Dosimetry in nuclear medicine therapy: what are the specifics in image quantification for dosimetry?

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A prerequisite to the calculation of the absorbed dose in targeted radiotherapy (TRT) is the determination of the localization and variation with time of the injected activity. This often requires quantitative scintigraphic imaging. The current quantitative imaging protocols can be divided in three broad categories: 2D, 2.5D and 3D, all used in the context of TRT, and yielding different compromises between accuracy and complexity that are discussed here. The relevance of a quantitative imaging procedure has to be reviewed in the light of the end point of the clinical dosimetry study: As far as radiation safety is concerned, some dosimetric approaches can be carried out using crude imaging protocols – and sometimes no imaging at all, and still were proved useful to derive the activity that can be safely injected to a given patient. Conversely, in some clinical situations, or when the end-point is to assess the efficacy of the treatment on a given cancer target, some sophisticated quantitative imaging approaches may be needed. In all situations, a very careful assessment of the technique used to derive the activity present in the patient must be performed, since activity quantification directly impacts the computation of absorbed dose.

Radiopharmaceutical dosimetry requires the determination of absorbed doses delivered to the patient. This requirement is especially important within the context of targeted radiotherapy (TRT), since the amount of activity injected is meant to induce deterministic effects at the level of the tumour targets, while sparing normal tissues. According to the MIRD formalism,[1] the calculation of absorbed dose can be broken down in independent steps according to:

$$\bar{D}_{(\text{target})} = \Sigma_{\text{source}} \tilde{A}_{\text{source}} \times S_{(\text{target} \leftarrow \text{source})} \qquad \text{Equation 1}$$

where $\bar{D}_{(\text{target})}$ is the mean absorbed dose in gray (Gy) in the considered target, $\tilde{A}_{\text{source}}$ is the total number of decays (the so-called cumulated activity) occurring in a given source, in Bq.s, and $S_{(\text{target} \leftarrow \text{source})}$ is the mean absorbed dose in the target, per decay from the source (S value). This formalism seemingly splits absorbed dose determination into 2 independent tasks: cumulated activity determination, and S value calculation. The situation is in fact a little more complex:

First of all, cumulated activity determination can itself be broken down into 2 independent tasks, namely absolute image quantification in all regions containing radioactivity (space) all along the radiopharmaceutical kinetics (time), and integration of the time-activity curve to derive cumulated activity. If

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absolute image quantification is known to be a challenge, even the later task is far from trivial, as the resulting accuracy relies on proper time sampling and relevant integration procedure.

Second, the two (and actually three) tasks that lead to absorbed dose determination are not really independent, in the sense that the global level of accuracy relies on the least accurate step. In other words, a very accurate S value determination, for example obtained from computed tomography (CT)-based patient geometry, will not necessarily result in greater absorbed dose assessment accuracy if image quantification or time sampling is wanting. This also explains why clinical dosimetry approaches should be carefully reported, by taking into account all aspects that lead to absorbed dose determination.[2] However, S value calculation has improved markedly over the last decade, mostly with the advent of patient-specific calculations based on CT-based geometry definition.[3] Acquisition time sampling is to be negotiated during the dosimetric protocol elaboration, mostly as a function of clinical constraints, and the derivation of cumulated activity from a given dataset requires care and attention but is certainly feasible with widely available software based on established methodology.

Accurate image quantification is a real issue in Nuclear Medicine, not only in the context of absorbed dose calculation,[4] but for many applications in which visual image analysis is not sufficient. Such applications include differential diagnosis, prognosis, therapy management, patient monitoring, and of course treatment planning in radiotherapy based on nuclear medicine images.

As a result, many efforts have been recently dedicated to the improvement of quantitative accuracy in single photon emission computed tomography (SPECT) and positron emission tomography (PET) imaging. In SPECT, sophisticated methods have been developed for attenuation correction,[5] scatter correction,[6, 7] compensation of the detector response function,[8] motion compensation [9] and partial volume effect correction,[10] with some of these methods becoming available in the software associated with gamma cameras.

Image-based dosimetry obviously benefits from these advances in the quantitative interpretation of the images. However, when the ultimate goal is to compute the absorbed dose to a patient in a context of TRT, specific aspects of quantitative imaging need to be considered as will be described in this paper.

Current clinical dosimetry is mostly based on SPECT or SPECT/CT procedures. The situation may evolve in the near future, with the more widespread use of PET in the context of TRT for pretherapeutic dosimetric evaluation. Following the hypothesis that activity quantification is easier in PET imaging than in SPECT due to the higher spatial resolution currently obtained with PET compared to SPECT, it could be beneficial to use PET-based pharmacokinetics to derive the cumulated activity that would be obtained from the ß- isotope used for therapy.[11] To do so, the availability of a positron-emitting isotope of the ß-emitter used for therapy has to be ascertained. Some "ß+ - ß– pairs" have been proposed in the literature, such as $^{124}I/^{131}I$, $^{86}Y/^{90}Y$ or $^{64}Cu/^{67}Cu$.[11] Since PET procedures are essentially designed for ^{18}F imaging, specific approaches appropriate for "exotic" positron emitters have to be validated. This is especially true for emitters that are "dirty isotopes", *i.e.* that are characterized by a low positron yield associated with a large high energy gamma photon emission with photon energy falling within the energy window of the PET scanner (without or after scattering in the patient). If high abundance high energy photons saturate the crystal of the scanner, PET imaging can also become especially challenging.

Some encouraging PET studies have been reported in the literature [12-15] but remain marginal in the field of image-based dosimetric studies. We therefore will focus this paper on SPECT and SPECT-CT based approaches for clinical dosimetry.

In the second section, we first explain why the "generic" approaches and tools recommended for improved quantitative accuracy in activity estimates are highly relevant in the context of TRT, and we briefly describe these.

