Dosimetry in Clinical Radiopharmaceutical Therapy of Cancer: Practicality Versus Perfection in Current Practice

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The use of radiopharmaceutical therapies (RPTs) in the treatment of cancers is growing rapidly, with more agents becoming available for clinical use in last few years and many new RPTs being in development. Dosimetry assessment is critical for personalized RPT, as administered activity should be assessed and optimized in order to maximize tumor-absorbed dose while keeping normal organs within defined safe dosages. However, many current clinical RPTs do not require patient-specific dosimetry based on current Food and Drug Administration-labeled approvals, and overall, dosimetry for RPT in clinical practice and trials is highly varied and underutilized. Several factors impede rigorous use of dosimetry, as compared with the more convenient and less resource-intensive practice of empiric dosing. We review various approaches to applying dosimetry for the assessment of activity in RPT and key clinical trials, the extent of dosimetry use, the relative pros and cons of dosimetry-based versus fixed activity, and practical limiting factors pertaining to current clinical practice.

Key Words: dosimetry; theranostics; radiopharmaceutical therapy; RPT; radionuclide

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Radiopharmaceutical therapies (RPTs) have been used in the treatment of cancers for many decades. Recent advances in theranostics have led to Food and Drug Administration (FDA) approval of new RPTs and a surge in the development of several novel radiotargeted small molecules or antibodies for therapy. Dosimetry assessment is important to maximizing absorbed radiation dose to tumor in order to optimize tumor response and minimize normal-organ absorbed dose and toxicity. Personalized dosimetry can help adjust for interpersonal variation in biodistribution and tolerance to RPT, as well as intrapersonal heterogeneity of tumor uptake, and can be used to maximize administered activity when repeat dosing might be precluded by the development of tumor resistance or antibodies, such as after radioimmunotherapy.

Despite the recognized need for, and advantages of, dosimetry for personalized RPT (1), the use of dosimetry in clinical care varies widely across different RPTs (2). It is notable that, currently, dosimetry has not been mandated for all FDA-approved RPTs. Furthermore, dosimetry is incorporated inconsistently in the development of novel agents; for example, the recently completed VISION trial with 177Lu-prostate-specific membrane antigen (PSMA) included a fixed activity in prespecified cycles. Dosimetry in routine clinical practice is limited by variations in methodologies for establishing administered activity in published studies and trials, and by the lack of large prospective studies showing superior outcomes and survival benefit for dosimetry-based treatments as compared with empiric dosing. Although guidelines have been developed for optimizing various RPTs with dosimetry (3,4), application of these for dosimetry remains inconsistent.

Integrating dosimetry into routine clinical care poses technical, logistical, and practical challenges. Key drawbacks include differences in methodology, need for elaborate scanning procedures and blood or urine sampling, suitability of paired diagnostic radiopharmaceuticals, and available processing software. The ease of using a fixed activity allows for uniform and universal use, leading to the predominance of this method for administering activity in clinical RPT.

We present an overview of administered activity in various RPTs, extent of use, and integration of dosimetry for activity in routine clinical care. We compare and contrast methodologies for determining administered activity and use of dosimetry in published studies and key trials for FDA-approved RPT. We enumerate logistic challenges and present our perspective for balanced use of dosimetry in clinical practice and trials. This review is limited to RPT in malignancies and is not meant to be a comprehensive review of the literature on all RPT, dosimetry methodologies or biology, which are discussed in other articles of this supplement to The Journal of Nuclear Medicine.

CLINICAL EVIDENCE AND PRACTICE: VARIATION IN DOSIMETRY ASSESSMENT AND SELECTION OF ADMINISTERED ACTIVITY FOR RPT

In current practice, RPT is administered differently for different agents. Several approaches have been used to determine activity for treatment, ranging from fixed activity dosing to that based on pre- or posttreatment dosimetry with or without posttreatment validation. Some agents include dosimetry in the package label, such as FDA-approved 131I-tositumomab and 131I-iobenguane (5), whereas others such as 223RaCl2 and 177Lu-DOTATATE (Lutathera; Advanced Accelerator Applications) do not (Table 1).
<table>
<thead>
<tr>
<th><strong>Agent</strong></th>
<th><strong>Indication</strong></th>
<th><strong>Cycles and intervals</strong></th>
<th><strong>Administered activity per cycle</strong></th>
<th><strong>Dosimetry required?</strong></th>
<th><strong>Organ constraints</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>131I-sodium iodide</td>
<td>Differentiated thyroid cancer, remnant ablation, adjuvant, treatment of metastatic disease; benign thyroid disease such as goiter</td>
<td>1</td>
<td>Empiric variable activity based on indication or dosimetry guided to 2 Gy to blood or 2,960 MBq (80 mCi) retained in WB at 48 h if diffuse lung metastases</td>
<td>No</td>
<td>2 Gy to blood</td>
</tr>
<tr>
<td>153Sm-lexidronam</td>
<td>Symptomatic osteoblastic metastases</td>
<td>1</td>
<td>Fixed-weight–based activity, 37 MBq/kg</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>89SrCl</td>
<td>Symptomatic osteoblastic metastases</td>
<td>1</td>
<td>Fixed activity, 148 MBq</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>223Ra-dichloride</td>
<td>Prostate cancer, metastatic disease to bone</td>
<td>6 at 4-wk intervals</td>
<td>Fixed-weight–based activity, 55 kBq/kg</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>177Lu-DOTATATE</td>
<td>Neuroendocrine tumor with somatostatin receptor expression</td>
<td>4 at 8-wk intervals</td>
<td>Fixed activity, 7.4 GBq</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>177Lu-PSMA-617</td>
<td>Prostate cancer, metastatic disease</td>
<td>4–6 cycles at 6-wk intervals</td>
<td>Fixed activity, 7.4 GBq</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>131I-MIBG/HSA-, 131I-Iobenguane*</td>
<td>Pheochromocytoma or paraganglioma</td>
<td>2 at 12-wk intervals</td>
<td>Fixed activity, for weight &gt;62.5 kg, 17.5 GBq; for weight &lt;62.5 kg, 296 MBq/kg</td>
<td>Yes, WB planar days 0, 1–2, 2–5</td>
<td>*12 Gy to red marrow, 16.5 Gy to lung, 18 Gy to kidney, and 31 Gy to liver</td>
</tr>
<tr>
<td>90Y-ibritumomab tiuxetan</td>
<td>Follicular or low-grade NHL</td>
<td>1</td>
<td>14.8 MBq/kg if platelets &gt;150,000; 11.1 MBq/kg if platelets &gt;100,000 and &lt;150,000</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>131I-tositumomab†</td>
<td>Relapsed or refractory NHL</td>
<td>1</td>
<td>Based on dosimetry: 75 cGy to WB if platelets &gt;150,000; 65 cGy to WB if platelets &gt;100,000 and &lt;150,000</td>
<td>Yes, WB planar days 0, 2–4, 6–7</td>
<td>75 or 65 cGy to WB</td>
</tr>
<tr>
<td>90Y-TheraSphere</td>
<td>Unresectable hepatocellular carcinoma</td>
<td>1 (whole-liver treatment often split over separate treatments)</td>
<td>80–150 Gy to liver</td>
<td>Yes, tomographic perfused liver volume and planar lung shunt</td>
<td>80–150 Gy to liver, &lt;30 Gy to lung per treatment and &lt;50 Gy cumulative</td>
</tr>
<tr>
<td>90Y-SIR-Spheres</td>
<td>Unresectable liver metastases from colorectal cancer</td>
<td>1 (whole-liver treatment often split over separate treatments)</td>
<td>Calculation based on body surface area, liver volume, involved tumor volume, and lung shunt</td>
<td>Yes, tomographic perfused liver volume and planar lung shunt</td>
<td>&lt;30 Gy to lung</td>
</tr>
</tbody>
</table>

