

The Impact of PET and SPECT on Dosimetry for Targeted Radionuclide Therapy

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Abstract

Targeted radionuclide therapy (TRT) is an increasingly used treatment modality for a range of cancers. To date, few treatments have involved the use of dosimetry either to plan treatment or to retrospectively ascertain the absorbed dose delivered during treatment. Also the correlation between absorbed dose and biological effect has been difficult to establish.

Tomographic methods permit the determination of the activity volume on a macroscopic scale at different time points. Proper attenuation correction in tomographic imaging requires a patient-specific attenuation map. This can be obtained from scintillation-camera transmission scanning, CT, or by using segmented scatter-emission images. Attenuation corrections can be performed either on the projection images, on the reconstructed images, or as part of an iterative reconstruction method. The problem of image quantification for therapy radionuclides, particularly for I-131, is exacerbated by the fact that most cameras are optimised for diagnostic imaging with Tc-99m. In addition, problems may arise when high activities are to be measured due to count losses and mis-positioned events, because of insufficient pile-up and dead time correction methods.

Sufficient image quantification, however, is only possible if all effects that degrade the quantitative content of the image have been corrected for. Monte Carlo simulations are an appealing tool that can help to model interactions occurring in the patient or in the detector system. This is helpful to develop and test correction techniques, or to help to define detectors better suited to quantitative imaging.

PET is probably the most accurate imaging method for the determination of activity concentrations in tissue. PET

Die Bedeutung von PET und SPECT für die Dosimetrie der Therapie mit offenen Radionukliden

Zusammenfassung

Die Therapie mit offenen radioaktiven Substanzen wird zunehmend häufiger zur Behandlung einer ganzen Reihe von Krebserkrankungen eingesetzt. Bis heute allerdings haben nur wenige Behandlungsarten eine Dosimetrie zur Therapieplanung oder zur retrospektiven Sicherstellung der erzielten Dosis eingesetzt. Des Weiteren ist es nicht leicht möglich, eine Korrelation zwischen der absorbierten Dosis und den biologischen Effekten herzustellen.

Tomographische Methoden erlauben die Bestimmung der makroskopischen räumlichen Aktivitätsverteilung zu unterschiedlichen Zeitpunkten. Zur Durchführung einer Schwächungskorrektur wird die patientenspezifische Verteilung der Schwächungskoeffizienten benötigt. Diese wird entweder aus Szintigrammen mit einer Transmissionsquelle, aus CT-Bildern oder aus segmentierten Szintigrammen im Streifenfenster gewonnen. Die Schwächungskorrektur kann entweder auf den Projektionsbildern, auf den rekonstruierten Schnitten oder im Zuge der iterativen Rekonstruktion durchgeführt werden. Die Schwierigkeit der Quantifizierung von Bilddaten von Therapienukliden, insbesondere bei der Verwendung von I-131, wird dadurch erhöht, dass die meisten Gamma-Kameras für die diagnostische Bildgebung mit Tc-99m optimiert sind. Weitere Ungenauigkeiten werden durch unzureichende „Pile-up“- oder Totzeitkorrekturen hervorgerufen, die einen Zählratenverlust oder eine Mispositionierung von Ereignissen verursachen können.

Eine ausreichende Quantifizierung der Bilddaten ist nur möglich, wenn alle Effekte, die zu einer Verschlechterung

imaging can be considered for pre-therapeutic treatment planning but ideally requires the use of a radioisotope from the same element as that used for treatment (e.g. I-124 for I-131; Y-86 for Y-90). Problems, however, are that

- *some of the positron emitting isotopes have a shorter half-life*
- *non-standard quantification procedures have to be performed*
- *the availability of the radiopharmaceutical is presently limited;*

Many 3D-tools and -techniques are now available to the physicist and clinician to enable absorbed dose calculations to both target and critical organs-at-risk. The challenge now facing nuclear medicine is to enable this methodology to be routinely available to the clinic, to ensure common standard operating procedures between centres and in particular to correlate response criteria with absorbed dose estimates.

Keywords: SPECT, PET, dosimetry, targeted radionuclide therapy

der Bildqualität führen, korrigiert worden sind. Zu diesem Zweck können Monte-Carlo-Simulationen als ein interessantes Werkzeug zur Modellierung der Wechselwirkungen der ionisierenden Strahlung im Patienten oder im Detektor einen wichtigen Beitrag leisten. Diese Simulationen sind insbesondere hilfreich, wenn es darum geht, Korrekturtechniken zu entwickeln und zu testen oder um besser geeignete Detektoren zur quantitativen Bildgebung zu finden.

Die Positronenemissionstomographie ist derzeit wahrscheinlich das genaueste Verfahren zur Bestimmung von Aktivitätskonzentrationen im Gewebe und könnte zur prätherapeutischen Behandlungsplanung eingesetzt werden. Dies erfordert jedoch ein Nuklid desselben Elements wie für die Therapie (z.B. I-124 für I-131, Y-86 für Y-90). Probleme ergeben sich jedoch aus der kürzeren Halbwertszeit einiger Positronenemitter, der Implementierung von nicht standardmäßig verfügbaren Quantifizierungsprozeduren sowie der Tatsache, dass einige Nuklide zurzeit nicht allgemein verfügbar sind.

Es existieren derzeit viele 3D-Werkzeuge und Techniken, die es dem Physiker und Kliniker ermöglichen, die absorbierte Dosis sowohl im Zielvolumen als auch in den kritischen Organen zu bestimmen. Die Herausforderung ist es jedoch, diese Methoden den Kliniken routinemäßig zur Verfügung zu stellen, eine Standardisierung der Prozeduren in verschiedenen Zentren anzustreben sowie die klinischen Ergebnisse mit den Dosisabschätzungen zu korrelieren.

Schlüsselwörter: SPECT, PET, Dosimetrie, Radionuklidtherapie

Introduction

Nuclear medicine makes a significant contribution to the health, health care and quality of life of European citizens, particularly in major clinical areas such as cancer and cardiovascular disease. Every year in Europe, over 10 million patients benefit from a nuclear medicine procedure, 90% of which are diagnostic (planar, PET, SPECT) and 10% therapeutic. These radionuclide therapies (or targeted radiotherapy, TRT) will increase in importance and number the coming years, in particular with the introduction of new molecules and radiopharmaceuticals, including radioimmunotherapy, through rapid developments in molecular biology and medicine. TRT (e.g. radioimmunotherapy) with new radiopharmaceuticals coupled to beta- or alpha-emitting isotopes are promising forms of radiotherapy for the treatment of different forms of cancer.

According to a survey carried out by the EANM radionuclide therapy committee [1] in 1999 there were 82892 patients treated with radionuclides in 18 European countries, i.e. 191 treatments per million inhabitants. The most frequent

therapy indication was and is “benign thyroid disease” with I-131 (69.1%). Another 26.6% of the indications were for malignant diseases. These numbers underline the necessity to carry out accurate dosimetry:

- to comply with the EU council directive 97/43/EURATOM (June 1997) [2] in which it is stated that “For all medical exposure of individuals for radiotherapeutic purposes (...) ¹ 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.” Individualised treatment planning has become routine practice for patients undergoing external beam radiotherapy and this directive is now becoming incorporated into national legislation, such as the IRMER regulations in the UK [3].
- to fulfil the clinical need for reliable individual patient dosimetry estimates to improve the efficacy of targeted radiotherapy.