In the third section, we then focus on the methodological approaches for quantification in the specific context of TRT. We explain why the generic quantification tools might not always be appropriate in the context of TRT, and why this application of quantification is either less or more demanding than alternative applications, as a function of the dosimetry question to be addressed. We also identify the additional steps required to perform well-controlled and accurate quantitative studies in the context of TRT, and discuss solutions that might be helpful to improve the robustness and reliability of image-based dosimetry.

We finally show and discuss how clinical dosim-

etry has been used to orient patient management and the quantitative imaging protocols that have been implemented for that purpose. The situation is indeed highly variable, as dosimetry can be implemented in clinical practice with different aims or end-points, in a variety of clinical applications, each of which with specific constraints that need to be addressed.

Generic requirements for quantitative studies

Goal of image quantification

In single photon emission imaging, the initial goal of quantification is to obtain images in which the pixel or voxel value ("pixel" is used here for 2D pixels and "voxel" for 3D volume elements) is at least proportional to the activity concentration in that pixel:

$$C_i = k.A_i \qquad \text{Equation 2}$$

where C_i is the value in pixel or voxel i per unit time and A_i is the activity concentration (kBq/mL) in the region sampled by this pixel/voxel i. k is the proportionality constant.

Establishing this proportionality relationship gives access to what is called "relative quantification": activity ratios between 2D or 3D regions in the body can be estimated by calculating the ratio of the average pixel/voxel values in two regions of interest (ROI). If the proportionality constant k is determined through a calibration experiment, then "absolute quantification" is feasible: the actual activity concentration in the region corresponding to a region or to pixel/voxel i can be deduced from the image.

In TRT, absorbed dose calculation is based on the assessment of the activity distribution, either over the whole-body, or at the organ or even pixel/voxel level. It is thus easy to understand that any effort towards improvement of the validity of Equation 2 will turn into a better estimate of the activity distribution A_i, hence a more accurate absorbed dose assessment.

Imaging protocols

It is well recognized that the most appropriate method to achieve accurate quantification in single photon imaging is to perform SPECT imaging. Planar imaging is hampered by the impossibility of untangling overlapped organs from the images and prevents from accurately assessing the activity concentration in a given organ or organ subregion. On the other hand, when activity is required for the whole-body (either to derive the absorbed dose to the bone marrow or to use the first scan - before the patient voids - for calibration), planar imaging appears to be much more practical than whole-body SPECT scanning.

Still, accurate quantification of SPECT images is not straightforward: a number of effects have to be accounted for before, during or after the image reconstruction process, to produce images in which equation 2 is almost verified. These effects include attenuation, Compton scatter, detector response function, motion and partial volume effect.

In that regard, the advent of SPECT/CT systems is a huge move toward accurate quantitative SPECT images.[16, 17] Indeed, SPECT/CT systems considerably facilitate the implementation of accurate attenuation correction, attenuation being the most adverse effect in SPECT image quantification.[18] In addition, even though outside the field of the present article, absorbed dose assessment also requires an estimation of tissue density and composition, and possibly organ delineation. It is thus obvious that these additional operations will largely benefit from the availability of a CT scan in addition to the SPECT scan providing activity concentration estimates.

Ideally, quantitative studies should thus be based on SPECT/CT imaging protocols, as those protocols clearly offer the richest information needed to compensate for effects impeding quantification.

Image reconstruction protocols

SPECT images are produced through tomographic reconstruction. To yield quantitative images, tomographic reconstruction must include or be associated with a number of corrections. The most critical correction is attenuation correction. Absence of attenuation correction prevents from both relative and absolute accurate quantification.

Accurate attenuation correction is now feasible in routine, the most reliable approach consisting in including the attenuation effect in the system matrix modelling the forward imaging process (*i.e.* modelling the relationship between the 3D activity dis-

tribution and the measured 2D projections). Such a modelling is largely facilitated by the knowledge of the body attenuation properties at the voxel level, obtained from CT scanners acquired in SPECT/CT hybrid systems.[16, 17] In the absence of SPECT/CT scanner, the attenuation properties of the body can be estimated either using a gamma transmission source associated with the gamma camera, or assuming a constant attenuation with the body contours delineated from the SPECT images.[5] The former solution can yield an accurate estimate of the body attenuation properties, but only few gamma cameras are equipped with a gamma transmission source. The latter solution is only reliable for brain studies, but only provides a poor estimate of the body attenuation properties in other regions (thorax or abdomen).

Most cameras have scatter corrections available, often based on the use of several energy windows to estimate scatter projections, and either subtract them from the usual projections after appropriate weighting, or introduce this estimate during the iterative reconstruction procedure.[19, 20] More sophisticated scatter corrections have been described but are not available on commercial machines yet. Scatter corrections do improve quantification and are well validated for ^{99m}Tc studies. The validity of a given scatter correction method for any other isotope needs to be checked first, for instance based on phantom studies, especially when the goal is to define a quantitative image reconstruction protocol.

The limited and spatially variant detector response function (DRF) does not introduce global quantitative error per se (*i.e.* over- or underestimation of the activity in the patient), but rather blur images by spreading "counts" around the actual voxel in which they should have been detected. Still, not correcting for the spatially variant DRF impacts local activity measurements, for instance at the organ level, as activity supposed to be detected in an organ might be detected in neighbouring regions. Spatially variant DRF can be rather easily compensated for during iterative reconstruction,[8] and this option is now available in commercial software. The overall effect is an improvement in the spatial resolution of the resulting images, which helps organ delineation, and reduces the spill-in and spill-out effects between neighbouring organs or structures (see below). When available, this correction improves the quantitative accuracy of the reconstructed images and should therefore be used.

Partial volume effect (PVE) is a direct consequence of limited DRF, and is also caused by the very image sampling process (this source of PVE is more precisely termed "tissue-fraction effect").[21] Limited spatial resolution in the reconstructed image causes blur between adjacent structures, and subsequent errors in local activity estimates. Even if the spatial variant DRF can now be compensated for, the spatial resolution in the reconstructed SPECT images remains limited, with a 6-8 mm spatial resolution at best. Activity in "hot" regions therefore spills in not-so-hot neighbouring regions, which is called spill-out. "Cold" regions or "warm" regions can thus be contaminated by neighbouring activity, resulting again in errors in local activity concentration estimates. Even if the spatial resolution in the reconstructed image was perfect, image sampling would still introduce PVE through the "tissue-fraction effect". A single voxel would frequently include tissues with different uptakes, so that the resulting voxel value would be an average of the uptakes of the different tissues weighted by the proportion of each tissue in the voxel of interest.