*The limits in the last column pertain to 131I-Iobenguane only.

†No longer commercially available.

NA = not applicable; HSA = high specific activity; NHL = non-Hodgkin Lymphoma.
Radioactive Iodine (RAI) Therapy for Differentiated Thyroid Cancer

One of the earliest reports of use of RAI dosimetry was described in 1962 by Benua et al. (6). Dosimetry has been found to be useful for planning RAI treatment of differentiated thyroid cancer, especially for treatment of metastatic disease using high activity. Dosimetry estimates are aimed primarily at limiting absorbed dose to critical organs such as bone (bone marrow) (2 Gy) and lung (2.96 GBq [80-mCi whole-body (WB) retention at 48 h]) (6,7).

Dosing schemes for the treatment of thyroid cancer have been based on an empiric fixed activity, upper-limit-of-blood and body/lung dosimetry, and quantitative tumor or lesion dosimetry. Clinicians commonly use a fixed activity based on American Thyroid Association guidelines, which recommend a risk-adapted approach to choosing the empiric activity of RAI while acknowledging that dosimetry methods may be best reserved for patients with distant metastases, especially those involving bones (which generally require larger activity), to avoid marrow and pulmonary toxicity (7). Generally, the flat activity ranges from 1.1 to 5.55 GBq (30–150 mCi) in postsurgical ablation settings and up to 11.1 GBq (300 mCi) for treatments of metastatic disease (8). American Thyroid Association guidelines (7) recommend 1.1 GBq (30 mCi) of activity for low-risk thyroid remnant ablation (low-volume central neck nodal metastasis with no other known gross residual disease or other adverse features), whereas a higher activity may be administered to patients with less than total or near-total thyroidectomy and in whom a larger remnant is suspected or for whom adjuvant therapy is intended. When RAI is intended for initial adjuvant therapy aimed at suspected microscopic residual disease, an activity of 3.7–5.5 GBq (100–150 mCi) is generally used. For administration of RAI in metastatic settings, a higher fixed activity of up to 7.4–9.25 GBq (200–250 mCi) may be used. American Thyroid Association guidelines have no firm recommendation for blood- or body-based dosimetry for RAI treatment for locoregional or distant metastatic disease.

Recent guidelines recommend greater individualization and deintensification, though there is general clinical ambivalence regarding RAI therapy, recognizing that a large number of patients have an excellent overall prognosis (7). Prospective blinded and randomized studies on deescalation of activity are limited, especially in low- or intermediate-risk patients; some include a small number of patients for remnant ablation (9,10). RAI dosimetry approaches vary but primarily assess the maximum tolerated absorbed radiation dose (MTD) to the bone marrow or the lesion or lung absorbed-dose limit; lesion-absorbed dose is rarely used clinically for establishing administered activity. (11–13). Bone marrow MTD is based on a surrogate threshold blood-absorbed dose of 2 Gy (6,14–19) and is generally performed before treatment, allowing for appropriate adjustment of activity. In a retrospective study (8), whereas an activity within 5.18 GBq (140 mCi) rarely exposed blood to more than 2 Gy, activity of 9.25 GBq (250 mCi) frequently exceeded the bone marrow threshold (in 22%–50% of patients), with the investigators noting that elder subjects were at higher risk for exceeding limits. Dosimetry is also preferred for those presenting with recurrent disease after receiving fixed-activity treatments, for maximizing treatment in high-risk patients to improve efficacy (11), and for those receiving RAI therapy using recombinant thyroid-stimulating hormone because of a more rapid clearance. Target-based dosimetry methods have generally used an absorbed dose of 300 Gy to the thyroid remnant and 80 Gy to metastatic lesions (20); however, technical limitations in the assessment of remnant or lesion size may lead to inaccuracies in the calculated absorbed dose (21).

There are very limited data on the activity and the absorbed radiation dose–response relationship and outcomes in metastatic disease, as wide variation in lesion-absorbed dose has been noted (12,22,23). Dosimetry generally comprises 131I-NaI scans at multiple time points combined with blood sampling. The poor imaging characteristics of 131I-NaI, the quantification heterogeneity of interlesional and intralesional uptake, and the inaccuracies in the measurement of lesion mass make establishing dose–response relationships all the more challenging.

Some of these challenges may be overcome using 124I-NaI PET imaging for lesion dosimetry and planning of treatments, especially in those who require a high-activity treatment (11,24). 124I-NaI PET/CT dosimetry imaging may simplify blood-absorbed dose assessment by requiring fewer blood samples (25) and improving remnant and individual-lesion dosimetry (26–28).

Although 124I-NaI PET–based dosimetry typically requires multiple sessions of serial PET/CT imaging, recent data suggest that a simplified approach, with imaging only at 24 and 96 h, may suffice for dosimetry (29). Additional data are emerging, but 124I is not yet FDA-approved and is limited in availability for wide use.

Bone-Targeted Therapy

153Sm-lexidronam, used for pain palliation, is administered in a fixed activity based on body weight—37 MBq/kg—as determined in phase I and II studies. RPT escalation studies used an empiric, non-dosimetry-based activity with clinical endpoints, though dosimetry was assessed for marrow and critical organs (30). A phase II study showed efficacy and pain control in 74% of patients. Similarly, 89SrCl2 is administered at a fixed activity of 148 MBq (4 mCi). Although 89Sr-chloride and 153Sm-ethylendiamine tetra (methylene phosphonic acid) yielded significant and durable pain relief, there are scant data on impact on patient survival.