¹ Omission for the sake of clarity

A number of centres worldwide have conducted theoretical as well as (pre)clinical experimental studies for TRT. Significant progress in the development of selective radionuclide carriers and optimal radioisotopes has been achieved in several centres. Evaluation of the efficacy of TRT by unsealed sources of radiation [4] depends on calculating the absorbed dose delivered to the patient's organ and tissues [5]. Oncology is the most common context in which these therapeutic methods are implemented, in which case the doses delivered are determined both in tumor targets and the normal tissues that are to be preserved [6]. As the administered activities are very high deterministic radiation effects are to be expected.

Individual patient dosimetry is presently the only possible way to:

- establish an individual minimum effective absorbed dose and maximum tolerated absorbed dose to tissue,
- predict tumor response and normal organ toxicity on the basis of pre-therapy dosimetry,
- increase the knowledge of clinical radionuclide radiobiology by correlation calculations and observed effects post-therapy,
- relate and compare the results to the radiation dosimetry routinely performed for external beam radiotherapy.

Absorbed dose calculations are based on modelled biodistribution data and on quantitative imaging procedures. The biodistribution of radioactive tracers (ligands) should be assessed separately for each individual patient, as it depends on a number of patient-specific parameters, such as gender, size of the subject and the amount of fatty tissue in the body, as well as the extent and nature of the disease. However to date, technicalities and knowledge have to be augmented and stimulated in order to achieve a more satisfactory correlation between absorbed dose estimates and treatment response or correlation with organ toxicity. Due to this, almost all TRT treatments today are based on empirical fixed administered activities, activities modified by clinical and/or pathological findings. This approach certainly leads to suboptimal under- or overdosing, as it is not individually tailored.

Currently, the errors of internal dosimetry calculations for diagnostic or therapeutic studies are in the order of magnitude of 30%–100% or even higher so that the situation is comparable to the situation of external beam therapy 30 or more years ago. The influence of the individual patient's radiation sensitivity and the knowledge of radiation induced biological effects are not taken into account when patient absorbed doses are calculated.

Basic methodology of internal dosimetry

Targeted radionuclide therapy (TRT) has been implemented as a treatment for various forms of cancer, as well as for benign disease, for over 60 years although to date, internal dosimetry for TRT has been employed only on a research

basis. Clinical trials involving radionuclides are usually governed by 'dose escalation studies', where 'dose' refers to the level of activity administered, rather than to the absorbed dose to either tumour or normal tissue.

Methods for calculating the absorbed dose received from administration of a radiopharmaceutical were first standardised in the 1960's by the Medical Internal Radiation Dosimetry (MIRD) committee (see e.g. [7]), with the initial aim of estimating average doses to critical organs resulting from diagnostic procedures. Essentially this methodology allows the calculation of absorbed dose using the simplified version of the basic equation:

$$\bar{D}(r_k \leftarrow r_h) = \tilde{A}_h S(r_k \leftarrow r_h)$$

$\bar{D}(r_k \leftarrow r_h)$: the mean absorbed dose to a target region r_k from the cumulated activity in source region r_h .

\tilde{A}_h : the cumulated activity (i.e. the integral of the activity-time curve from zero to infinity) in a given target region r_h .

$S(r_k \leftarrow r_h)$: the radionuclide specific S factor for target region r_k and source region r_h per unit cumulated activity in source region r_h .

\tilde{A} denotes the total number of radioactive decays occurring within an organ in which a radiopharmaceutical accumulates (the 'source organ'). The MIRD S factor accounts for the energy released from each radioactive decay and the relative geometry of the source organ and the organ for which the absorbed dose is to be calculated. Thus, the cumulated activity is dependent on biological parameters whilst the S factor deals with the physical components of the absorbed dose.

MIRD S factors have been published as look-up tables for any given pair of relative organs for a comprehensive range of clinically relevant radionuclides [8]. For a full exposition of the MIRD schema the reader is referred to the various pamphlets and books published by the MIRD committee. Further methodologies for dosimetry have been developed [9–10], although the basic principles behind each are essentially identical.

Whilst MIRD methodology, as traditionally employed, provides a relatively simple means to perform internal dosimetry, adaptations and alternative methods are required to deal with *therapeutic* applications of radiopharmaceuticals.

Whilst the basic principles of dosimetry hold for all dosimetric calculations, the application of these methods and in particular in the determination of the required input parameters is not straightforward. The method of administration may be intra-venous, intra-arterial or by direct infusion as well as oral. Different methods of administration, for example, will require different approaches to dosimetry calculations. For example, in the case of an intra-tumoural administration of a radiopharmaceutical the dose gradient can be dramatic and a mean dose over the whole tumour can be meaningless. For intracavitary administrations, the dose to the cavity wall has

been calculated using an absorbed fraction of 0.5 rather than 1 since only half of the energy is assumed to be deposited in the wall.

Furthermore, an increasing range of radionuclides are being employed for TRT, including alpha and pure beta emitters as well as low energy electron emitters as Auger electron emitters, and the mechanism and localisation of uptake can vary for different therapy procedures. To be clinically useful dosimetric calculations must be performed for both target organs (which may include focal and primary lesions) and for organs-at-risk, which frequently includes the red marrow as well as organs such as the kidneys, liver and heart. In particular, the accuracy with which dosimetry may be carried out is adversely affected by heterogeneity of radiopharmaceutical uptake at both a macroscopic and microscopic scale and by non-standard organ geometries [11]. In a recent publication by ICRU the different aspects on heterogeneity of activity uptake in tissues and tumours have been addressed [12].

One example of a recent clinical application of dosimetry is the application of Y-90-Ibritumomab Tiuxetan (the first radiopharmaceutical for radioimmunotherapy which is licensed in Europe and the USA) to the radioimmunotherapy of NHL by Wiseman et al [13]. In this study pre-therapeutic image based dosimetry for an administration of 15 MBq/kg Y-90-Ibritumomab Tiuxetan (Zevalin) radioimmunotherapy for NHL was performed. Patients were given a tracer administered dose of 185 MBq In-111-ibritumomab tiuxetan on day 0, evaluated with dosimetry, and then a therapeutic administered activity of 7.4–15 MBq/kg Y-90-ibritumomab tiuxetan on day 7. The residence times for Y-90 in blood and major organs were estimated from In-111 [14]. One of the findings was that the median absorbed dose for Y-90 was 0.97 Gy (sacral image-derived method) to red marrow and that the haematological toxicity did not correlate with estimates of red marrow radiation absorbed dose [14].

The lack of standardised dosimetric practice is due in part to the relatively low numbers of patients treated at any one centre and due to the lack of medical physicists involved in dosimetry. However the increasing number of multi-centre trials involving TRT will enable more data to be collated and processed according to similar protocols [15–24].

Macro-dosimetry

Patient-specific absorbed dose calculations for tumours and for normal organs present two main challenges. The first, and arguably the most significant barrier to routine accurate dosimetry, is that of image quantification, by which the counts recorded in an image may be converted to absolute values of activity. The second issue that arises is that of the absorbed dose calculation itself, and particularly the need to deal with problems caused by a non-uniform uptake of activity and by non-standard organ geometries. A comprehensive overview on methods and instrumentation for dosimetry is compiled by the MIRDO committee and published in pamphlet

[25]. The ICRU 67 report [12] summarizes the current status of internal dosimetry including small scale and macro dosimetry as well as radiobiological considerations. For the assessment of the biokinetics (the “time-activity curve”) for pre-therapeutic or therapeutic dose calculations several methods can be used according to their respective capabilities.

