Spatial Dose Mapping for Individualizing Radioiodine Treatment

When the MIRD Committee and the International Commission on Radiological Protection (ICRP) published their biokinetic models and dose factors for a standard man (*1,2*), life became easy for the nuclear medicine physician who wants to assess internal radiation doses from the administration of diagnostic and therapeutic radiopharmaceuticals. All that needs to be done is to procure the appropriate publication with a list of organ-specific absorbed doses per unit of activity and to input numbers for

the activities administered. Those who are more conscientious or need more precise data apply quantitative scintigraphic imaging, probe measurements, or blood sampling to measure the number of decays in the whole body and in cumulating organs and use computer codes such as MIRDOSE3 (*3*) or OLINDA (*4*). In either case, the procedure results in a complete list of organ-specific absorbed doses and corresponding effective doses, providing an assessment of the individual stochastic risk. What remains to be done?

The excellence and merit of the MIRD committee and ICRP are beyond question. However, the biokinetic models currently used are often based on human tissue distribution

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data collected at a time when diagnostic instrumentation was much less sophisticated. On pages 143–149 of this issue of *The Journal of Nuclear Medicine,* Kolbert et al. (*5*) impressively show the need for more detailed investigations of the biokinetics of radiopharmaceuticals with the application of modern diagnostic techniques, including spatial dose map generation.

A particularly good example for this need is the treatment of differentiated thyroid cancer (DTC) with ^{131}I because, for the purpose of improved image quantification, ^{131}I can be replaced by the positron-emitting isotope ^{124}I. As present, strategies with respect to the dosage of ^{131}I for the treatment of DTC consist mainly of the administration of fixed standard activities (*6,7*); variability in the biokinetics and therefore the individuality of patients is not considered at all.

The ideal activity of radioiodine for the treatment of thyroid cancer is the smallest possible amount that delivers a lethal dose of radiation to the entire lesion or metastasis while minimizing side effects. The very nature of empiric fixed activities means that no attempt is made to determine either the minimum amount of radioiodine that will deliver a lethal dose or the maximum allowable reasonably safe absorbed dose.

The method of lesion dose–based activity administration first introduced by Maxon et al. (*8,9*), which aims for a remnant absorbed dose of 300 Gy or a dose absorbed by metastases or lesions of 80 Gy, and the approach of Benua et al. (*10*), a dose concept that is based on a pretherapeutic blood dose assessment and that aims for a blood absorbed dose of 2 Gy, have not been used extensively.

Benua et al. observed bone marrow depression more frequently for blood absorbed doses exceeding a limit of 2 Gy but only rarely for lower doses (*10*). If the therapeutic activity is limited to 7.4 GBq, then the blood dose is below the limit of 2 Gy for most patients, even for those who are hypothyroid and who have reduced renal function. This deduction could be made from the recently published results of several international multicenter trials investigating ^{131}I biokinetics after the use of recombinant human thyroid-stimulating hormone (*11,12*). In these studies, the blood absorbed dose was calculated with a modified method taking into account patient-specific parameters.

The work by Kolbert et al. (*5*) and previous work by Sgouros et al. (*13*) using ^{124}I PET images for quantification and 3-dimensional internal dosimetry software for assessing biokinetics and 3-dimensional dose distributions in tumors and normal organs after the administration of ^{131}I for the treatment of DTC add new and valuable information to the dosimetry of thyroid cancer treatment with ^{131}I.

Using PET results as inputs to a fully 3-dimensional dose-planning program, Sgouros et al. (*13*) obtained the spatial distributions of absorbed doses, isodose contours, dose volume histograms, and mean absorbed dose estimates for a total of 56 tumors. The mean absorbed doses for individual tumors ranged from 1.2 to 540 Gy. The distribution of absorbed doses within individual tumors was wide, ranging from a minimum of 0.3 Gy to a maximum of 4,000 Gy, showing the high variability of dose ranges even within a single patient (*13*).

Kolbert et al. (*5*) provide dose volume histograms and mean absorbed doses for 14 normal organs, including organs for which comprehensive doses have not been published (for example,

the salivary glands). This work also shows good agreement between the absorbed dose to the heart chamber and the blood absorbed dose as measured according to the method of Benua et al. (*10*), thus indirectly confirming the validity of the method of Benua et al. At present, therefore, the blood-based dosimetry approach seems to be the only approach that is directly linked to clinical results and that is supported by sufficiently well measured dose data.

The absorbed dose in the target tissue is the determinant of successful therapy, and in metastatic thyroid carcinoma, a high administered activity is required to achieve high tumor doses. Unintentional radiation exposure of healthy organs, however, limits the maximum applicable radioiodine activity. A reasonable limit of the absorbed dose to the red marrow and the dose assessment data published by the MIRD committee (*1*) and ICRP (*2*) might be used to estimate the maximum activity to be administered to patients. However, severe bone marrow depression, which is a limiting factor, was observed after treatment with activities of 11 GBq or even less (*14*); this effect cannot be explained by use of the tables provided by the MIRD Committee (*1*) and by the ICRP (*2*) for calculating the corresponding doses.