α-emitting 223RaCl2 marked a paradigm shift in the use of RPT, expanding it from palliation alone to the treatment of bone metastases. The ALSYMPCA trial noted pain relief, improved overall survival, and a delay in symptomatic skeletal events in patients with metastatic castration-resistant prostate cancer treated with 223RaCl2 (31, 32). 223RaCl2 (Xofigo; Bayer) is administered in 6 cycles of 55 kBq/kg each, does not require dosimetry assessment, and is based on phase I and II studies that used fixed-weight-based activity escalation with clinical endpoints to determine maximum tolerated activity. The phase I trial gave single administrations of up to 250 kBq/kg, which was later escalated to multiple infusions of 55 kBq/kg every 4 wk (33). A phase II trial used 6 infusions of 55 kBq/kg or 88 kBq/kg and an extended regimen of 12 infusions of 55 kBq/kg, with no improvement in outcomes at higher activity, though higher rates of complications were noted (34). Recent phase I/II study data on retreatment used an additional 6 infusions of 55 kBq/kg (35) without any dosimetry estimates and reported good tolerance and low toxicity, allowing for additional treatment beyond the standard regimen at the same fixed-activity regimen.

That the hematologic toxicities associated with the current standard regimen are relatively minor suggests that some patients may be eligible for more infusions or higher administered activities. Prior treatments, extent of bone marrow involvement, and combination treatments may lead to higher toxicities, limiting benefit (36). It could be argued that dosimetry would help optimize treatments in such situations. However, quantitative imaging to inform
activity selection is difficult because of lack of a validated companion diagnostic for dosimetry and scant, polychromatic photon emissions from $^{222}$Ra that require prolonged image acquisition times (37). Bone tracers such as $^{99m}$Tc-based bone scans or Na$^{18}$F PET may be used for lesion-based dosimetry (37,38) but are not ideal theranostic pairs, given differences in biodistribution and lack of bowel excretion, similar to $^{222}$RaCl$_2$ (39).

Peptide Receptor Radionuclide Therapy (PRRT) with $^{177}$Lu-DOTATATE

PRRT with $^{177}$Lu-DOTATATE was approved by the FDA in 2018 after the multicenter, randomized 2-arm NETTER1 study. $^{177}$Lu-DOTATATE is administered in a fixed activity of 7.4 GBq/cycle over 4 cycles, each approximately 8 wk apart (40,41), without requiring any dosimetry for establishing treatment activity or number of cycles, similar to the schema in the NETTER1 study. Currently, most centers use fixed-activity–based dosing schedules without performing any dosimetry for kidney-, marrow-, or lesion-absorbed dose; modifications of the activity or the number of administrations is based primarily on clinical risk factors or toxicity (mainly hematologic). Activity is modified primarily by lowering the fixed activity rather than by dosimetry. Initial studies assessed a total activity threshold averaging 26.4 GBq for $^{177}$Lu-octreotate treatments. These studies were based on planar dosimetry data from only 5 patients and on a kidney-absorbed dose limit of 23 Gy adapted from radiation oncology–derived limits and not established from prospective dosimetry of actual kidney-absorbed dose (42). Overall, wide variation in the estimated kidney-absorbed dose across studies performed using varying methodologies (43) suggests undertreatment of most patients (relative to the allowable maximum kidney-absorbed dose) and possible overtreatment of a subset of patients with fixed activity. $^{68}$Ga- or $^{64}$Cu-DOTATATE imaging establishes somatostatin receptor–expressing lesions and is used primarily for patient selection. Although dosimetry is more feasible with $^{64}$Cu-DOTATATE imaging, given the longer half-life of $^{64}$Cu, its accuracy is not yet established and use for dosimetry with clinical PRRT remains to be validated. Evaluation of kidney-absorbed dose can be based on the posttreatment $^{177}$Lu-DOTATATE imaging and is recommended in those with preexisting renal conditions or at higher risk for renal toxicity (44,45) but is not routinely assessed in all patients. Repeat treatments are ideally most optimally planned based on patient response, tolerance, and presence of residual disease. They noted that only 25% of patients had to be restricted to treatment with exactly 4 cycles, per the commonly accepted treatment protocol, whereas almost half the patients received more than 4 (range, 5–10) cycles of treatment. In 61% of patients, the predefined absorbed dose threshold of 23 Gy was reached. Although the 2-Gy bone marrow–absorbed dose was not reached in any patient, 22% of therapies were stopped because of hematologic toxicity before reaching 23 Gy to the kidneys. Transient grade 3 or 4 hematologic toxicity of any kind was seen in 15% of patients, and therapy generally was continued after the nadir had passed. Interestingly, the difference between dosimetry-based and fixed activity can be seen in the fact that median progression-free survival (PFS) and overall survival were longer in patients in whom the absorbed dose to the kidneys reached 23 Gy than in those who did not reach this threshold; this discrepancy remained statistically significant even after excluding those who stopped treatment because of progression during treatment. This finding highlights differences from the standard approach of fixed dosing.

Overall, the wide variation in estimated kidney-absorbed dose across studies performed using varying methodologies (43) suggests undertreatment of most patients (relative to the allowable maximum kidney-absorbed dose) and possible overtreatment of a subset of patients with fixed activity. Moreover, the kidney-absorbed dose thresholds are not established through formal activity escalation studies but are radiation oncology–derived thresholds.

PSMA-Targeted Therapy for Prostate Cancer

PSMA-targeted therapy for prostate cancer is not currently FDA-approved at the time of preparation of this article but has shown evidence of efficacy in 2 prospective randomized trials of patients with metastatic prostate cancer (46,47). The first phase III registration study of a $^{177}$Lu-PSMA–directed therapy (VISION trial) showed improvements in radiologic PFS and overall survival compared with the standard of care (46), and a randomized phase II trial (TheraP trial) showed improvement in PFS and prostate-specific antigen response compared with second-line chemotherapy (47). In the VISION trial, $^{177}$Lu-PSMA-617 was given at the fixed activity of 7.4 GBq for each of the 4 cycles at 6-wk intervals; additional cycles based on patient response, tolerance, and presence of residual disease were also administrated as a fixed activity with no interim dosimetry. In published studies, including the VISION trial, pre-treatment assessment was limited to $^{68}$Ga-PSMA PET imaging, primarily used for establishing targetable PSMA-expressing lesions; dosimetry was not included in either pre- or posttreatment imaging when deciding to continue, discontinue, or repeat treatment (48–50). Similarly, a phase II study of randomized patients used a fixed activity of 6.0 GBq ($n = 14$) or 7.4 GBq ($n = 15$).