Scintillation camera imaging

Photons are emitted in the patient and undergo a certain number of interactions until they are (or are not) finally detected. The photon transport depends on the interaction probabilities in tissue, which vary within the body, arising in attenuation and scatter of the photons. A minor part of the photons emerging from the patient body pass through a collimator, whose role is to make sure that only orthogonal projections of the source will impinge on the crystal. The photons then interact in the crystal creating scintillation light that is detected by a position sensitive array of light sensitive detectors (i.e. PM, photo multiplying tubes). By using appropriate electronics for the conversion of the light to an electrical signal the position and the energy of the impinging photon which falls within a predetermined energy window is registered as a count in the image. The counts are then used to quantify the activity distribution in the patient. by using e.g. regions of interest (ROI) techniques. All these processes have to be considered for activity quantification calculations. The main corrections needed for absolute quantification are attenuation, scatter, collimator efficiency, detector sensitivity, septal penetration and eventually high count rate corrections.

At a low pulse rate, the number of counts collected during a preset time interval is limited, which makes the statistical uncertainty high and produces noisy images. However the time resolution of the camera has to be considered at high activities (such as those encountered for therapeutic applications) and thus for high photon fluence rates that impinge on the scintillation crystal.

When using radionuclides emitting high energy photons, large septal penetration can occur, and therefore images can no longer be considered as orthogonal projections of an activity distribution. An accurate method of revealing such effects is to use Monte Carlo methods for simulating the total process of photon transport and interactions. For example for ^{131}I , the scatter component is complex, due to the higher principal energy (364 keV), and the contribution of non-negligible higher energy photons (637 and 723 keV). Interactions that need to be modelled occur in the patient, the collimator and the camera head, and include septal penetration [26].

Planar image-based dosimetry

To date the majority of dosimetric calculations, where they have been carried out, have employed planar images. Mostly

the anterior-posterior method has been used for the quantification. Imaging is possible with gamma-emitting radionuclides that are used for therapy (for example I-131, Sm-153, Re-186 and Re-188), whilst in cases that pure beta-emitters have been administered, dose estimates have been made using a surrogate radioisotope such as In-111 for Y-90 [27]. Planar imaging is less resource intensive than SPECT or PET-based imaging and has a spatial resolution around 10 mm, although contrast is decreased and it is necessary to distinguish tumour or organ uptake from uptake in underlying or overlying organs. Also for the A/P method the matching of the two projections and the transmission image is crucial for accurate quantification. Planar imaging has been used widely in many recent clinical studies [28–39].

SPECT image-based dosimetry

The disadvantage of planar imaging is the lack of three-dimensional information. This can be partially solved by the addition of three-dimensional anatomical images from CT or MRI [28, 40–45] although this will not yield the true 3D-distribution of radioactivity. As the conjugate view method cannot correct appropriately for overlapping tissues quantitative SPECT imaging leads to a more accurate determination of the actual tissue activity concentration. It is particularly advantageous for measuring organ activities in body structures with overlying structures [25]. Examples of the application of this technique to preclinical and clinical studies can be found in [46–73]. As well as the increased resources required to obtain a time-sequential series of SPECT scans following the administration of a therapy or pre-therapy tracer radiopharmaceutical, post-acquisition image processing is also more involved. The most notable of these is image reconstruction, for which a number of algorithms have been developed. However, the ability of SPECT imaging to identify the distribution of uptake within the target organ offers the potential in many cases for improved dosimetric accuracy.

Quantitative SPECT imaging

Emission tomography methods significantly reduce the macroscopic superimposition of activity in the reconstructed data and permit the determination of the activity volume on a macroscopic scale. Tomographic image reconstruction can be performed by analytical methods, using filtered back-projection, although many contemporary reconstruction methods now work on an iterative basis where the aim is to generate a set of estimated projections from a first guess of the activity distribution. The estimated projections are compared to the measured projections and updated based on the differences. The comparison, updating, and stopping criterion can be performed based on various approaches, e.g. the maximum-likelihood or the ordered-subsets expectation maximization algorithms. An advantage of the iterative methods is that compen-

sation for physical limitations can be modelled in the reconstruction process [74]. It is also possible to account for scatter during the iterative reconstruction process [75]. For a more explicit review of reconstruction algorithms in SPECT is found in Bruyant [76] and the textbook by Wernick and Aarsvold [77].

In SPECT imaging, the attenuation of homogeneous regions can be estimated using a body contour and a single value of the effective attenuation coefficient. For non-homogeneous regions, a patient-specific attenuation map is required. This can be obtained from scintillation-camera transmission scanning [78], CT [79, 80], or by using segmented scatter-emission images [81, 82]. Attenuation corrections can be performed either on the projection images, on the reconstructed images, or as part of an iterative reconstruction method. A full review of attenuation correction for emission tomography is given by Zaidi and Hasegawa [83] and also addressed in [77].

The problem of image quantification for therapy radionuclides, particularly for I-131, is exacerbated by the fact that most of the cameras are optimised for diagnostic imaging with Tc-99m.

Monte Carlo methods and quantitative SPECT imaging

Sufficient image quantification is only possible if all effects that degrade the quantitative content of the image have been corrected for. Monte Carlo simulations are an appealing tool that can help to model interactions occurring in the patient and in the detector system. This is helpful to develop and test correction techniques, and to help to define detector geometries better suited to quantitative imaging. As a consequence there are a growing number of articles [84, 85] and textbooks [86, 87] being published in the field of nuclear medicine that involve Monte Carlo techniques particularly with respect to quantitative imaging.

There are basically two kinds of Monte Carlo codes that can be used in nuclear imaging: *Generic Monte Carlo codes* and *Specific Monte Carlo codes*.

Generic Monte Carlo codes come from the world of high energy physics. They were mostly created in major nuclear research centres, and were developed to deal with radiation propagation in matter. Codes like ETRAN and its derivatives [88], EGS [89], MCNP [90] or Geant [91] belong to that category. They have been widely used by the scientific community and possess an established user database. They usually are part of an extensive research program – i.e. involving several permanent people committed to the development, debugging and maintenance of the code. This explains why these codes can generally be considered as standards against which other codes can benchmark. One major drawback is that they usually have not been designed to deal explicitly with nuclear imaging. This often makes it very difficult to use them within that area. For example, it is important to

make sure that ‘low energies’ such as those encountered in nuclear imaging are dealt with correctly.

Specific Monte Carlo codes, on the other hand, have been specifically designed for nuclear imaging. They can be differentiated by the way detection modelling is dealt with: in SPECT for example, some codes model explicitly interactions that occur in the collimator, other just consider photons that impact the detection head with the right solid angle (optical selection). The main possible drawback of ‘homemade’ Monte Carlo codes is the lack of support with time: Being mostly the product of a single lab, the continuity of a given code is often not granted. Also the way physics interactions are dealt with is in general less reviewed – or at least by a smaller user community – than for general Monte Carlo codes.