Up-to-date, although several methods for PVE compensations have been described in the literature and are applicable to PET and SPECT studies,[21] none is available on the workstations distributed by companies. Given the importance of PVE correction for accurate quantification in small structures, it is expected that this situation will soon change, as the reported PVE compensation methods tend to always improve quantitative accuracy, even if not reaching perfectly accurate quantification.

Last but not least, but probably not so important in the context of TRT, motion correction is currently attracting a lot of attention. Both cardiac and respiratory motions can be corrected in SPECT studies,[22] although this is far from being of practical use in routine. The applications for which motion correction will significantly impact diagnosis still needs to be identified, cardiac imaging being probably one of these. It is unlikely that compensation of physiological motion will largely impact the accuracy of absorbed dose quantification in the case of TRT, with possibly one exception being the assessment of the absorbed dose to the liver, as this organ is significantly affected by respiratory motion. In that specific case, respiratory motion correction might be desirable.

In short, attenuation correction, scatter correction and spatially variant DRF corrections (all available from the modern software associated with gamma-camera) all contribute to the improvement of SPECT image quantitative accuracy, and should ideally all be used when the objective of the imaging study is dosimetry. However, additional considerations have to be taken into account to make the most of image reconstruction protocols including these corrections, as will now be discussed. Also, SPECT/CT may not always be available and alternative solutions then need to be considered to approach reliable quantification for absorbed dose calculation.

Methodological approaches for quantification in the context of TRT

As explained above, it is anticipated that any improvement in activity quantification based on generic corrections developed for imaging studies will favourably impact image-based absorbed dose calculation. However, the context of TRT implies additional constraints that have to be taken into account when designing a quantitative imaging protocol. These constraints are discussed below and solutions are proposed to make the best of current imaging capabilities to achieve reliable imaging-based dosimetry.

Need for absolute quantification

An extremely important aspect is that quantitative imaging for TRT requires absolute quantification. In other words, it is not enough to perform corrections so that Equation 2 is roughly verified, but the proportionality factor k has to be determined, to derive activity values expressed in Bq or Bq/mL.

This is far from being a minor detail, as it raises the problem of system calibration. The easiest calibration procedure consists in using a point-like source of precisely known activity, and then imaging and reconstructing this source as would be done in a clinical protocol. The ratio of the total activity measured in the reconstructed image over the actual source activity then yields the calibration factor.[23] However, using such a simple experimental set-up does not reproduce the attenuation and scatter properties of a real patient. Subsequent use of the calibration factor measured using this basic experiment will thus assume perfectly accurate attenuation and scatter corrections.

These two corrections indeed impact the magnitude of the detected activity, unlike DRF, PVE, and motion corrections that only impact the spatial distribution of the activity in the image, and do not change the total activity in the reconstructed images.

An alternative to determine the calibration factor in a situation closer to that of a real acquisition is to use a not-so-small source with known activity (small sphere or cylinder for instance),[24] possibly by placing the source near the patient during the patient scanning protocol or by performing an additional calibration acquisition. Images are then reconstructed following the patient reconstruction protocol, i.e. including all corrections available in the console. The calibration factor can then be derived by measuring the signal level in a region encompassing the small source and comparing it to the known activity of the source. In some sense, this approach adapts calibration to patient-specific imaging conditions and better accounts for the effect of attenuation and scatter correction in the patient. However, the resulting calibration factor will depend on the region drawn in the image to estimate the number of counts corresponding to the known activity set in the source. Ideally, the region should be large enough to account for all activity coming from the source, but when the source sets close to the patient, care has to be taken so that the measurement is not affected by activity coming from patient uptake.

Some author deduced the calibration factor from geometrical objects filled with radioactivity immerged in a water phantom after empirical attenuation correction.[25] The most refined approach used anthropomorphic shaped organs in a water phantom, where organ positioning and phantom dimensions were modified for each patient in order to mimic the real clinical situation.[26]

Another option – often used for planar whole-body activity determination – is to perform the first acquisition just after radiopharmaceutical injection and before the patient voids, and assume that the total number of events detected over the whole body of the patient represents the total injected activity (patient relative calibration). This semi-quantitative approach relies on the hypothesis that all corrections implemented (attenuation correction, scatter correction, etc.) are spatially invariant, i.e. that a detected event represents the same amount of activity

(or activity concentration), not only over the field of view, but also over the whole patient. This strongly advocates using a pixel-based attenuation correction (over the whole patient) rather than a mean attenuation correction factor derived on a region of the patient. Additionally, since the same calibration factor obtained at day 0 after injection is used to derive radiopharmaceutical kinetics, the underlying hypothesis is that corrections also are valid from one day to the next, regardless of relative variations in organ/tissue activity content.

In any case, the method used for calibration should always be clearly reported.[2] Ideally, its repeatability should also be documented through test/re-test procedures.

Imaging protocols for quantification in the context of TRT

Three broad types of imaging protocols of various complexities have been proposed to achieve quantitative imaging in the context of TRT. Their respective relevance actually depends on the end-point of the dosimetric study. In this section, we present these three approaches and discuss the accuracy and level of quantification (whole-body, organ or voxel) that can be expected for each of them.