Given the possibility of salivary gland and marrow toxicity, dosimetry has been focused mostly on absorbed dose to salivary glands and marrow, whereas few data are on absorbed dose to tumors; variations in methodology are notable across studies.
Using posttreatment dosimetry, for 2 treatments averaging 6–7.4 GBq/cycle, salivary gland– and kidney-absorbed dose was found to be 1.2–2.8 Gy/GBq and 0.5–0.7 Gy/GBq, respectively. Reported lesion-absorbed dose estimates are extremely variable, ranging from 1.2 to 47.5 Gy/GBq (52–54).

The relationship between reported dose (activity or absorbed dose) and response is variable; in 40 patients treated with activity ranging from 4 to 9 GBq, no correlation was noted between activity and toxicity or response, though a trend toward an increasing response was noted at the highest level of treatment activity (55). The clinical parameters for assessing response vary; objective response by imaging and biochemical (prostate-specific antigen) response are commonly used instead of survival data. A recent report on voxel-based dosimetry also showed large variations in absorbed dose and no significant dose-effect relationship (56).

However, several of these studies were underpowered and did not provide adequate counter evidence to studies in which such relationships were demonstrated (57). A significant correlation has been noted between WB tumor-absorbed dose and prostate-specific antigen response such that patients receiving less than 10 Gy were less likely to achieve at least a 50% decrease in prostate-specific antigen (57) than those who received a higher dose. The inconsistent patient response across studies may be explained by the large variations in lesion-absorbed dose observed (58), small sample size, differences in selection of patients, and variable dosimetry methods.

The data on outcomes from the VISION trial are encouraging, showing a significantly prolonged PFS (median, 8.7 vs. 3.4 mo.) and overall survival (median, 15.3 vs. 11.3 mo.) for those treated with 177Lu-PSMA-617 plus standard care, versus the standard of care (46). However, outcome data in prior studies have been variable. In a phase II study, 43 patients with metastatic castration-resistant prostate cancer were randomized to receive either 6.0 GBq (n = 14) or 7.4 GBq (n = 29) of 177Lu-PSMA; the median overall survival was 14 mo; however, no significant differences were noted between the 2 activity arms (51).

Single-time-point posttreatment imaging with SPECT/CT-based dosimetry was described recently (59) but is not yet widely applied. Other techniques, such as based on modeling using pharmacokinetic data, are being explored (59). Data from smaller cohorts for activity computation from a single posttreatment scan that can be applied to a much broader patient population showed the best estimate of tumor activity at 72 h after injection of the treatment (59).

Several groups outside the United States have published data on the use of 225Ac-PSMA, primarily using a fixed-activity schema. Again, the amount of activity and number of cycles (69,61) vary widely, and none of the groups used individual dosimetry to plan overall activity or number of treatments, relying mainly on clinical parameters for tumor burden and toxicity (62,63). For 225Ac-PSMA agents, a higher toxicity profile has limited patient treatments, highlighting the need for dosimetry. However, dosimetry for 225Ac-PSMA treatments is more complex, and although limited, published studies have generally used scan and clearance data to project from 177Lu-PSMA-617 studies (64). However, dosimetry data are limited to a few normal organs, and no tumor-absorbed dose data are available.

131I-Metiodobenzylguanidine (MIBG) Therapy

131I-MIBG therapy is well established for the treatment of metastatic neuroblastoma, as well as metastatic paragangliomas and pheochromocytoma. Although 131I-MIBG has been extensively used over the past 2 decades, distinct variations in approach are evident. For treatment of paragangliomas and pheochromocytomas with conventional non-high specific activity 131I-Iobenguane (high specific activity) administrarion of an empiric activity or an activity fixed by body weight has been the predominant approach (65). However, the FDA-approved (July 2018) agent for paragangliomas and pheochromocytoma, high-specific-activity 131I-MIBG, or 131I-Iobenguane (Azeda; Progenics Pharmaceuticals), incorporates upfront dosimetry estimates in treatment planning for unresectable, locally advanced, or metastatic pheochromocytoma or paragangliomas (66); RPT activity for 131I-Iobenguane is determined after dosimetry using 3 WB scans over 3–5 d. Although a standard treatment regimen consists of 2 treatments given at least 90 d apart, each with an activity of 18.5 GBq (500 mCi), or 296 MBq/kg (8 mCi/kg) for a body weight of less than 62.5 kg, the activity is reduced on the basis of a dosimetry assessment for absorbed dose to normal organs, including lung, kidney, liver, and marrow (66). An activity–response relationship was noted, with more responses after 2 treatment cycles than after 1 cycle in phase I or II studies (67). Toxicity was mainly hematologic, and 25% of heavily pretreated patients required supportive care, with recovery noted in most. Dosimetry is key for such subgroups of patients for whom individual optimization and assessment of appropriate, probably lower, bone marrow–absorbed dose thresholds would need to be done.

For neuroblastoma, a predominantly pediatric disease, 131I-MIBG activity is weight-based, including multiple infusions of either low-activity (37–148 MBq/kg, or 1–4 mCi/kg) or high-activity (296–666 MBq/kg, or 8–18 mCi/kg) 131I-MIBG therapy (68). Dose-escalation studies used an activity range of 296–666 MBq/kg (8–18 mCi/kg), as generally used in clinical RPT (69). Myelosuppression is the most common adverse event that limits maximum activity; high-activity treatments often require supportive treatment such as platelet or stem cell transfusions, highlighting the critical role of marrow dosimetry (4). Those who respond to high-activity 131I-MIBG treatments may benefit from additional treatment based on red marrow activity and guided by a dosimetry index (70). Pretreatment 131I-MIBG imaging–derived absorbed dose estimates appear to be reproducible but can underestimate therapeutic activity and exhibit large interpatient variations in WB- and tumor-absorbed dose (71–73). Repeat treatments raise additional concerns about the indirectness and potential inaccuracy of methods for measuring absorbed dose to normal organs (besides marrow, WB, and red marrow). Large intrapatient variations in WB-absorbed dose were shown via WB counting without use of imaging for absorbed dose estimates and a maximum 4-Gy total absorbed dose for 2 treatments (74). Technical differences distinguish 123I-MIBG and 131I-MIBG when used for dosimetry, given the shorter half-life of the 123I isotope. However, integrating dosimetry into routine 123I-MIBG diagnostic assessments remains attractive because of its feasibility and lower absorbed dose. The ability of 123I-MIBG to predict WB-absorbed dose (75) and serial 123I-MIBG WB scans for normal-organ–absorbed dose for planning tandem high-activity treatments in neuroblastoma has been shown and routinely used in some institutions (76). 124I-MIBG (not FDA-approved) provides the advantages of multiple-time-point imaging, PET quantitation for dosimetry calculations, and superior lesion detection and scoring. However, limited availability and cost have restricted its utilization (77,78).