A collaborative effort has been carried out recently by a group of laboratories involved in the field in order to create a Monte Carlo code dedicated to nuclear imaging but based on a generic Monte Carlo code. That code, Gate [92] is based on Geant4. The user can create the experiment through the use of a macro language via a dedicated scripting mechanism that extends the native command interpreter of Geant4 and allows performing and controlling the Monte Carlo simula-

tion in an intuitive manner (<http://www-lphe.epfl.ch/~PET/research/gate/>).

As an example in Figure 1 a Monte Carlo simulation of the influence of septal penetration and scatter of I-131 photons on a high energy collimator of a gamma camera is shown (top left: resulting image, top right: scatter only, bottom left: septal penetration, bottom right: geometric photons). The numbers in the upper right corner denote the percentage of photons. In the case of I-131 only 47% of detected photons counted by a gamma camera are geometric photons. The rest comes either from septal penetration or scatter.

One major limit of Monte Carlo methods is linked to the statistic required to accurately simulate a given experimental setting: The number of simulated particles has to be very high, and therefore implies heavy computing power.

In SPECT, photons that reach the detector head first impact the collimator. Since only one out of 10000 photons – or less – that hit the detector head actually cross the collimator and are detected; this highlights how inefficient this process is from a computing perspective.

In order to decrease computing time, analytical modelling of physical effects can sometimes be carried out, such as

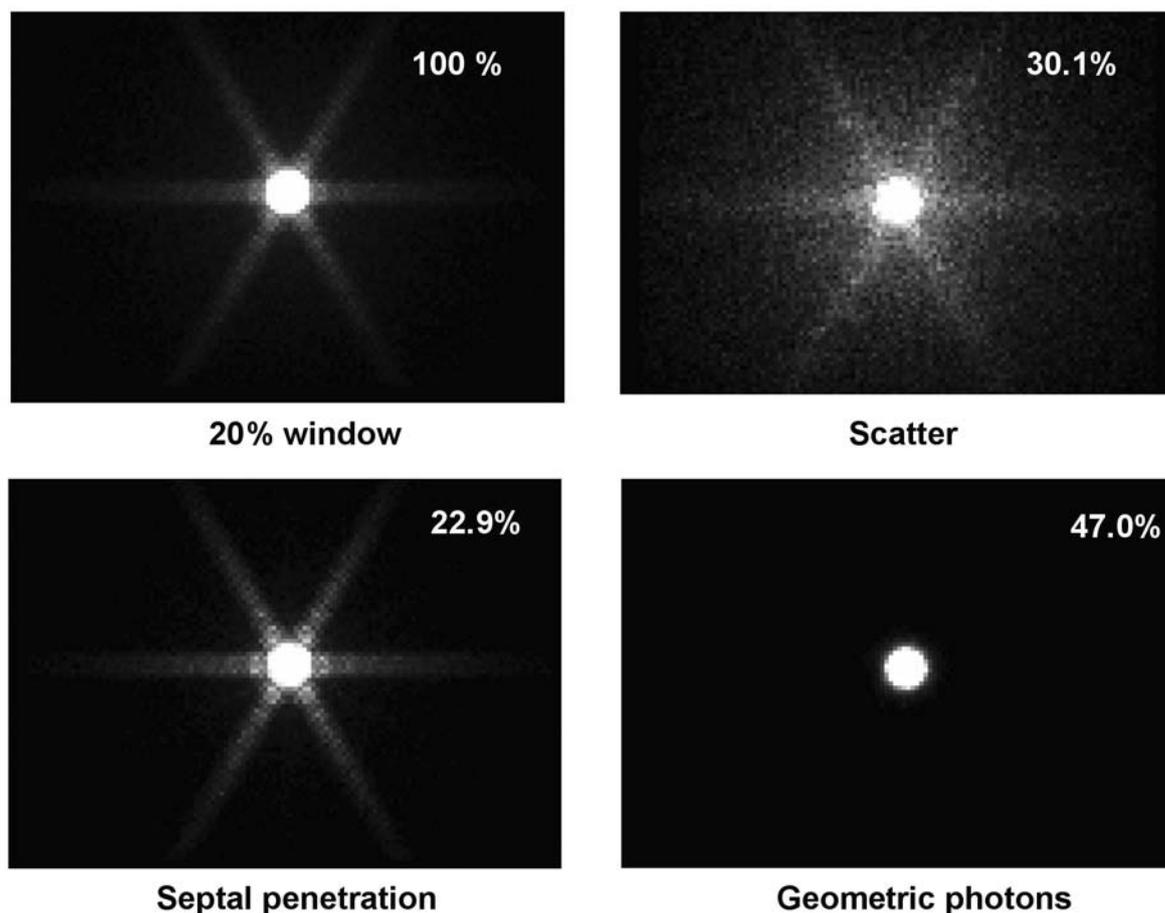


Figure 1 Monte Carlo simulation of the influence of septal penetration and scatter of I-131 photons on a high energy collimator of a gamma camera (top left: resulting image, top right: scatter only, bottom left: septal penetration, bottom right: geometric photons).

optical selection of photons that impinge the collimator, but this may not be always feasible: For example, when modelling gamma cameras for high energy radionuclides such as I-131, one has to consider explicit interaction modelling in the collimator, since septal penetration cannot be neglected in that case.

Variance reduction techniques can be implemented, but are not available in every code proposed to the scientific community. The validation of those techniques is itself a field of research, so one has to be very cautious when dealing with variance reduction.

Monte Carlo modelling of radiation interactions in matter fall in the ‘embarrassingly parallel problem’ category: Photons that interact with the detector are independent, and therefore it is equivalent to simulate 10^9 photons on a single machine or 10^8 photons on 10 different machines, thus paving the way for cluster computing [93]. Apart from the trivial caveat related to random seed generation, one has to be aware of some specific aspects of image detection, for example dead time modelling, or pileup effect implementation require serious attention to the simulation setup in a parallel environment.

Another drastic limitation is the difficulty to validate the results given by a simulation. Experimental validation has to be carried out for simple i.e. feasible in practice setting, that may not allow for as thorough a validation as would be required.

PET-based dosimetry

PET is presently the most accurate method for the determination of activity concentrations in tissue. PET is based on electronic collimation and thereby offers a wide acceptance angle for detecting emitted annihilation photons. Consequently, the sensitivity of PET per disintegration with comparable axial fields of view is two orders of magnitude greater than that of SPECT cameras. Quantification techniques are well established with PET. For dosimetry, PET offers improved spatial resolution over SPECT. The measured line integrals must be corrected for a number of background and physical effects before reconstruction, such as subtraction of random coincidences, detector normalization, dead time, attenuation and scatter corrections.

In PET, correction for attenuation depends on the total distance travelled by both annihilation photons and is independent of the emission point along the ray defined by these photons. The most accurate attenuation correction techniques are based on measured transmission data acquired before (pre-injection), during (simultaneous) or after (post-injection) the emission scan. Alternative methods to compensate for photon attenuation in reconstructed images use assumed distribution and boundary of attenuation coefficients, segmented transmission images, or consistency condition criteria [94].