2D PLANAR IMAGING

Based on considerations discussed in imaging protocol section above, the feasibility of activity quantification using planar imaging appears questionable. However, in many applications, whole-body dosimetry is required. Planar imaging remains the easiest and least time-consuming approach for whole body imaging. Yet, as already discussed, planar imaging does not provide the 3D information needed to account for organ overlap and differential attenuation properties. Still, rough attenuation and scatter corrections can be performed in planar imaging, and organ overlap can be partially compensated for using some sort of background correction. Any scatter correction available on the console (usually based on multiple energy windows) can be used to compensate the projection(s) for scatter. Attenuation correction is usually based on the geometric mean of two conjugate views (*i.e.* two views recorded 180° apart) and possibly includes a thickness correction based on a patient thickness estimate.[4] This is by no way an accurate correction, but is only an empirical compensation approach.

Organ overlap can be reduced first by drawing small organ ROIs to reduce the impact of overlap and second by using background subtraction: background regions can be defined for each organ but this procedure remains highly subjective. For each organ, the average activity in the associated background region can be subtracted from the average activity in the corresponding organ region of interest. It should be underlined that the accuracy of quantification from 2D imaging highly depends on the way calibration is performed.

This quantitative procedure is intrinsically approximate, as fundamental 3D information is lacking in 2D-only imaging procedure. As a result, such an approach can be used to estimate activity at the organ level, but it is not appropriate to assess activity at the voxel level, since even the notion of 3D voxels does not exist in that approach.

Previous studies have reported various levels of quantitative accuracy obtained using a planar-only approach with ^{111}In imaging.[27-29] The overall conclusion is that accuracy in organ activity measurement is highly variable, with either over or underestimation of activity, and magnitudes of error up to 50% or even more. In short, whole body planar imaging is easy to perform, but the quantitative accuracy in activity estimate at the organ level is hard to predict.

2.5D IMAGING: PLANAR SCINTIGRAPHIC IMAGING COMBINED WITH CT

To make up for the 3D information missing in planar imaging protocols, it has been proposed to introduce 3D information based on the patient CT scan.[28, 30] The idea is to retrieve the 3D morphological information and attenuation properties from the CT, and use them to correct the planar acquisitions for attenuation. The organs of interest must first be segmented in 3D using the CT. An important assumption of this approach is that activity in a segmented volume of interest (VOI) is constant. The theoretical contribution of each VOI to 2D regions drawn on the planar projection is calculated based on a system matrix modelling the forward imaging process, similar to what is performed in iterative reconstruction. The difference is that in SPECT iterative reconstruction, each element (i,j) of the system matrix represents the probability that a photon

emitted in voxel j be detected in projection pixel i. In the approach described here, called QPlanar by He *et al.*,[28] each element (i,j) of the system matrix represents the probability that a photon emitted from organ VOI j be detected in the projection ROI i. The number of elements of the system matrix is thus simply equal to the product of the number of organ VOI drawn in the CT by the number of organ ROI drawn in the projection(s). To recover the organ VOI activity, an iterative algorithm such as the maximum likelihood expectation maximization (MLEM) can be used.[28] The algorithm yields one activity value per organ VOI. The accuracy of this approach will depend first on the relevance of the assumption of uniform uptake per organ, second on the alignment between the organ VOIs drawn in the CT and the true organ projections in the planar images,[31] and third on the accuracy of the forward model used to estimate the system matrix. As CT is required in this approach, the forward model can easily include the effect of attenuation, based on the attenuation coefficients derived from the CT images. The model can also include a modelling of the impact of scatter and distance dependent DRF if available for the considered camera. Alternatively, projections could be first corrected for scatter, and the system matrix could model attenuation only, or attenuation and distance dependent DRF for increased accuracy.

This approach has been assessed for ^{111}In imaging,[28] where the authors showed that the resulting accuracy was much improved compared to that obtained using a planar imaging protocol only (without taking advantage of the CT). They also found that the accuracy was actually close to that obtained using fully SPECT imaging combined with CT, with errors in organ activity estimates lower than 15%, compared to errors less than 5% when using fully SPECT/CT imaging.

The advantage of this approach is that it only requires planar imaging, which is convenient for whole-body acquisition, but takes advantages of the 3D CT to introduce 3D information needed for improving quantitative information. A limitation of course is that for whole-body dosimetry, a whole body CT scan is needed, with associated X-ray exposure. However, given that the patients undergoing these imaging protocols for dosimetry purpose also undergo TRT, this limitation is not as severe as when imaging is performed for diagnosis purpose only. A second limitation is that this procedure only yields an average activity value per organ, implying that subsequent absorbed dose calculation at the voxel level is not relevant. Last, the possible misregistration of the organ VOI obtained from the CT with the organ projections reduces the accuracy of organ activity estimates, especially for small organs or organs with low activity concentrations compared to neighbouring organs.[31]

In the following, this approach will be noted 2.5 imaging, as it combines 2D scintigraphic imaging with 3D CT.

3D IMAGING: SPECT/CT

The most complete information that can be used to perform accurate quantification in the context of TRT is from SPECT/CT imaging. Here, all generic methods described in the image reconstruction protocols section to obtain quantitative SPECT images can be used if available on the workstation, including attenuation correction based on the CT data, scatter correction, and distance dependent DRF correction. These corrections are best implemented in iterative reconstruction algorithm, such as MLEM or OSEM. Ideally, PVE correction should also be used, especially when activity in small organs such as small tumours or kidneys is of interest. When using SPECT/CT imaging for activity quantification, the only difference compared to the protocol used for applications other than TRT that need quantification is that one has to determine the calibration factor needed to convert counts into activity.