Radioimmunotherapy

Two radioimmunotherapy agents—90Y-ibritumomab tiuxetan and 131I-tositumomab—have been approved by the FDA for treating...
non-Hodgkin lymphoma. Pretreatment imaging assessment with 111In-ibritumomab tiuxetan was previously required before treatment with 90Y-ibritumomab tiuxetan. However, that requirement was meant mainly to ensure optimal biodistribution before therapy and was subsequently eliminated as a prerequisite to treatment. The FDA-approved treatment regimen for patients who had less than 25% bone marrow involvement includes a single treatment with activity based on body weight (14.8 or 11.1 MBq/kg [0.4 mCi or 0.3 mCi/kg] for patients with normal platelet counts or between 110,000 and 150,000, respectively; maximum activity limited to 1.18 GBq [32 mCi]).

Initial 90Y-ibritumomab tiuxetan studies did not demonstrate a definitive correlation between hematologic toxicity and planar imaging–derived estimates of absorbed dose to the red marrow and WB (79). A report from 4 clinical trials that included 179 patients with relapsed or refractory non-Hodgkin lymphoma also noted a lack of correlation between hematologic toxicity and absorbed dose to the red marrow or WB or between hematologic toxicity and effective half-life in blood (80). Similarly, dosimetry failed to predict hematologic toxicity in 50 patients with advanced follicular non-Hodgkin lymphoma receiving 90Y-ibritumomab tiuxetan in the front-line consolidation setting (81). Organ dosimetry estimates using WB dosimetry and SPECT/CT have shown over a 3-fold interpersonal variability in administered activity/MBq and allowed for activity escalation to the myeloablative range (82), highlighting challenges to integrating routine dosimetry into treatment.

In contrast, activity for 131I-tositumomab (Bexxar; GlaxoSmithKline) was based on individual pretreatment dosimetry with maximum WB-absorbed dose limiting the total activity to patients, performed both with 131I-tositumomab as the theranostic pair and with 131I-tositumomab as a single treatment with no repeat cycles or repeat treatment recommendations, given the antibody’s murine origin. The maximum activity for individuals was determined from a prospective dosimetry-driven dose-escalation approach that showed a response relationship for WB-absorbed dose and hematologic toxicity. Because of the high variability (up to 4-fold) of 131I excretion and clearance, the 131I-tositumomab regimen used a simplified method to determine activity based on patient-specific kinetics to deliver a 0.65- or 0.75-Gy WB-absorbed dose.

A correlation between body-surface-area–corrected bone marrow–absorbed dose and hematologic toxicity using 131I-rituximab has been noted. Using dosimetry based on WB SPECT/CT for marrow, Boucek et al. (83) noted a strong correlation between WB effective half-life and marrow effective half-life of antibody, as well as finding that the bone marrow activity concentration was proportional to activity per unit weight, height, or body surface area; however, Sgouros et al., using 3-dimensional SPECT-based dosimetry, found no correlation between WB tumor burden and hematologic toxicity (84). Less severe declines in platelet counts with 131I-tositumomab than with 90Y-ibritumomab tiuxetan (85) suggest that dosimetry could be beneficial in predicting toxicity profiles. Other studies of 131I-tositumomab dosimetry observed trends toward increased tumor regression with higher tumor-absorbed dose (86–89). Tumor dose uniformity and tumor size are important factors (84,88,90), and correlations were observed between higher tumor-absorbed dose and longer PFS (86,89). Additionally, heavily pretreated patients may have higher marrow toxicity, and dosimetry estimates based on WB may not be predictive of toxicity.

The activity of 131I-tositumomab, based on a 75-cGy WB-absorbed dose, showed less toxicity in patients who had not had prior therapies than in those who had previously received a mean of 4 different chemotherapies. A higher 131I-tositumomab activity was feasible in patients who had not had prior stem cell transplants, unlike those who had received a transplant (91).

In the myeloablative setting, the radioimmunotherapy activity depends on the non–bone-marrow critical-organ threshold. Studies in this setting report on treatment efficacy (92–94), but direct comparisons of dosimetry and nondosimetry approaches in this setting were not feasible.

90Y-Microsphere Therapies

90Y-microsphere therapies are directed into a single organ or compartment, limiting RPT uptake to that organ or compartment. Since activity is localized to the organ of delivery and systemic absorption is low, dosimetry is meant primarily to maximize the absorbed dose to the lesions and limit the dose absorbed by the remainder of the healthy organ where the lesion is located (such as liver). Currently, 2 FDA-approved RPT 90Y-microspheres (SIR-Spheres [SIRTex] or TheraSphere [Boston Scientific]) are clinically used for selective internal radiation therapy of liver metastasis. Calculation of the activity is based on liver and lesion volume derived from CT measurements. Pretreatment imaging with 99mTc-macroaggregated albumin is used to assess biodistribution, exclude extrahepatic perfusion, and measure pulmonary activity. Estimation of the radiation dose to the lung can affect activity. The calculations are easy to perform using designated methodology and worksheets or software (95–97). Although several groups have shown the feasibility of dosimetry using planar or SPECT imaging, such approaches remain limited to the groups’ institutions (98). 99mTc-macroaggregated albumin is not an ideal surrogate for 90Y-microspheres but is a reasonable predictor of normal liver-absorbed dose; data from small studies suggest a good correlation with posttreatment dosimetry for tumor and normal liver using SPECT/CT (98,99) or PET/CT (100).

Data on the use of dosimetry in improving outcomes are emerging (101); a recent prospective multicenter study called DOSISPHERE randomly assigned locally advanced hepatocellular carcinoma patients (1:1) to receive either standard dosimetry (120 ± 20 Gy) targeted to the perfused lobe or personalized dosimetry based on at least 205 Gy targeted to the index lesion. Personalized dosimetry treatments improved objective response rates (71%) over standardized dosimetry treatments (36%) (102). Although small in size, the study supports the use of personalized dosimetry. Large phase II or III systematic studies using dosimetry to establish dosing regimens, efficacy, and outcomes are limited.