PET imaging can be considered for treatment planning but ideally requires the use of a radioisotope from the same ele-

ment as that used for treatment (for example I-124 for I-131 or Y-86 for Y-90). I-124 has been applied to dosimetric assessments as early as 1986 [95] particularly for the dosimetry of radioiodine therapy of benign thyroid diseases [96, 97]. In 1991 the use of I-124 was proposed for quantifying in vivo tumor concentration and biodistribution for radioimmunotherapy [98–100]. An additional application was the approach to treatment planning of I-131 mIBG targeted radiotherapy [101]. Due to the complex decay process of I-124, the quantification process cannot be performed in the same way as for F-18. Pentlow et al. [102] measured resolution, linearity and the ability to quantify the activity contents of imaged spheres of different sizes and activities in different background activities. It was shown that the quantification process for I-124 could reproduce the activities administered. Compared to conventional PET nuclides, resolution and quantification were only slightly degraded [102, 103]. In addition, the sphere detectability was also only slightly worse if imaging time was increased to compensate for the lower positron abundance.

PET with I-124 was also successfully applied to the measurement of thyroid volume [104, 105]. Today’s state of the art of PET I-124 based thyroid dosimetry is described in a recent paper by Sgouros et al. [106] in which it shown that when using the PET results as input to a fully 3D dose planning program spatial distributions of absorbed dose, isodose contours, dose-volume histograms and mean absorbed dose estimates can be obtained. An example of PET based dosimetry is shown in Figure 2. In this figure summed coronal I-124 PET image slices obtained on day of I-124 administration (day 0) and on subsequent 2 days are shown in conjunction with the absorbed dose map for tumor 2.

Another application of PET quantification to dosimetry is the use of Y-86 for therapy planning of somatostatin receptor positive tumours [107–114]. The complex decay process of Y-86, however, makes the use of extensive corrections for quantification necessary which are not easily implemented into standard PET or PET/CT scanners. Helisch et al. [112] e.g. showed that the image quality and quantification process is superior when using Y-86-DOTA-Phe1-Tyr3-octreotide compared to In-111-pentetretotide. They conclude that compared to Y-86, dosimetry with In-111 overestimated doses to kidneys and spleen, whereas the absorbed dose to the tumour-free liver was underestimated. However, both dosimetric approaches detected the two patients with an exceptionally high radiation burden to the kidneys that carried a potential risk of renal failure following radionuclide therapy [113].

When applying appropriate corrections to the PET images a dose dependence of the radiation nephrotoxicity after Y-90-DOTATOC therapy was shown [114]. Individual renal volume, dose rate, and fractionation play important roles in an accurate dosimetry estimation that enables prediction of risk of renal function impairment [114].

In the near future other radioisotopes such as Ga-66 [115] or Ce-134/La-134, a radionuclide generator producing an

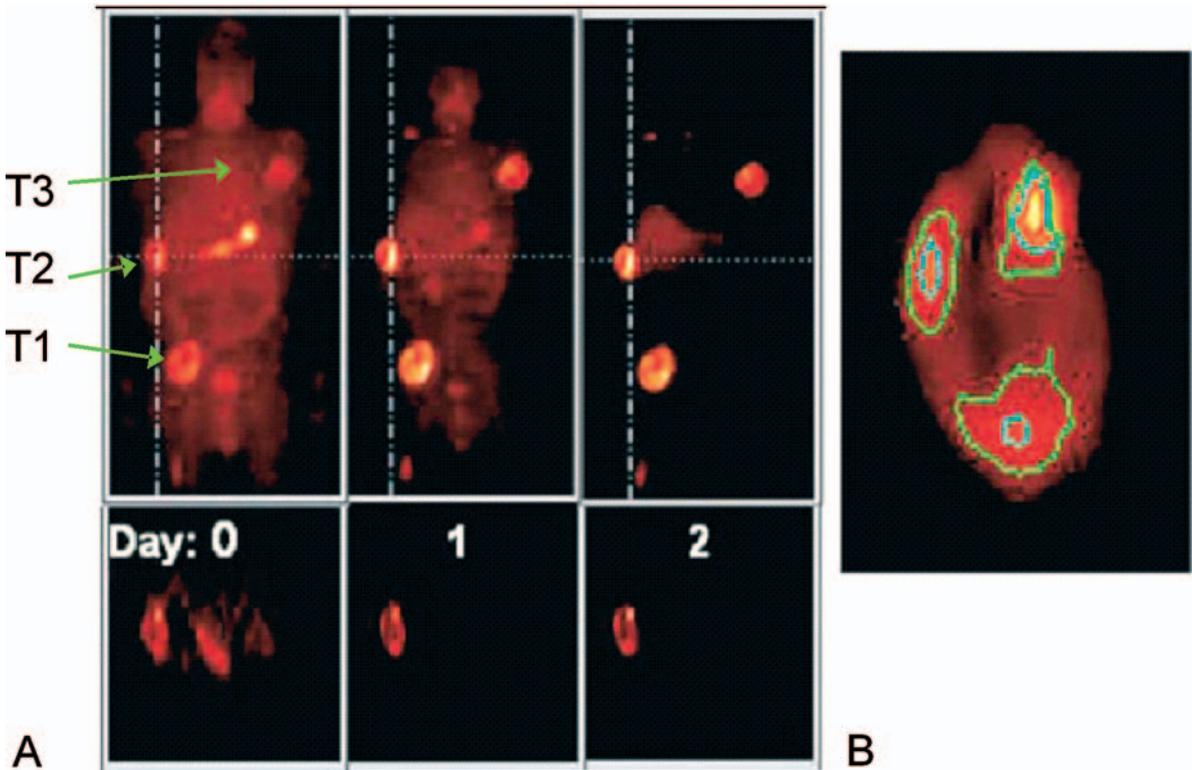


Figure 2 Example of PET based dosimetry (taken from Sgouros et al. [106]).
 (A) Summed coronal I-124 PET image slices obtained on day of I-124 administration (day 0) and on subsequent 2 days are depicted using same intensity level. Cross-hairs show plane of intersection for corresponding transverse slices through tumor 2, shown immediately below coronal images.
 (B) Image of absorbed dose distribution in tumor 2, magnified to highlight spatial distribution of absorbed dose within this tumor. Color-coded isodose contours are superimposed as follows: yellow = 75%, red = 50%, blue = 25%, and green = 10% of maximum absorbed dose to tumor (400 Gy). Three different foci of enhanced absorbed dose are observed and designated 1–3 as shown.

Reprinted by permission of the Society of Nuclear Medicine from Sgouros et al. [106].

Auger electron- and positron-emitting radionuclide [116], may also play an important role for PET based dosimetry for targeted radiotherapy.

Problems that have to be overcome include

- many of the surrogate isotopes used have such a short half-life that the time-activity curve does not reflect the complete biokinetics of the radionuclide used for therapy (such as Y-86/Y-90);
- special quantification procedures have to be performed as the standard quantification procedures fail due to additional gamma emissions of the isotopes used which are detected in the coincidence window (such as Y-86) of the PET systems;
- the availability of the PET-radiopharmaceutical often is restricted to very few centres which have access to a cyclotron for nuclide production;
- the software of newer PET/CT systems does not easily allow the application of non-standard corrections.