Fully 3D SPECT/CT imaging yields an activity map, resulting in activity estimates at the voxel level. It is thus the recommended approach when dosimetry at the voxel level is required. However, a word of caution is needed here. It is not because SPECT/CT protocols yield activity estimates at the voxel level that these voxel activity estimates are reliable at the voxel level. Indeed, in most evaluation studies, it is shown that SPECT/CT imaging can yield accurate quantification in VOI, but the considered VOI are usually not restricted to 1 voxel and usually cover a large number of voxels. This means that the average activity in a subset of neighbour voxels is close to the activity in the corresponding organ, but not necessarily that the activity in a given voxel is close to the true activity in the corresponding region. Activity in single voxels will be accurate only if the noise level in the image is very low. In ad-

dition, due to image sampling, activity in a single voxel usually represents the average activity of the different tissues actually present in that voxel (what is called the tissue-fraction effect). For any TRT application, the relevance of activity quantification and subsequent absorbed dose calculation at the voxel level must therefore be questioned. From a purely theoretical point of view, activity quantification at the voxel-level is of course desirable, as a step forward absorbed dose gradient determination within a given organ or tissue for instance. However, a high-resolution scale (where high-resolution means few mm here, or even fractions of a mm, i.e. the range of ß- emitters usually used for TRT) is currently out of reach using state-of-the-art whole body SPECT/CT images, where voxels are usually about 4x4x4 mm, and where the spatial resolution of SPECT images is usually close to 1 cm due to smoothing operations frequently applied.

Relevance of the different protocols

Activity determination based on SPECT/CT imaging in the context of TRT has already been largely assessed in the literature.[23-28, 32-34] When compared with 2D or 2.5D imaging protocols, it has always been found to be of greater accuracy at the organ level. Ideally, it is clear that this should be the preferred approach for activity estimation in the context of TRT. However, repeating whole-body SPECT/CT imaging at different time points yields repeated long acquisition protocols for the patient. When considering only organ activity estimation, however (as opposed to activity estimate at the voxel level), it might be possible to reduce the acquisition time conventionally used based on image quality considerations by a ~2 factor without a significant effect on quantification accuracy, even if still using whole-body SPECT/CT.[35] Also, the extremely encouraging results obtained with 2.5D imaging [28, 34-35] at the organ level suggest that it might be a valuable alternative to 3D imaging, at a reduced cost in terms of acquisition duration and processing complexity. Yet, if whole-body scanning is needed, the 2.5D approach still requires a whole-body CT to be performed.

Whatever the approach used for activity quantification (2D, 2.5D or 3D), a great care should be taken when delineating VOIs when activity value per organ (or tissue) is of interest. Indeed, errors in the definition of the VOI can strongly impact the accuracy of activity estimates, especially with small organs with low uptake.[33, 36] The best way for delineating VOIs from SPECT/CT imaging still needs to be identified in the context of absorbed dose calculation.

Cumulated activity estimates from serial scintigraphic imaging

As stated above, TRT dosimetry requires the computation of cumulated activity from time-activity curves (TAC) in ROI or VOI. It is therefore necessary to perform quantitative imaging several times, using one of the three approaches described previously. These serial measurements must then be combined to estimate the cumulated activity, either over the whole body, at the organ level, or even at the voxel level. This combination of measurements raises the issue of correct registration of measurements made at different times. When measurements are made at the organ level, two approaches can be used to draw the organ ROI or VOI over the serial scans. They can be drawn on the first scan, and then kept unchanged and just manually relocated on the subsequent scans. The second option is to redraw ROI in each scan. None of these options is flawless.

In the first case, given that the patient is not exactly in the same position from one scan to another, and that organ positions can change from one imaging session to another, the initial ROI or VOI might not have the optimal shape (*i.e.* the one closest to the actual contour of the organ) and the optimal location (*i.e.* position with respect to the actual organ position) in subsequent scans. In addition, if the organ changes in size, keeping the ROI unchanged from one scan to another introduces errors.[37]

In the second approach, variability in ROI or VOI drawing brings an additional source of errors in measurements. This variability can be somehow controlled by checking the consistency of the ROI areas or VOI volumes from one scan to the next, but if the organ morphology actually changes between scans, this consistency test will not be appropriate. The most reasonable approach is certainly to repeat the measurement several times to get an estimate of the measurement variability and account for the variability in the subsequent calculation of absorbed dose.

When measurements are made at the voxel level,

serial scans have then to be accurately registered at the voxel level. This might seem extremely challenging at first sight. However, at least in 3D, sophisticated registration procedures can be used to align serial SPECT scans, based on the alignment of the associated serial CT data, which contain high-resolution details needed for accurate registration. In PET/CT, such an approach can yield a registration accuracy of the order of the voxel size, at least locally.[38] Whether such accuracy can be achieved in SPECT/CT remains to be demonstrated. Such accurate registration at the voxel level is needed to expect reliable TAC at the voxel level, hence reliable cumulated activity at the voxel level. Small shift might still be acceptable, given that the spatial resolution in the SPECT images is limited to about 1 cm, so that no sharp changes in activity values are usually observed between adjacent voxels.

Repeating whole-body SPECT/CT at different time points as required for determining the cumulated activity might be clinically unpractical. As a result, it has been proposed to use so-called hybrid protocols, in which 2D or 2.5D protocols are used for each time point except one, for which a 3D SPECT/CT protocol is used instead.[34, 39] Such 3D data also make it possible to reproduce the 2D or 2.5D protocol for this time point, hence derive the rescaling parameter to be applied to the measurements made at all other time points to account for the bias introduced by the simplified 2D or 2.5D protocols. Such a hybrid approach assumes that the errors introduced by considering a 2D (or 2.5D) protocol are constant over time, i.e. do not depend on the activity distribution at a given time point. Even if this assumption is wrong because activity distribution changes over time, hence so do the biases introduced by attenuation and scatter, the expectation is that quantification will still be more accurate than with no rescaling at all. It has indeed been shown in a series of phantom measurements that the accuracy in residence time estimate using a hybrid 2.5/3D approach was close to that obtained using a 3D-only procedure for all time points,[34] while the results for a hybrid 2D/3D approach were poorer than those obtained with either a 2.5D or a 3D approach at all time points.[34] Considering the hybrid 2.5/3D approaches might thus be a valuable option to practically achieve good accuracy in organ activity estimates.

Quality control of activity quantification in the context of TRT

Quantitative imaging is different for pretherapeutic dosimetry or for therapeutic dosimetry. In the first case, the therapeutic isotope can be used (with low activity), or a surrogate isotope can be employed (*i.e.* ^{111}In for ^{90}Y therapy). Conventional imaging situations are usually considered, for which most quantitative procedures have been validated and expected accuracy has been reported.