UNMET NEEDS

Activity and Radiation Dose–Response and Outcome-Based Data

Although studies have shown the value of dosimetry in RPT, supporting data are heterogeneous and there are limited outcome-based data demonstrating the superiority of dosimetry-based over standardized or non–dosimetry-based approaches across all RPTs. For thyroid cancer treatment, the optimal activity level and the use of dosimetry remain highly controversial (103). Given the high variation in activity and dosimetry methods for determining activity and tumor-absorbed dose across studies, comparison of outcomes based on published data is difficult. Small studies show efficacy to be related to mean lesion-absorbed dose, though again with large variations in disease stage and extent, differentiation, and lesion size (104). Use of dosimetry instead of empiric activity...
may allow for lower hematologic toxicity. The current limit of 2 Gy (200 rads) to the blood may be exceeded in about 1%–22% of patients using empiric treatment with 3.7 – 11.1 GBq (100–300 mCi) of activity as compared with dosimetry-based activity (105); this difference is higher for patients 70 y or older (22%–38%) than in those younger than 70 y (8%–15%) or when 9.25 GBq (250 mCi) of empiric activity is used (50%) (8). Additionally, small studies observed a higher likelihood of response using dosimetry-based activity in patients with locoregional disease (104) and in those who experienced recurrence after treatment with an empiric dosage (106). The activity and absorbed dose–response relationship remains unclear, with some studies supporting a correlation (20) and others showing a lack of correlation (107). Prospective randomized studies are lacking, given that survival studies require long follow-up periods because of good survival in this population.

The activity and absorbed dose–response relationship for hematotoxicity with PRRT also remains unclear. In a study of 200 patients with neuroendocrine tumors, no dose–response correlation was seen using blood-based bone marrow dosimetry (108). Attempts to limit hematologic toxicity remain challenged by the inherent difficulties of image-based bone marrow dosimetry and the absence of validation studies and prior treatments in the patients studied (109–112). (Dosimetry methodology for bone marrow estimates poses several issues, which are discussed elsewhere in this supplement to The Journal of Nuclear Medicine.) Overall, whereas more recent data have emerged on dosimetry, the specific clinical situations in which to perform dosimetry—and how—remain controversial, as does dosimetry’s impact on outcomes. A large variation in lesion AD has also been noted from 177Lu-PSMA studies and may explain variable response rates and toxicities in patients. Use of individualized dosimetry may be leveraged to improve response and decrease toxicity (58). Variations in the lesion-absorbed dose from current published data lead to questions about the need for activity based on lesion-absorbed dose. On the other hand, given the multitude of published studies that use a fixed empiric activity, without dosimetry, and nevertheless showed clinical utility and better responses with increasing cycles of treatment, empiric dosing is the predominant method in providing clinically relevant RPT. However, whether dosimetry-based activity in these patients would have provided significantly superior responses can be known only from randomized trials, which are lacking.

Assessing Optimal Administration Activity: Lesion Versus Normal-Tissue Limits

Individualized dosimetry studies for PRRT have focused on renal and marrow dosimetry (113–115). Dosimetry of 200 patients with WB and blood showed that for a renal threshold of 23 Gy and a blood threshold of 2 Gy, 50% of patients could be treated with more than 4 cycles of 7.4 GBq of 177Lu-octreotate and 20% of patients could be treated with fewer than 4 cycles (113). Renal toxicity can be mitigated with amino acids, the overall incidence of grade 3–4 renal toxicities appears low, and long-term hematotoxicity appeared in about 11% of patients (41,116). However, current clinical activity is limited by the 23- to 28-Gy absorbed dose to the kidneys, based on prior retrospective or prospective dosimetry studies (45,117,118). The 23- to 28-Gy threshold is highly debated, as it is extrapolated from the results of external-beam radiotherapy (EBRT) (119) and may not be ideal for RPT. Some have noted that the renal threshold may be as high as 40 Gy for those without preexisting conditions (120). Additionally, such renal-based thresholding prevents maximizing the dose absorbed by the tumor, and current fixed-activity schemata frequently fall short of in vivo saturation of somatostatin receptors in tumor lesions (121).

Thresholds for all RPTs and for all normal organs are based on the EBRT data (119), which is in turn based on organ volume and assumption of uniform distribution of radiation in organs. Large ranges are applicable to EBRT on the basis of organ exposure: for example, 23–50 Gy can be applied for the whole kidney, or one third of the kidney volume exposed for a 5/5 tolerance dose (the radiation dose that would result in 5% risk of severe complications within 5 y after irradiation) (119). The systemic distribution for RPT leads to the assumption that the entire organ is exposed, likely producing conservative estimates for total activity. In addition, the relative biologic effectiveness of RPT differs significantly from that of EBRT because of a more prolonged but slower radiation dose rate that also depends on the isotope and linear energy transfer. Establishing appropriate RPT thresholds is especially relevant in treatments given the likelihood of delivering a lower absorbed dose with fixed activity/cycles to lesions. Treating to the maximum limits is important, and those limits may differ according to radiopharmaceutical kinetics and the radionuclide used. Fixed dosing may not reach maximum organ limits or maximize the lesion-absorbed dose in many patients.

It is also important to delineate what parameters should be regarded as MTD. Generally, a 2-Gy limit to the marrow or blood is used to limit hematologic toxicity, a common occurrence with RPT. However even with this threshold, hematologic toxicity remains extremely unpredictable across different RPTs. Moreover, universal application of this threshold has limitations in patients for whom narrow disease is the predominant presentation, such as those with neuroblastoma or hematologic toxicities, and different parameters for MTD are required. The impact of prior chemotherapy or radiation therapy creates unpredictable adverse-event profiles that require a better understanding of how combination therapies, including radiosensitizing chemotherapy, may contribute to short-and long-term hematologic complications. Such knowledge can be gained via well-designed trials and further prospective or randomized investigations (122,123).

As such, endpoint parameters for dosimetry should include assessments of the absorbed dose to tumor and normal organs in order to optimize the tumor-to-background ratio for RPT delivery. Although fixed-activity regimens are easy to administer, it is likely that a subgroup of the population will be under- or overtreated. These subpopulations—for instance, patients with a higher disease burden, preexisting conditions affecting key organs, heavily pre-treated, or receiving combination therapies—should be identified and their treatment based on individual dosimetry. Dosimetry imaging should be integrated early in the process of establishing MTD, and activity should be recommended upfront so that it can be further tailored on the basis of clinical response, side effects, and lab findings.