Three-dimensional dosimetry

In volumes-of-interest that are large relative to the spatial resolution of the imaging system for a given radionuclide, it is often possible to discern a heterogeneous uptake of a radio-pharmaceutical throughout a tumour or organ. In this case it can be misleading to quote a mean absorbed dose, with the problem exacerbated by the difficulty of delineating an outline within which the absorbed dose is to be calculated. One possible solution is to quote a maximum absorbed dose, although overall response is likely to be dependent on the extent of the volume that receives a low absorbed dose. A more comprehensive approach is to calculate the absorbed dose distribution throughout the tumour and generate dose-volume histograms [12]. This can be achieved by registering sequential tomographic data so that each voxel within the VOI occupies the same coordinate throughout the series of scans. The mean absorbed dose in each voxel can then be calculated independently for each coordinate [117]. For this

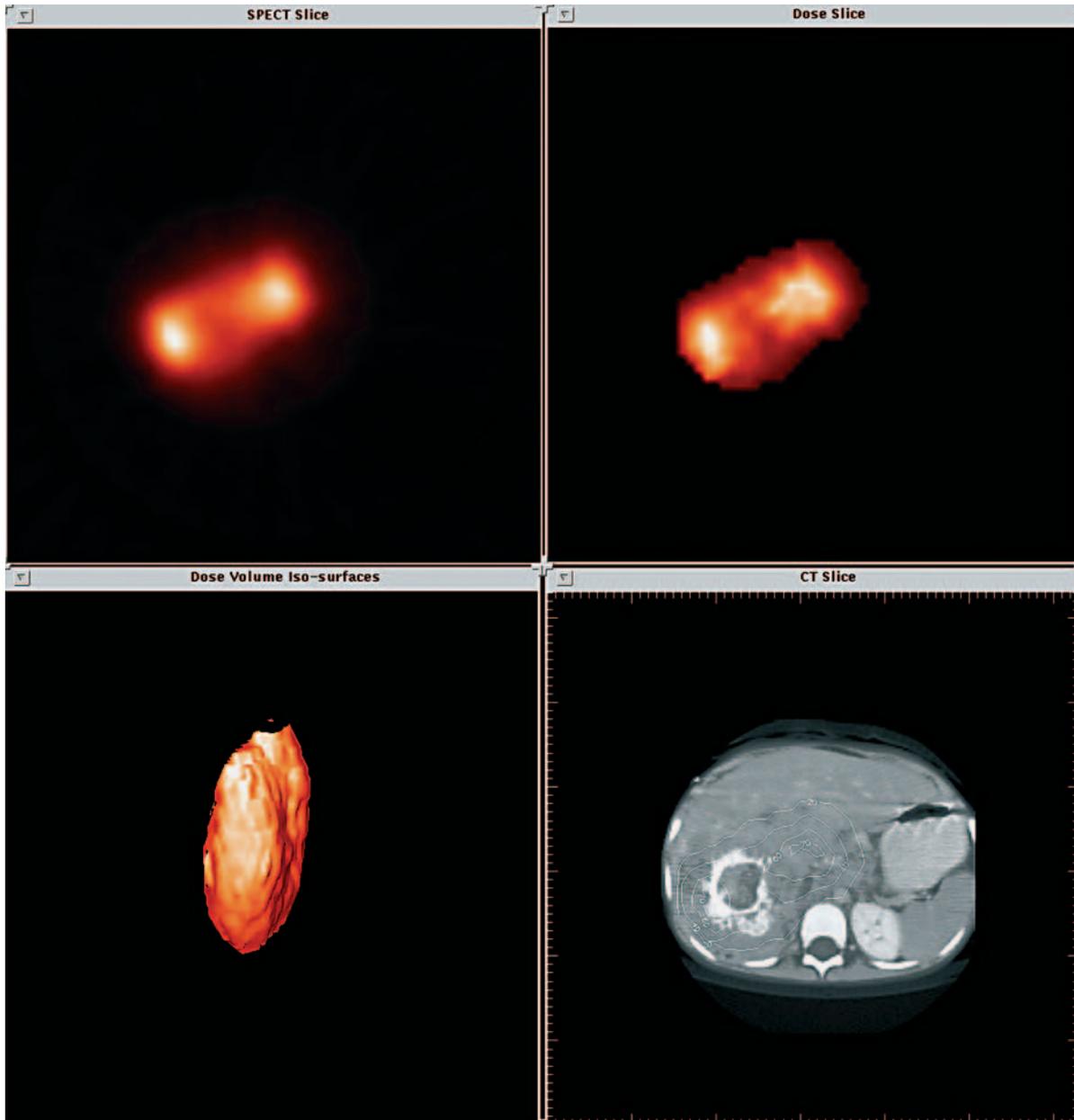


Figure 3 Transaxial slice of a dose distribution resulting from I-131 mIBG therapy of neuroblastoma, Top Left: SPECT slice acquired post-therapy. Top right: Corresponding absorbed dose distribution. Bottom left: Rendered view of absorbed dose distribution. Bottom right: Isodose contours from targeted therapy superimposed onto registered CT slice.

technique voxel S values are required. The MIRD pamphlet 17 [118] gives S values for a range of radionuclides for voxels with edge 0.1 mm, 3 mm and 6 mm. Image registration is becoming a more routinely used tool in medicine, due largely to an increasing interest in the incorporation of functional and MR data with CT for external beam radiotherapy planning and by the advent of dual modality scanners [119]. The voxel based calculation of absorbed dose distributions, however, requires specialised software solutions which, at the time of writing, are not commercially available.

An example of the application of SPECT to three-dimensional dose calculations is shown in Figure 3 in which a transaxial slice of a dose distribution resulting from I-131 mIBG therapy of neuroblastoma can be seen. On the top left a SPECT slice acquired post-therapy, on the top right the corresponding absorbed dose distribution, on the bottom left the rendered view of absorbed dose distribution and on the bottom right the isodose contours from targeted therapy superimposed onto registered CT slice are shown.

Conclusions

Internal dosimetry for TRT is a field of research that is attracting increasing attention. Developments in methodology and the increase in computing power that has been employed successfully for external beam radiotherapy have now enabled routine and accurate dosimetry to become a realisable goal in the near future. Many tools and techniques are now available to physicists and clinicians to enable absorbed dose calculations to both target and critical organs-at-risk. The challenge now facing nuclear medicine is to improve these methodologies to be routinely available to the clinic, to ensure common standard operating procedures between centres and in particular to correlate response criteria with absorbed dose estimates. This will provide a solid grounding for planning patient treatment on an individual basis, and will lead to radical improvements in the understanding and administration of targeted radiotherapy and it will provide the clinicians with the tools essential for the full evaluation and optimisation of ongoing and newly emerging therapies.

Although clinical dosimetry requires standardized procedures for absorbed dose calculations, it is known that there is a heterogeneous activity distribution in all organs or tumours. The radiopharmaceuticals per se are targeting special tissue compartments and thus inherently heterogeneous in their distributions. The calculated absorbed doses or mean absorbed doses are based on the input of the spatial distribution of activity that relies on the imaging modality used. Thus, in future, internal dosimetry with radionuclides is in the urgent need of high resolution imaging of activity distributions.