In the second situation, dosimetry is performed after therapeutic injection, and quantitative imaging is done for the injected isotope, and for a high activity. This second situation also covers treatments administered in 2 sessions, with a fixed (high) activity followed by a variable (high) activity injection, calculated to deliver a total pre-fixed absorbed dose (*i.e.* the first injection is used to perform absorbed dose calculation, and the activity of the second injection is computed from the initial dosimetric study). For this second situation, in which count rates can be extremely high, the quantitative protocols have usually not been validated. Because absorbed dose calculation relies on absolute quantification, there is a need to validate the accuracy of the supposedly quantitative imaging protocols also in count-rate conditions close to those encountered in patients. Indeed, as discussed above, absolute activity quantification depends on a calibration factor, which might itself depend on the count-rate, because of camera dead-time.

In the context of TRT, apart from the situation of high count rates requiring specific validation studies, the use of nuclides that are not common in conventional Nuclear Medicine procedures also requires specific adaptation of the imaging protocols and specific validation studies. Indeed, these nuclides might raise unusual issues, such as septal penetration for high-energy radionuclides (*e.g.*, ^{131}I), or downscatter of high energy photons in lower energy windows for all nuclides including several gamma energies, or even contribution of bremsstrahlung radiation from beta particles affecting gamma imaging. It should be underlined that most of the corrections developed for improved quantitative imaging briefly described in the image reconstruction protocols section have been widely validated for ^{99m}Tc, but often not for other radionuclides. Using attenuation and scatter corrections for nuclides with

several emission energies like ^{111}In or ^{166}Ho needs adaptation.[33, 40] Similarly, quantitative imaging for ^{131}I needs specific acquisition and processing protocols.[20, 23] The performance of correction methods obtained for a nuclide should never be extrapolated to another. The adapted implementation of a correction method to another nuclide should always be first thoroughly validated.

For radionuclides producing bremsstrahlung (with or without gamma photons), bremsstrahlung can also be taken advantage of for imaging, although bremsstrahlung medical imaging is still in its infancy, not to mention quantitative bremsstrahlung imaging, especially due to the continuous energy distribution of the resulting photons.[41-44]

The quality control of the activity quantification procedures should include, under different count-rate conditions, both the determination of the average bias in activity estimates but also the characterization of the variability of the bias under different experimental settings, including a variety in patient anatomy and biodistribution. The impact of errors in VOI definition should also be systematically studied.[33, 36] Thorough quality control is of course difficult to achieve, as it requires performing a rather large number of experiments or simulations.[34] Still, this should be considered as a necessary step before performing quantitative imaging in the context of TRT. To facilitate this validation phase, part of the quantification protocols could be based on shared simulated data, as this has also been proposed in a pure imaging context.[45] Although the assessment of the quantification procedure accuracy cannot be based on simulated data only, it is usually found that using such data is extremely helpful for identifying potential systematic biases and understanding their origin. Since the absorbed dose determination involves multiple steps, each of them prone to errors or uncertainties, it is tempting to benefit from the ever-growing computing power associated to versatile Monte-Carlo codes [46] to model the whole process from quantitative imaging to absorbed dose calculation. A "virtual multi-centric intercomparison" could possibly explain the variations observed when the same (virtual) patient is dealt with in different institutions.

A reference clinical situation, involving a realistic anthropomorphic phantom and clinically based reference biokinetics could be used to assess the quality of the estimate of the reference absorbed dose at the whole body, organ or voxel level. Then, each participating centre would receive a patient data set specifically modelled according to its requirements (camera characteristics, number of time points, imaging procedure, additional data, etc.), in order to carry out, for the (virtual) patient, the dosimetric procedure that is normally implemented in the nuclear medicine department.

Intermediary results, associated with the implemented protocol, would then be sent to the reference centre, to compare the results obtained by each participating centre with the reference results. Increasing the number of participating centres would feed a database that would ultimately be used to derive the critical steps and pitfalls in clinical nuclear medicine dosimetry. Such a project, called "DosiTest", is currently being developed, but only preliminary results and proofs of concepts have been presented so far.[47, 48]

An important step is to characterize the way errors in activity estimates propagate through the whole chain of absorbed dose calculation.[49] For instance, if the uncertainty affecting the activity estimate at each time point is known, the uncertainty affecting the absorbed dose estimate can be derived under certain conditions.[50] Any improvement in activity estimates will translate into an improvement in absorbed dose estimate, but not necessarily of the same magnitude. Overall, it has been shown that the magnitude of the error in absorbed dose estimates is usually less than the magnitude of the errors in activity estimates.[23, 24]

Relevance of quantitative imaging in clinical dosimetry practice

Quantitative imaging for clinical dosimetry is only one of the steps that lead to the computation of absorbed doses delivered to both tumours or normal (critical) tissues. As seen previously, there are many ways to address quantitative imaging, corresponding to different complexity-accuracy compromises.

A major limit that hindered the development of clinical dosimetry is the seemingly absence of absorbed dose / effect relationship. This led the EANM therapy committee to conclude that *"Although dosimetry has been of enormous value in the preclinical phase of radiopharmaceutical development, its clinical use to optimise administered activity on an individual patient basis has been less evident"*.[51]

Indeed, as acknowledged by Sgouros: *"The objective of dosimetry in targeted radionuclide therapy is to provide information that will help improve patient care. With this objective, estimated absorbed dose is useful to the extent that it relates to response".*[52]

How quantitative imaging impacts dosimetry can thus be discussed by reversing the problem, *i.e.* by starting by clinical indications where dosimetry was proven to be useful, and then see what quantitative imaging protocol - if any - was implemented.