Considerations for Combination Therapies

Therapies combining RPT with radiation or chemotherapy are gaining interest and, although aimed at improving outcomes, risk increased toxicities. Although dosimetry may not entirely predict the biologic variances and toxicities of a coadministered biologic agent, dosimetry may be useful in assessing the biodistribution of combination treatments and normal-organ dosimetry. Incorporation
of dosimetry has, however, been limited thus far. The combination of $^{153}$Sm-lexidronam and $^{223}$RaCl$_2$ with docetaxel (124) guided treatments using a flat activity escalation schema based on the clinical MTD for single-agent use of $^{153}$Sm,$^{223}$RaCl$_2$ and docetaxel and on the clinical dose-limiting toxicity, without dosimetry (125). Incorporation of dosimetry in clinical trials with $^{177}$Lu-DOTATATE or $^{177}$Lu PSMA-617 (https://www.clinicaltrials.gov/) has been limited. Similarly, trials of $^{131}$I-MIBG combined with chemotherapy or sensitizing agents used a fixed weight-based activity; varying toxicity profiles and response rates have been seen (126).

Limitations to Current Dosimetry Methodologies

In general, dosimetry methods are based on assessing average absorbed dose in organs (127) using MIRD age-dependent hermaphrodite phantoms (Oak Ridge National Laboratory), Monte Carlo simulations for organ-absorbed cross-radiation doses, or simplified calculations of self-absorbed radiation doses to organs. Safe limits or tolerance limits for normal organs are based on data derived from external-beam therapies, complicating analysis insofar as the biologic effects of radiation for EBRT differ from those for RPT, affecting apoptosis, structural and physiologic changes in the cell, and DNA damage.

Intrapersonal variation adds complexity as well. RPT is associated with individual biologic variation in distribution and tissue absorption related to WB, to blood and organ clearance, and to microdistribution, complicating assessment. Biologic and pharmacokinetic differences, as well as the effect of the RPT ligand/molecule or biologic agent, contribute further to individual variation due to difference in penetration causing heterogeneous distribution, affecting uniformity of absorbed-dose rate within normal and tumor tissue. Additional complications include the complex geometric configuration of the target tissue, self-dosing, and cross-tissue dose assessment.

Dosimetry Challenges with $\alpha$-Emitters

Dosimetry for $\alpha$-emitters is limited by insufficient $\gamma$-emissions and the likelihood of daughter radionuclide on-target migration decay versus off-target migration decay. Imaging is possible if the decay consists of $\gamma$-emissions, such as in $^{223}$Ra or $^{227}$Th decay (128). This approach is limited in practice, however, as most of the $\gamma$-emissions are in low quantities, requiring longer imaging times for optimal assessment of targeting and uptake in organs.

Using preclinical data for dosimetry is not ideal. Such data are often inaccurate when translated into human beings, probably because of different kinetics and affinity profiles, greater in vivo heterogeneity, and nonuniformity of RPT within lesions based on size, location, and tumor microenvironment. For instance, quantification of $^{223}$Ra-chloride using phantoms has been shown to be feasible, but significant challenges remain, including validation and reproducibility (129).

Microdosimetry and modeling methods enhance assessments of local effects (130,131) but are difficult to perform and require expertise. A more suitable option would be to use an isotope with a short-lived daughter isotope to restrict all subsequent radiation to the target tumor and clear rapidly, avoiding off-target toxic effects—unless the daughter is excreted rapidly or is relatively nontoxic by virtue of its biodistribution. The general assumption uses a relative biologic effectiveness of 5 and instant decay of unstable daughter nuclides (69). Given the complexity of dosimetry, several phase I or II clinical studies have used activity based on body weight, such as the use of $^{213}$Bi-HuM195 and $^{225}$Ac-lintuzumab in leukemia patients (132,133). Ongoing studies (NCT02998047, NCT0257596, NCT03441048, and NCT0374643) are treating with a weight-based activity schema (134).

Although some phase I studies such as $^{227}$Th-BAY 2315497 in prostate cancer (NCT03724747) and $^{225}$Ac-FPI-1434 (NCT0374643) include either posttreatment dosimetry assessment or pretreatment $^{111}$In-dosimetry, the activity dose escalation is fixed, based on body weight.

Technical Aspects of Imaging

Use of planar and SPECT imaging versus PET imaging poses technical challenges for dosimetry. SPECT imaging is superior to planar imaging, but attenuation and scatter effects require complex corrections (135). SPECT imaging also includes key technical factors that are important for accurate dosimetry but are not universally available, such as dead times, conversion factors, and calibration of the sources and cameras. For $^{177}$Lu-SPECT quantitation, for example, dead times may impact dose estimates by up to about 22%, requiring corrections (136,137).

Multiple-time-point SPECT imaging is ideal but time-intensive. The use of pre- versus posttherapy assessment and the ideal single time point for WB and SPECT imaging must be examined in larger multicenter studies. As data are emerging on the use of single-time-point imaging (138–140), validation of such methods across various RPTs is critical. Although PET enables easier and more accurate dosimetry than does SPECT imaging, some RPTs do not offer companion PET imaging suitable for dosimetry. An example is $^{68}$Ga-DOTATATE/PSMA, for which a short half-life limits multiple-time-point imaging.

Reconstruction parameters and dosimetry calculation methods using commercially available software also vary widely across centers. Although software packages have grown more available through vendors in recent years, the methodology used by each vendor is different; details of the exact methodologies and comparative assessments are unavailable as well. Additionally, specific research groups or centers may perform detailed dosimetry according to internally developed methods. Efforts at harmonization are ongoing (141,142), but no formal accreditation program for quantitative SPECT/CT exists for multicenter trials.

Resources and Expertise

Many centers lack the necessary trained personnel, such as medical physicists or certified, dosimetry-trained technicians who can calculate activity. To address this challenge, a simplified schema or worksheet to calculate activity, such as that developed for SIR-Spheres or $^{131}$I-tositumomab, should be developed for each RPT. Many steps of the dosimetry calculation could feasibly be automated, particularly as more data emerge supporting the clinical utility of tumor dose–response relationships, such as the data from the DOSISPHERE study. A template developed by the International Atomic Energy Agency allows for biodistribution assessments that can be leveraged for organ-level dosimetry, based on the assumption of a uniform distribution of activity (143).

Another challenge of dosimetry is that patients must visit centers multiple times to satisfy the requirements of multiple-time-point imaging. With technologic advances and evolving strategies, it is important to develop simplified approaches that can easily be applied to common RPTs across clinical settings. A more practical alternative may be found in single-time-point imaging. For example, whereas $^{131}$I-NaI dosimetry requires multiple-time-point imaging, quantitation with planar and SPECT imaging may
be overcome by novel techniques using $^{124}$I-Nal (23,29,144–146).
Simplified methods with single or no blood sampling and single WB $^{131}$I imaging have been described but are not widely used (147–151).