How can the differences between model calculations and observations be explained? A major correction has to be made regarding the whole-body residence time. In the MIRD (*1*) and ICRP (*2*) dose estimate reports, the half-life of radioiodine excretion has been set at 8 h, corresponding to 11.1 h of whole-body residence time. Half-lives typically observed in thyroid cancer patients are longer, especially under hypothyroid conditions. Mean whole-body residence times have been reported to be 24.1 h in patients treated after thyroid hormone withdrawal and 17.3 h in euthyroid patients after exogenous stimulation with recombinant human thyroid-stimulating hormone (*11*). The increase in this easily measurable parameter alone, however, is not sufficient to explain

the observed discrepancies. The highest whole-body residence time (45.8 h), observed by Hänscheid et al. (*11*), was about 4 times the value assumed by the model calculations. From the absorbed dose per unit of activity reported by the ICRP for red marrow (*2*) corrected for this factor, it can be deduced that even for the respective patient's red marrow, the dose should not have exceeded 2 Gy if the activity administered was limited to 14 GBq. The blood dose for this patient— 0.35 mGy/MBq (*11*)—would have been 5 Gy at 14 GBq, with a high risk of severe bone marrow depression (*10*).

Obviously, the assumption used by the ICRP (*2*) that activity not taken up by the thyroid, stomach, or small intestine is distributed uniformly throughout the remaining body is not appropriate. The residence time in blood was found to be about 14% of the whole-body residence time (*11*), although total blood volume represents only 7% of the body. Radioiodine not specifically bound is confined mainly to a rapidly equilibrating compartment of extracellular water with a distribution volume of about 20 L. Concentrations must be expected to be higher in blood, red bone marrow, liver, and lungs than in bone, connective tissue, or body fat. The data presented by Kolbert et al. (*5*) confirm this assumption. Doses in the liver and lungs are higher than those predicted by the MIRD (*1*) and ICRP (*2*) models. Mean organ doses are more or less comparable to the observed blood dose; consequently, the activity concentration will be only slightly lower than that in blood but will be significantly higher than that which would be expected for a uniform distribution throughout the body. Unfortunately, no information is presented on red marrow doses by Kolbert et al. (*5*).

This example shows that it might be worthwhile to use modern diagnostic techniques with the potential to generate spatial dose maps to confirm or improve data on biokinetics for individualized patient treatment. The patients included in the study by Kolbert et al. (*5*) were euthyroid, and

their biokinetics should be like those in healthy individuals with blocked thyroid iodine uptake. The results obtained should be applicable not only for radioiodine therapy or estimation of organ doses from deiodination in labeled antibody studies, as claimed by the authors, but also in diagnostic investigations with other iodine nuclides, such as ^{123}I and [124]I. This technique could also lead to improved dose estimates with the MIRD (*1*) and ICRP (*2*) models for the diagnostic use of these radionuclides. To be able to make use of the data reported by Kolbert et al. (*5*) for this purpose, it would be highly desirable to obtain additional information on the measured organ residence times.

Knowledge of mean organ absorbed doses is useful mainly for collective dose assessments and risk analysis in dedicated diagnostic or therapeutic procedures. For high-dose therapies, however, dosimetry is performed to determine the maximum safe dosage for an individual patient. As Kolbert et al. (*5*) pointed out, considerable interindividual differences are observed regarding organ doses. It is a challenge to reliably estimate organ doses from a series of planar scans to predict the maximum therapeutic activity that will not induce serious adverse effects in other organs. Up to now, the correlation between assessed doses and observed toxicities in targeted radiotherapy has not been satisfactory (see, for example, the report by Wiseman et al. (*15*)). Only a few studies have reported on evidence of a relationship between dose and functional organ impairment (*16,17*). Those studies were characterized by meticulous organ residence time evaluations that included all corrections potentially affecting the outcome.

Kolbert et al. (*5*) present a method of organ dosimetry that goes a step further, with the potential to improve dosimetry considerably. A series of tomographic images inaugurate the option to deduce a 3-dimensional dose map for the individual patient. For many years, it has been a long-term objective of nuclear medicine physicians to

treat patients on the basis of such information. The required tools seem to be increasingly within reach. However, 3-dimensional dosimetry is far from being easy or straightforward. In particular, the use of ^{124}I for absolute quantification requires expertise and a well-designed software package. It also should be noted that the issue of "stunning" has not been discussed yet in the context of the use of diagnostic ^{124}I activity.

It is both promising and challenging to proceed in establishing a reliable and generally applicable procedure for exact dosimetry for the individual patient as preparation for patient-specific organ dose–limited therapy in nuclear medicine.

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