At the moment, clinical dosimetry is performed with several aims (endpoints):

— Clinical dosimetry - at least within the EU - has to be carried out to comply with EURATOM directive 97/43 that explicitly states that "*For all medical exposure of individuals for radiotherapeutic purposes, … exposures of target volumes shall be individually planned; taking into account that doses of non-target volumes and tissues shall be as low as reasonably achievable and consistent with the intended radiotherapeutic purpose of the exposure"*.[53]

— As toxicity is most often the factor that limits activity administration, patient specific dosimetry can be used as a means to derive the maximum activity that can be safely injected to the patient. According to the pathology and the treatment considered, the first line critical organ/tissue can be the bone marrow, the kidney, the liver, the lungs, etc.

— A somehow more ambitious approach consists in trying to compute the absorbed dose delivered to the tumour target(s). The aim is to derive the activity to administer in order to deliver a preset absorbed dose to a given target. However, since targets can be multiple, small (for example in residual disease), this third objective can be hard to achieve in practice.

Depending on the combination {disease, treatment, end-point}, very different approaches have been reported in the literature. Table I presents the achievements obtained in various clinical situations, for various pathologies and radiolabelled vectors, in terms of absorbed dose (or derivates) - effect relationship, and sort the activity determination step according to the global approach followed by the authors, from no imaging at all to refined SPECT/CT procedures.

Differentiated thyroid cancer treatment with ^{131}I

Differentiated thyroid cancer (DTC) treatment is important within the field of molecular radiotherapy as it represents the largest number of patients and treating sites. A review article on radioiodine therapy dosimetry in benign thyroid disease and differentiated thyroid carcinoma was recently presented by Salvatori and Luster.[54] It is generally considered that myelotoxicity is the earliest adverse effect, hence the Dosimetry Committee of the EANM has proposed a standard operating procedure where pretherapeutic dosimetry is used to limit the absorbed dose to the blood (as a surrogate to the absorbed dose to the bone marrow) under 2 Gy.[55] Activity determination in the whole body "*should be monitored by conjugate views of whole-body imaging with a dual-headed gamma camera or by conjugate whole-body counting with a probe using a fixed geometry*".

Moving in direction of efficacy assessment, Verburg *et al.* reported on how absorbed dose to the blood could predict the success of the ablation rate of cancer remnants.[56] In that situation, blood absorbed dose was derived from external counting of whole-body radioactivity (non-imaging technique).

Flux *et al.* recently presented a dose-effect correlation for radioiodine ablation in DTC.[57] A non-imaging technique was used to derive absorbed doses to the blood and bone marrow, however, absorbed dose to the remnants was assessed from 3 to 4 SPECT scans from 24 hours to 96 hours. The dosimetric approach used a "maximum voxel uptake" value to derive activity present in thyroid remnants.

An article from Sisson *et al.*[58] reported on the situation of a solitary iodine-avid metastasis of thyroid carcinoma to the skull. The dosimetric approach was based on serial co-registered SPECT images, CT-derived density maps and CT-defined masks for tumour and brain regions. Absorbed dose calculations indicated the delivery of 1 970 and 2 870 cGy to the tumour for two ^{131}I treatments (administered activities of 7.4 and 7.5 GBq) with a consecutive volume diminution of the tumour. This case report, although not strictly speaking proving an absorbed dose effect relationship, highlights how SPECT/CT based dosimetry can help in deriving patient-specific injected activity for TRT.

Neuroendocrine tumours treatment with ^{131}I-labelled mIBG

In Matthay *et al.*,[59] whole body absorbed dose (derived from external counting) correlated well with toxicity, but so did injected activity! In addi-

TABLE I.—*Evidence of an absorbed dose effect relationship as a function of the treatment, biological end point and activity determination protocol.*

Treatment	End Point	External counting	Planar imaging	2.5D imaging	3D SPECT
^{131}I in Differenciated Thyroid Cancer	$D_{Bone\ Marrow}$ <2 Gy to limit Bone Marrow toxicity	(55)	(55)		
	Success of ablation rate	(56)			(57)
	Absorbed dose to a metastasis				(58)
^{131}I-mIBG in NET	$D_{Whole\ Body}$/hematologic toxicity	(59-60)			
	Tumour self absorbed dose / Tumour response		(59)		
^{131}I-labelled monoclonal antibodies (NHL RIT)	$D_{Whole\ Body}$/hematologic toxicity		(61)		
	Equivalent Uniform Dose / Tumour response				(62)
^{90}Y-labelled monoclonal antibodies (NHL RIT)	$D_{Bone\ Marrow}$ / Toxicity correlation?			(65-67)	
90Y-SIR spheres in HCC treatment	BED / Liver complication probability				(69)

tion, self-absorbed dose derived from planar imaging correlated with tumour decrease, but again, so did injected activity.

A recent study from Buckley *et al.*[60] showed that whole-body absorbed dose obtained from external counting (non-imaging technique) correlated with bone marrow toxicity, whereas injected activity did not. The conclusions were that "even in a highly heterogeneous and heavily pretreated patient population, a whole-body absorbed dose can be prescribed accurately and is a more accurate predictor of hematologic toxicity than is administered activity".

Non Hogdkin lymphoma radioimmunotherapy

BEXXAR™

Bexxar™, an anti-CD20 monoclonal antibody labelled with ^{131}I obtained FDA approval in the USA. The administration mode is based on whole-body absorbed dose calculations based on 3 consecutive planar imaging sessions prior to therapy. Administered activity is calculated in order to deliver less than 65 (or 75 cGy), *i.e.* the maximum tolerated absorbed dose.[61]

In a long lasting quest for establishing an absorbed dose efficacy relationship in the treatment of non Hogdkin lymphoma (NHL) with Bexxar™, the team from Ann Arbor [62] recently presented the first absorbed dose/response relationship observed in that context. The equivalent uniform dose (EUD), obtained from fully 3D dosimetry based on quantitative SPECT/CT, correlated well with response as long as the cold antibody effect was taken into account.