Studies have demonstrated the feasibility of using $^{124}$I-PET for dosimetry to predict absorbed dose in the treatment of thyroid cancer (152). However, parameters must be thoroughly optimized to compensate for several factors liable to impair accurate quantification, including a low positron ratio of 23%, a complex decay schema, and coincidence and annihilation photon emissions (153). Similar simplified approaches have been investigated for PRRT (115,139,154–157). Single-time-point PET imaging after treatment showed a high correlation with conventional posttreatment 3-time-point SPECT/CT imaging for $^{90}$Y-DOTATOC (139). Others have used multiple-time-point imaging at cycle 1 to derive an effective half-life for individual patients that is then integrated into subsequent cycles at 24-h imaging (154). Single-time-point imaging at 24 or 96 h after treatment for all cycles has shown feasibility and acceptable levels of uncertainty (115,156).

**Tradeoffs: Access, Cost, Use**

Use of dosimetry is limited by its complexity and practical difficulty, as well as time constraints. Ideally, individualized activity, informed by dosimetry and data, would be administered to all patients undergoing any type of RPT; in practice, however, widespread, routine application of radiation dosimetry will depend on the availability of resources such as equipment, personnel, expertise, and funding.

Administration of RPTs such as PRRT, radioimmunotherapy, and radioembolization is time-intensive for clinical and supportive staff; dosimetry adds further burdens of time and energy to an already intensive process. Centers may prefer empiric dosing methods that do not require time-intensive procedures and detailed calculations, such as the several FDA-approved RPT agents that feature fixed treatment schemata and are easily integrated into clinical practice. Centers lacking inpatient treatment facilities may steer patients toward lower-dose empiric treatments rather than the higher activity that dosimetry may determine to be necessary; without the requirements of imaging and dose calculations, administration of empiric or fixed activity without dosimetry is simple, fast, and convenient.

Lack of financial reimbursement represents an additional challenge to dosimetry-based treatment planning in RPT, as poor reimbursement rates compound the already high costs associated with multiple imaging procedures, specialized personnel, and other necessary resources. Although reimbursement for SPECT imaging for dosimetry is available, it has yet to be universally adopted and approved across all RPTs. (Reimbursement codes for medical physicist and dosimetry calculations of RPT are discussed elsewhere in this supplement to *The Journal of Nuclear Medicine*.)

Costs associated with inpatient therapies may limit their use, especially in the United States. Certain RPTs are administered in an inpatient setting because of considerations regarding activity and radiation exposure to the public and caregivers and require special hospital rooms, layouts, or structures, which add to the cost.

**Challenges with Clinical Trials**

Overall, the use of RPT in clinical practice should be informed by clinical trials. It is beyond the scope of this publication to discuss design details for trials testing RPT, but it can be said that current use of dosimetry in RPT is variable and suboptimal. The clinical trials that led to recent approvals of RPTs did not incorporate dosimetry and provided little or no absorbed dose data for tumor and normal tissues. This one-size-fits-all approach also results in under- or overtreating, delivering absorbed radiation doses and activity that differ by orders of magnitude between individuals (158) and resulting in incomplete remissions or cures. Fixed activity, as used in PRRT, falls short of the recommended 23-Gy kidney-absorbed dose, and about 73% of patients could receive more cycles of therapy (115). The lack of optimizing to presumed MTD jeopardizes efficacy. Moving forward, these issues will grow only more consequential with the growth of combined therapies and other therapeutic modalities.

For clinical trials and the evaluation of novel therapeutics, dosimetry should form an integral part of phase I assessment as pretherapeutic treatment planning to establish organ-absorbed dose, to assess MTD and maximum tolerated activity, and to recommend a phase II dose. Dosimetry of normal-organ and WB exposure must be established for safety. If dose escalation is planned, these assessments should be performed at each dose level and correlated with lab data on safety. Additional benefit would be derived from posttreatment dosimetry in phase I to assess the actual dose delivered. For phase II studies, dosimetry may be used to establish the dose–response relationship and efficacy. Limited dosimetry to assess actual activity and to plan repeat cycles and establish relevant dose–response relationships may be important.

A methodologic balance should be struck to encourage practicality and broaden the use of RPT with dosimetry. Methodologies should aim to obtain dosimetry in critical normal organs and lesions while keeping future clinical translation in perspective. For example, whereas multiple imaging examinations before and after each treatment cycle provide the most comprehensive estimates, the demanding schedules lower patient enrollment and compliance, delay treatments, and cause anxiety in patients otherwise eager to initiate treatment. For certain RPTs, multiple sessions of scanning and blood sampling that last up to several days or even weeks can lead to patient fatigue. Such issues impede timelines and increase cost in studies sponsored by the drug development industry, as well as those initiated by investigators. Detailed dosimetry data from the developmental phase may be used to develop simpler methodologies for clinical practice. It should be recognized that dosimetry for clinical trials with α-emitters can be even more challenging, and given the issues discussed here, a less onerous posttreatment approach to dosimetry is desirable.

For multicenter trials, the establishment of standardized procedures across multiple centers represents a further challenge. Intense effort is required to ensure a shared, uniform methodology and the cross-calibration of systems at all centers. In such situations, it is vital that appropriate phantoms and traceable calibration be made available, ensuring comparability of image processing, reconstruction, volume delineation, and volumetric assessment. Maximizing use thus requires simpler dosimetry procedures that provide reasonable assessments for clinical administration at low resource costs. Cross-collaborations between facilities that have dosimetry capabilities and those that do not may be possible. Efforts to promote such collaboration are under way (159).

Engaging with and understanding the needs of industry are important as well: industry can champion the growth of RPT by supporting the development of novel RPTs in pursuit of commercial interests. Establishing easily adaptable and balanced methodologies should be a priority for all.
CONCLUSION

Although dosimetry assessment is recognized as important for personalized RPT and as critical in certain settings, its use remains low overall and uneven across RPTs and institutions. As clinical experience with RPT has widened, the shortcomings and logistics preventing routine application of dosimetry in clinical RPT have become more apparent, whereas fixed-activity regimens' convenience and ease of integration into clinical practice have enabled their wide use. As such, identifying clinical situations in which dosimetry can complement and enhance the therapeutic effect of empiric dosing can be advantageous. Critical further steps to expand the use of dosimetry include standardization of dosimetry use in management decisions on RPT activity, automation of key processes, and well-conducted multicenter prospective trials of dosimetry-driven versus empiric therapy that provide evidence of better outcomes for dosimetry-based treatments. However, balanced optimization is essential so that dosimetry methodology is not so rigorous as to undercut the benefit that can otherwise be achieved with an empiric-activity approach.

DISCLOSURE

The opinions expressed in this publication are the author(s)' own and do not reflect the view of the National Institutes of Health, the Department of Health and Human Services, or the United States government. No other potential conflict of interest relevant to this article was reported.

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