other risk factors)	No response
5	Yes ( <sup>131</sup> I, no <sup>177</sup> Lu)	Yes (SPECT and dosimetry)	Subset ( <sup>131</sup> I, suspected lung mets)	No response
6	No	No (not performed)	No	No
7	No	No (not performed)	No	No
8	No	No (not performed)	No	Yes (internal trials)
9	No	No (not performed)	No	Yes (internal trials)
10	No	No (not performed)	No	No
11	Yes	Yes (SPECT and dosimetry)	Subset (attending physician driven)	No
12	Yes ( <sup>131</sup> I, <sup>90</sup> Y, <sup>131</sup> I-iodobenguane, no <sup>177</sup> Lu)	Yes (SPECT)	Subset (unspecified)	Yes (internal trials)
13	No	No (not performed)	No	Yes (internal trials)
14	Yes	No	Subset ( <sup>131</sup> I, suspected lung mets, <sup>177</sup> Lu pending)	No
15	Yes	Yes (unspecified)	Subset (all <sup>90</sup> Y, <sup>177</sup> Lu renal insufficiency, previously treated, borderline marrow function, previously irradiated organs)	Yes (internal and external trials)
16	No	No (not performed)	No	No
17	Yes	Yes (SPECT)	Subset ( <sup>177</sup> Lu-DOTATATE)	Yes (internal trials)
18	Yes	Yes (SPECT and dosimetry)	Subset ( <sup>131</sup> I, compromised renal function; <sup>177</sup> Lu, compromised renal function or low blood counts for marrow toxicity)	Yes (internal trials)
19	Yes	Yes (SPECT)	Subset (unspecified)	Yes (internal trials)
20	No	Yes (SPECT)	Subset ( <sup>177</sup> Lu, all except those who cannot return)	Yes (internal trials)

Mets = metastases.

## DISCUSSION

It appears that only limited clinical RPT dosimetry is currently being performed in the United States and Canada. The nearly exclusive use of clinical dosimetry on only those cases for which patient management is actionable through a decrease in administered activity for safety purposes (never an increase) suggests that a lack of reimbursement for the drug above the standard recommended dosage appears to be a primary factor. Lack of understanding of how to bill for dosimetry, and perhaps concern about insufficient reimbursement for dosimetry calculations, appear to be real but secondary factors. For this physicist-centric

sampling, the lack of clinical RPT dosimetry was not due to a lack of infrastructure. Unsolicited comments volunteered by respondents include the following:

- “Despite the low numbers, we are fully set up with multiple software and expertise for dosimetry, which I keep up to date and always ready when necessary.”
- “Although I’m not doing routine clinical dosimetry. I think we are prepared to move into a more routine clinical scenario . . .”
- “Also set up to start Lu-177 Dosimetry but have not done our first patient yet. Plan is to start on a limited patient group based on [nuclear medicine] physician request . . .”

Standardization, quantitation, and reproducibility of reported dosimetry findings continue to be a challenge but do not appear to be at the heart of reticence to use dosimetry in clinical practice and will likely require improvement for future clinical use.

The pathway to clinical dosimetry-guided therapies optimized for individual patients (as necessary) will depend on cooperation by major stakeholders in this space on overcoming some major challenges. Professional societies (Society of Nuclear Medicine and Molecular Imaging, American Society for Radiation Oncology, American Association of Physicists in Medicine) must convince payers, including Medicare, to reimburse the field at a sustainable level for the medically justifiable use of dosimetry. This will be contingent on generating and sharing well-curated dosimetry data for currently approved therapeutic radiopharmaceuticals to learn the necessary dose-effect relationships for the kidney up to 40 Gy and, secondarily, marrow up to 2 Gy for  $^{177}\text{Lu}$  radiopharmaceuticals. There must be clinical trials in which investigators prospectively modify patient-administered activity on the basis of image-based dosimetry measurements. For these trials, flexibility built into chemistry, manufacturing, and control sections of the regulatory filings must be developed for vials with smaller activity denominations (e.g., 1.85-GBq vials), providing for smaller injected activity increments.

Both RPT and quantitative SPECT imaging are rapidly evolving spaces. An increasing number of reports are emerging on the use of posttherapy SPECT imaging to assess response (or lack of response) to RPT, and therapy decisions are being based on these results. This trend is not dosimetry-based, but it is a step toward the normalization of treatment decisions based on SPECT imaging, which is an incremental step in the right direction.

Finally, ethics will play a part in the evolution of the use of clinical dosimetry. In the current scientific and economic milieu, it is difficult to justify patient time, inconvenience, and potential costs, unless benefits to safety or outcome for the patient can be expected. The results of this informal survey seem to bear out that this approach is largely being followed. However, with careful trial designs and modest improvements in technology and standardization, it is not difficult to visualize a future in which it will be unethical to not use dosimetry in mainstream RPT.

## CONCLUSION

The results of the survey suggest that clinical use of personal dosimetry in the United States and Canada is quite rare, even at dosimetry-capable sites. This is understandable in the current clinical and reimbursement environment where common performance of dosimetry is likely an unsustainable practice because an increase in administered activity is not possible from a practicality standpoint and reimbursement for the dosimetry aspect is unclear and insufficient. As promising as current RPT therapies are, the cold

reality is that our already-approved RPT drugs are only slightly better-performing than alternative non-RPT therapies for their currently approved indications from a survival benefit standpoint. However, RPT exhibits substantial quality-of-life benefits, and encouraging positive results for clinical trials targeting earlier disease are emerging. While our field continues to innovate and develop new and exciting highly targeting radiopharmaceuticals, it is existentially imperative that we develop the necessary safety and efficacy data to expand the use of our current armamentarium of approved radiopharmaceuticals in a smarter way than we do now. This implies embedding dosimetry and other quantitative imaging approaches into postmarketing clinical trials to enable reimbursable models for more patient-centric therapies. The infrastructure is already in place and poised to grow as necessity demands. It is the science that needs to be done.

## DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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