References

- [1] Chatal, J.F., Hoefnagel, C.A.: Radionuclide therapy. *Lancet* **354** (1999) 931–935
- [2] Nuis, A.: Health protection of individuals against the dangers of ionising radiation in relation to medical exposure: Council directive 97/43 EURATOM 30-6-1997
- [3] Dept of Health. The Ionising Radiation (Medical Exposure) Regulations 2000. SI 2000 No. 1059. 2000
- [4] DeNardo, S.J.: Tumor-targeted radionuclide therapy: Trial design driven by patient dosimetry. *J Nucl Med* **41** (2000) 104–106
- [5] Hoefnagel, C.A., Clarke, S.E., Fischer, M., Chatal, J.F., Lewington, V.J., Nilsson, S., Troncone, L., Vieira, M.R.: Radionuclide therapy practice and facilities in Europe. *EANM Radionuclide Therapy Committee. Eur J Nucl Med* **26** (1999) 277–82
- [6] Howell, R.W., Wessels, B.W., et al.: The MIRDO perspective 1999. Medical Internal Radiation Dose Committee. *J Nucl Med* **40** (1999) 3S–10S
- [7] Loevinger, R.B.: MIRDO primer for absorbed dose calculations. Society of Nuclear Medicine. New York 1988
- [8] Snyder, W.S., Ford, M.R., Warner, G.G., Watson, S.B.: Absorbed Dose per Unit Cumulated Activity for Selected Radionuclides and Organs (PART 1). Society of Nuclear Medicine. Reston, VA 1975
- [9] Marinelli, L., Quimby, E., Hine, G.: Dosage Determination with Radioactive Isotopes. II Practical Considerations in Therapy and Protection. *American Journal of Roent and Radium Therapy* **59** (1948) 260–280
- [10] ICRP53. International Commission on Radiological Protection. Radiation dose from Radiopharmaceuticals. ICRP Publication 53. Pergamon Press, New York 1988
- [11] Langmuir, V.K., Fowler, J.F., Knox, S.J., Wessels, B.W., Sutherland, R.M., Wong, J.Y.C.: Radiobiology of Radiolabeled Antibody Therapy As Applied to Tumor Dosimetry. *Medical Physics* **20** (1993) 601–610
- [12] ICRU Report 67 – Dose Specifications in Nuclear Medicine. ICRU 2002
- [13] Wiseman, G.A., Leigh, B., Erwin, W.D., Lamonica, D., Kornmehl, E., Spies, S.M., Silverman, D.H.S., Witzig, T.E., Sparks, R.B., White, C.A.: Radiation dosimetry results for Zevalin radioimmunotherapy of rituximab-refractory non-Hodgkin lymphoma. *Cancer* **94** (2002) 1349–1357
- [14] Wiseman, G.A., White, C.A., Stabin, M., Dunn, W.L., Erwin, W., Dahlbom, M., Raubitschek, A., Karvelis, K., Schultheiss, T., Witzig, T.E., Belanger, R., Spies, S., Silverman, D.H.S., Berlfein, J.R., Ding, E., Grillo-Lopez, A.J.: Phase I/II Y-90-Zevalin (yttrium-90 ibritumomab tiuxetan, IDEC-Y2B8) radioimmunotherapy dosimetry results in relapsed or refractory non-Hodgkin's lymphoma. *European J Nucl Med* **27** (2000) 766–777
- [15] Vose, J.M., Wahl, R.L., Saleh, M., Rohatiner, A.Z., Knox, S.J., Radford, J.A., Zelenetz, A.D., Tidmarsh, G.F., Stagg, R.J., Kaminski, M.S.: Multicenter phase II study of iodine-131 tositumomab for chemotherapy-relapsed/refractory low-grade and transformed low-grade B-cell non-Hodgkin's lymphomas. *Journal of Clinical Oncology* **18** (2000) 1316–1323
- [16] Kostakoglu, L., Goldsmith, S.J., Buchegger, F., Lewington, V., Leonard, J.P., Hledge, T., Ketterer, N., Kovacovics, T., Valente, N., Bischof-Delaloye, A.: Preliminary results of a multicenter dosimetry, efficacy and safety study with iodine-131 tositumomab in treatment of non-Hodgkin's lymphoma (NHL). *European J Nucl Med* **28** (2001) OS73
- [17] Wiseman, G.A., White, C.A., Sparks, R.B., Erwin, W.D., Podoloff, D.A., Lamonica, D., Bartlett, N.L., Parker, J.A., Dunn, W.L., Spies, S.M., Belanger, R., Witzig, T.E., Leigh, B.R.: Biodistribution and dosimetry results from a phase III prospectively randomized controlled trial of Zevalin (TM) radioimmunotherapy for low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. *Critical Reviews in Oncology Hematology* **39** (2001) 181–194
- [18] Rajendran, J.G., Eary, J.F., Bensinger, W., Durack, L.D., Vernon, C., Fritzberg, A.: High-dose Ho-166-DOTMP in myeloablative treatment of multiple myeloma: Pharmacokinetics, biodistribution, and absorbed dose estimation. *J Nucl Med* **43** (2002) 1383–1390
- [19] Virgolini, I., Britton, K., Buscombe, J., Moncayo, R., Paganelli, G., Riva, P.: In-111- and Y-90-DOTA-1anreotide: Results and implications of the MAURITIUS trial. *Seminars in Nuclear Medicine* **32** (2002) 148–155
- [20] Flower, M.A., Fielding, S.L.: Radiation dosimetry for I-131-mIBG therapy of neuroblastoma. *Physics in Medicine and Biology* **41** (1996) 1933–1940
- [21] Luster, M., Sherman, S.I., Skarulis, M.C., Reynolds, J.R., Lassmann, M., Hanscheid, H., Reiners, C.: Comparison of radioiodine biokinetics following the administration of recombinant human thyroid stimulating hormone and after thyroid hormone withdrawal in thyroid carcinoma. *European J Nucl Med and Molecular Imaging* **30** (2003) 1371–1377
- [22] Koral, K.F., Dewaraja, Y., Li, J., Lin, Q., Regan, D.D., Zasadny, K.R., Rommelfanger, S.G., Francis, I.R., Kaminski, M.S., Wahl, R.L.: Update on hybrid conjugate-view SPECT tumor dosimetry and response in 131I-tositumomab therapy of previously untreated lymphoma patients. *J Nucl Med* **44** (2003) 457–464
- [23] Kendler, D., Donnemiller, E., Oberladstatter, M., Erler, H., Gabriel, M., Riccabona, G.: An individual dosimetric approach to 153Sm-EDTMP therapy for pain palliation in bone metastases in correlation with clinical results. *Nucl Med Commun* **25** (2004) 367–373
- [24] Meredith, R., Shen, S., Macey, D., Khazaeli, M.B., Carey, D., Robert, F., LoBuglio, A.: Comparison of biodistribution, dosimetry, and outcome from clinical trials of radionuclide-CC49 antibody therapy. *Cancer Biother Radiopharm* **18** (2003) 393–404
- [25] Siegel, J.A., Thomas, S.R., Stubbs, J.B., Stabin, M.G., Hays, M.T., Koral, K.F., Robertson, J.S., Howell, R.W., Wessels, B.W., Fisher, D.R., Weber, D.A., Brill, A.B.: MIRDO pamphlet no. 16: Techniques for

