Will SPECT/CT Cameras Soon Be Able to Display Absorbed Doses? Dosimetry from Single-Activity-Concentration Measurements

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Many nuclear medicine physicians treating patients with radiopharmaceuticals have an ambivalent relationship to dosimetry. On the one hand, they appreciate that, in addition to the visual impression of retention, they have objective information on the absorbed doses actually imparted to target tissue and healthy organs at risk. On the other hand, they usually omit dosimetry because they want to avoid additional burden on the patient, they do not have trained staff and expertise available, or they consider the effort-to-benefit ratio as insufficient. In fact, it is very challenging providing dosimetry with the highest accuracy to a majority of patients in daily clinical practice (*1*).

Theranostics is a frequently used term these days. However, only talking about it does not improve patient care. For personalized treatment, dosimetry data will have to be collected regularly from many patients (*2*). Data on the influence of absorbed doses on the response and toxicity of treatment with radiopharmaceuticals, which are actually a prerequisite for evidence-based individualized therapy, are still lacking for many applications. Such data would be useful not only for the individual patient but also, for example, for collecting data beyond the activities administered to describe the dose dependence of potentially radiation-related secondary malignancies, or for optimizing a treatment method. For a treatment modality for which the ratio of absorbed doses in tumors and critical organs turns out to be much higher in the first treatment cycle, the dosage regimen should be adjusted accordingly.

What needs to be done to perform dosimetry? The absorbed dose is defined as the energy imparted by ionizing radiation per unit tissue mass. Neglecting energy deposition by radiation originating from decays outside the volume of interest, the total energy imparted is the product of the average energy deposited per radioactive decay and the number of decays in the tissue. Although the energy release per decay is known from the physical properties of the isotope, the number of decays can be determined only by measurement. Repeated measurements over several days are usually necessary to accurately capture an individual activity kinetics, that is, the time function of the activity concentration in a tissue. The number of decays per unit tissue mass is then obtained by integrating the activity concentration function over time. The procedure is so complex that it needs to be considerably simplified for routine dosimetry in patients.

In this issue, Jackson et al. (*3*) describe a method to estimate absorbed radiation doses in accumulating tissues after treatment with ^{177}Lu-prostate-specific membrane antigen (PSMA)-617 from a single quantifying measurement of the 3-dimensional activity distribution in the patient. The publication follows similar efforts for other frequently used radiopharmaceuticals (*4–8*), aimed at making absorbed doses assessable for an increasing number of patients with reasonable accuracy and—except for a single imaging procedure, which must be performed anyway for medical indications—very little additional effort.

Can such a simplified dosimetry from only one measurement work at all?

Mathematically, the problem is underdetermined. A single measurement can fix only one of several free parameters that define real activity kinetics. Therefore, for meaningful absorbed dose estimates, certain characteristics of the kinetics under consideration must be known and, within certain limits, must be uniform among the individuals concerned. This is often the case and is a prerequisite for being able to meaningfully indicate average dose coefficients per administered activity in nuclear medicine diagnostics or per incorporated activity in radiation protection.

For individualizing dosimetry in patients, however, measurements are indispensable, as fixed absorbed dose coefficients can lead to considerable errors if major deviations from the expected biokinetic behavior occur. A simple example in which one measurement is sufficient to precisely define the biokinetics is the dosimetry in healthy individuals after accidental incorporation of ^{131}I, radioiodine. Although thyroid iodine uptake may vary depending on individual iodine supply, the effective half-life of radioiodine in the thyroid gland is known to be about 7.3 d, resulting from the fact that the biologic half-life is an order of magnitude longer than the physical half-life. This rule no longer applies in hyperthyroid patients with a short biologic half-life. The kinetics is then defined by 2 free parameters, the maximum uptake and the effective half-life in the thyroid gland.

However, after observing high correlations of readings at 4 and 8 d after activity administration with the calculated doses after complete dosimetry in patients with benign thyroid disease, Bockisch et al. (*4*) provided empiric factors applicable to deduce

thyroid-absorbed doses from a single uptake measurement after 4 or 8 d. The observation in that study can be substantiated mathematically from a property of monoexponential decay functions. Within an interval of 0.75–2.5 times the effective half-life, which is favorable for the measurement, the time integral can be deduced with less than 10% error from only a single activity quantification and its time after the administration (5). Deviations of the biokinetics from a monoexponential decay function, such as might be due to a second component resulting in a biexponential decay function, potentially increase the error of the dose estimate but do not generally prevent useful results (7,8).

Since the decay-function values are representative of the time integral only in this time window, the half-life must lie within a known limited range to allow selection of a valid measurement time. In radioiodine therapy of benign thyroid diseases, effective half-lives typically range between 3 and 7 d, setting the preferable time point of measurement to 6 or 7 d after the administration. Earlier times of measurement are to be preferred for therapies of neuroendocrine tumors with somatostatin analogs labeled with [177]Lu (7) or [90]Y (8), especially if the absorbed dose in the kidneys is to be measured. For measurements outside the valid time window, the method is not useful because the errors increase rapidly. Dose estimates can then be based only on empiric knowledge, such as about the typical effective half-life in a tissue (6).

The method described by Jackson et al. (3) for ^{177}Lu-PSMA-617 is also based on empiric data on biokinetics. Time integrals of activity concentrations and absorbed doses in tissues are estimated from single measurements by factors deduced empirically by averaging observations in patients. Such an approach leads to good results if the interindividual scattering of biokinetic parameters is small. The factors derived by Jackson et al. show a low variance, especially when the time of measurement is suitably chosen. For ^{177}Lu-PSMA-617, too, a dominant decay component is likely to be present in most tissues. The effect described above, that in a given time window the measured values are representative of the time integral, is also present in this work, even if the mathematic background as described by Hänscheid et al. (5,7) and Madsen et al. (8) is not explicitly used. Depending on the half-life of the dominant component, its integral can be determined with a small error if the measurement time is suitably selected, which leads to a small scatter of the factors. Dispersion is larger for early or late measurements.

It should be mentioned that, because of the methodology used, the data presented by Jackson et al. (3) and their applicability cannot yet be considered as confirmed. The empiric factors were derived monocentrically from a small number of patients, excluding outliers, and then tested for applicability in the same patient group. The accuracy, therefore, may be overestimated for statistical reasons. The validity of these factors and their applicability to patients of other centers undergoing PSMA-targeted radiotherapy must be independently verified, especially if ligands other than ^{177}Lu-PSMA-617 are to be used.

Nonetheless, another procedure for routine dosimetry in everyday clinical practice with a radiopharmaceutical of increasing importance is presented. Although, theoretically, dose estimates based on a single measurement can give erroneous results for a few individuals with uncommon biokinetics, application of the available methods to generally collect dosimetry data is useful for a majority of patients. Ideally, the proposed approaches should be validated and evaluated independently, and the most appropriate procedures should be recommended in the respective guidelines to ensure consistency and comparable results. Suitable and appropriately corrected SPECT/CT imaging with a traceable quantification would then enable the display of activity concentrations, and modern cameras could use these methods to directly display absorbed doses—an important step toward a general individualized theranostics.

DISCLOSURE

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