ZEVALIN™ AND ^{90}Y-LABELLED MONOCLONAL ANTIBODIES FOR NHL THERAPY

Zevalin™, an anti-CD20 monoclonal antibody labelled with ^{90}Y has obtained FDA approval in the USA and EMA approval in the EU. Since ^{90}Y is a pure ß- emitter, when pretherapeutic dosimetry is performed, it is usually based on quantitative imaging of an ^{111}In-labelled surrogate (even though bremsstrahlung imaging has also been proposed). Since the preliminary study by Wiseman *et al.*[63] many studies have been reported to describe the dosimetry of ^{111}In-ibritumomab tiuxetan.[25-26, 64] Most reported large variations in absorbed dose results, even for studies carried out with similar formalisms (usually 2D planar), however, little evidence of a correlation between absorbed dose and effect was presented, both for haematological toxicity or treatment efficacy.

Ferrer *et al.*[65] compared different approaches of bone marrow dosimetry in a subset of five patients benefiting from NHL RIT with hLL2 (anti-CD22 monoclonal antibody). A 2.5D imaging protocol was based on 5 WB acquisitions (ranging from 1 hour postinjection to day 5) and a CT-based attenuation correction, where 3D attenuation maps were projected along the posterior-anterior axis. When compared to 2 approaches based on non-imaging blood-based activity measurements, the imaging-based approach alone seemed to provide for a correlation with bone marrow toxicity. Results were obtained for 5 patients only, and should be confirmed. Equivalent findings on Zevalin™ were presented at last EANM meeting, for 13 patients, where only 2.5D

and 3D protocols yielded a correlation between the absorbed dose to bone marrow and haematological toxicity, whereas even a refined 2D protocol led no correlation at all.[66, 67] Since the full analysis of the results is still ongoing, these encouraging preliminary results should be taken with care.

Neuroendocrine tumour peptide therapy

Neuroendocrine tumour peptide therapy has benefited from a very active research over the last years, and many vectors have been proposed to target the tumours. As in RIT, several isotopes have been tested (^{131}I, ^{90}Y and ^{177}Lu), leading to a variety of clinical procedures, ranging from no dosimetry at all to refined PET-based approaches.[68] We will discuss here only some of the protocols that have relevance from a quantitative imaging point of view.

In peptide therapy, the kidneys represent the critical organ, particularly after ^{90}Y-DOTATOC injection. Good correlation between Biological Equivalent Dose (BED) and kidney toxicity was observed for ^{90}Y-labelled peptide,[13] with a very refined ^{86}Y-PET imaging-based protocol, as long as patient-specific kidney volume (obtained from a CT) was used. PET/CT based dosimetry falls outside of the scope of this article but these results suggest that accurate quantitative imaging, as more easily achievable in PET/CT (and hopefully 3D SPECT/CT) than in 2D or 2.5D single photon imaging might help demonstrating correlations between absorbed dose and toxicity or efficacy within the context of peptide therapy.

Treatment of hepato-cellular carcinoma with 90Y-SIR spheres

The treatment of non-resectable hepato-cellular carcinoma (HCC) can be performed with ^{90}Y-selective internal radiation (SIR) spheres. However, the maximum delivered absorbed dose is limited by liver parenchyma. A study performed by Strigari *et al.* (69) demonstrated that BED vs. liver complication probability could be obtained from bremsstrahlung imaging combined with CT. A clear absorbed dose-response correlation was demonstrated. However, tumour response varied according to the criteria applied (EASL guidelines or RECIST). This highlights the importance of the definition of the end-point when trying to show evidence of absorbed dose effect relationships.

The specific situation of bone marrow toxicity

Bone marrow is often the absorbed dose limiting organ in molecular radiotherapy. Its dosimetry is challenging since bone marrow is a very heterogeneous tissue at the microscopic scale, scattered through the patient's body. Dosimetric approaches to bone marrow dosimetry range from external counting techniques to sophisticated 3D SPECT-based quantification.[70]

Summary

Many results can be found in the literature highlighting how dosimetry can help in optimising targeted radiotherapy. However, the different articles presented here illustrate the large variety of techniques implemented for deriving dosimetric parameters, from no imaging at all to very refined quantitative imaging procedures (not mentioning the growing impact of quantitative PET). This in part is due to a shift in the end-point, from deriving the activity to inject in order to insure a safe treatment (with a fixed absorbed dose to the bone marrow, or blood), to optimising the chances of cure by calculating the absorbed dose to the tumour burden.

Conclusions

From the analysis of the various clinical situations in which targeted radiotherapy is being delivered, and given the very different protocols used to derive absorbed doses, it is not surprising that absorbed dose effect correlation was seldom put in evidence to date.

Recent evidences have convincingly demonstrated that quantitative imaging is of paramount importance in progressing in direction of patient-specific predictive dosimetry. However, the disease and the biological end-point also determine the level of refinement that needs to be implemented to reach the "holy gray" as defined by Brans *et al.*[51]

In some situations, very simple approaches will still provide for a better management of the patient, to avoid unnecessary therapy or to increase activity while staying under the threshold of appearance of toxic effects. In more complex situations, more refined approaches, including a priori knowledge or

modelling of the radiobiological behaviour of the targets considered may be necessary.[69, 71, 72]

In conclusion, the analysis of reported procedures indicate that:

— No standard protocol will answer all the needs of all TRT procedures.

— Quantitative dosimetry can be implemented in different ways, each of them needing to be carefully designed, tested, and optimized for the purpose. Protocols involving 2.5D or 3D imaging yield the most accurate estimates of cumulated activity, based on phantom and simulation results. Lack of evidence of absorbed-dose / effect relationships when using such protocols suggest that accurate estimate of cumulated activity is certainly necessary but probably not sufficient to demonstrate the relationship between the absorbed dose and effect or toxicity.

— There is a need for a multicentric comparison of dosimetric procedures. Monte-Carlo modelling may help in fulfilling that objective.

— The definition of the biologic (or clinical) endpoint has a direct consequence on the clinical dosimetric protocol (and hence the quantitative imaging procedure) that needs to be implemented, even though the underlying phenomena still remain to be explained.

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