- quantitative radiopharmaceutical biodistribution data acquisition and analysis for use in human radiation dose estimates. *J Nucl Med* **40** (1999) 37S–61S
- [26] Dewaraja, Y.K., Ljungberg, M., Koral, K.F.: Accuracy of I-131 tumor quantification in radioimmunotherapy using SPECT imaging with an ultra-high-energy collimator: Monte Carlo study. *J Nucl Med* **41** (2000) 1760–1767
- [27] DeNardo, S.J., Kramer, E.L., O'Donnell, R.T., Richman, C.M., Salako, Q.A., Shen, S., Noz, M., Glenn, S.D., Ceriani, R.L., DeNardo, G.L.: Radioimmunotherapy for breast cancer using indium-111/yttrium-90 BrE-3: Results of a phase I clinical trial. *J Nucl Med* **38** (1997) 1180–1185
- [28] Sjogreen, K., Ljungberg, M., Strand, S.E.: An activity quantification method based on registration of CT and whole-body scintillation camera images, with application to I-131. *J Nucl Med* **43** (2002) 972–982
- [29] Koral, K.F., Zasadny, K.R., Swailm, F.M., Buchbinder, S.F., Francis, I.R., Kaminski, M.S., Wahl, R.L.: Importance of Intra-Therapy Single-Photon Emission Tomographic Imaging in Calculating Tumor Dosimetry for A Lymphoma Patient. *European J Nucl Med* **18** (1991) 432–435
- [30] Erdi, A.K., Wessels, B.W., Dejager, R., Erdi, Y.E., Atkins, F.B., Yorke, E.D., Smith, L., Huang, E., Smiddy, M., Murray, J., Varma, V.M., McCabe, R., McNellis, R., John, C., Ney, A., Nochomovitz, L., Hanna, M.G.: Tumor-activity confirmation and isodose curve display for patients receiving iodine-131-labeled 16.88-human monoclonal-antibody. *Cancer* **73** (1994) 932–944
- [31] Koral, K.F., Zasadny, K.R., Kessler, M.L., Luo, J.Q., Buchbinder, S.F., Kaminski, M.S., Francis, I., Wahl, R.L.: CT-SPECT fusion plus conjugate views for determining dosimetry in iodine-131-monoclonal antibody therapy of lymphoma patients. *J Nucl Med* **35** (1994) 1714–1720
- [32] Korppi-Tommola, E.T., Kairemo, K.J.A., Jekunen, A.P., Niskanen, E.O., Savolainen, S.E.: Double-tracer dosimetry of organs in assessment of bone marrow involvement by two monoclonal antibodies. *Acta Oncologica* **35** (1996) 357–365
- [33] DeNardo, S.J., DeNardo, G.L., Kukis, D.L., Shen, S., Kroger, L.A., DeNardo, D.A., Goldstein, D.S., Mirick, G.R., Salako, Q., Mausner, L.F., Srivastava, S.C., Meares, C.E.: Cu-67-2IT-BAT-Lym-1 pharmacokinetics, radiation dosimetry, toxicity and tumor regression in patients with lymphoma. *J Nucl Med* **40** (1999) 302–310
- [34] Koral, K.F., Li, J., Dewaraja, Y., Barrett, C.L., Regan, D.D., Zasadny, K.R., Rommelfanger, S.G., Francis, I.R., Kaminski, M.S., Wahl, R.L.: I-131 anti-B1 therapy/tracer uptake ratio using a new procedure for fusion of tracer images to computed tomography images. *Clinical Cancer Research* **5** (1999) 3004S–3009S
- [35] Lundqvist, H., Lubberink, M., Tolmachev, V., Lovqvist, A., Sundin, A., Beshara, S., Bruskin, A., Carlsson, J., Westlin, J.E.: Positron emission tomography and radioimmunotargeting – General aspects. *Acta Oncologica* **38** (1999) 335–341
- [36] Koral, K.F., Dewaraja, Y., Li, J., Barrett, C.L., Regan, D.D., Zasadny, K.R., Rommelfanger, S.G., Francis, I.R., Kaminski, M.S., Wahl, R.L.: Initial results for hybrid SPECT-conjugate-view tumor dosimetry in I-131-anti-B-1 antibody therapy of previously untreated patients with lymphoma. *J Nucl Med* **41** (2000) 1579–1586
- [37] Koral, K.F., Dewaraja, Y., Clarke, L.A., Li, J., Zasadny, K.R., Rommelfanger, S.G., Francis, I.R., Kaminski, M.S., Wahl, R.L.: Tumor-absorbed-dose estimates versus response in tositumomab therapy of previously untreated patients with follicular non-Hodgkin's lymphoma: Preliminary report. *Cancer Biotherapy and Radiopharmaceuticals* **15** (2000) 347–355
- [38] Koral, K.F., Francis, I.R., Kroll, S., Zasadny, K.R., Kaminski, M.S., Wahl, R.L.: Volume reduction versus radiation dose for tumors in previously untreated lymphoma patients who received iodine-131 tositumomab therapy – Conjugate views compared with a hybrid method. *Cancer* **94** (2002) 1258–1263
- [39] Orlova, A., Hoglund, J., Lubberink, M., Lebeda, O., Gedda, L., Lundqvist, H., Tolmachev, V., Sundin, A.: Comparative biodistribution of the radiohalogenated (Br, I and At) antibody A33. Implications for in vivo dosimetry. *Cancer Biotherapy and Radiopharmaceuticals* **17** (2002) 385–396
- [40] Siegel, J.A., Wu, R.K., Maurer, A.H.: The Buildup Factor – Effect of Scatter on Absolute Volume Determination. *J Nucl Med* **26** (1985) 390–394
- [41] Guy, M.J., Castellano-Smith, I.A., Flower, M.A., Flux, G.D., Ott, R.J., Visvikis, D.: DETECT – Dual energy transmission estimation CT – for improved attenuation correction in SPECT and PET. *IEEE Transactions on Nuclear Science* **45** (1998) 1261–1267
- [42] Kolbert, K.S., Sgouros, G., Scott, A.M., Bronstein, J.E., Malane, R.A., Zhang, J.J., Kalaigian, H., McNamara, S., Schwartz, L., Larson, S.M.: Implementation and evaluation of patient-specific three-dimensional internal dosimetry. *J Nucl Med* **38** (1997) 301–308
- [43] Laitinen, J.O., Kairemo, K.J.A., Jekunen, A.P., Korppi-Tommola, T., Tenhunen, M.: The effect of three dimensional activity distribution on the dose planning of radioimmunotherapy for patients with advanced intraperitoneal pseudomyxoma. *Cancer* **80** (1997) 2545–2552
- [44] Sgouros, G., Squeri, S., Ballangrud, A.M., Kolbert, K.S., Teitcher, J.B., Panageas, K.S., Finn, R.D., Divgi, C.R., Larson, S.M., Zelenetz, A.D.: Patient-specific, 3-dimensional dosimetry in non-Hodgkin's lymphoma patients treated with I-131-anti-B1 antibody: Assessment of tumor dose-response. *J Nucl Med* **44** (2003) 260–268
- [45] Papavasileiou, P., Flux, G.D., Flower, M.A., Guy, M.J.: Automated CT marker segmentation for image registration in radionuclide therapy. *Physics in Medicine and Biology* **46** (2001) N269–N279
- [46] Strand, S.E., Jonsson, B.A., Ljungberg, M., Tennvall, J.: Radioimmunotherapy Dosimetry – A Review. *Acta Oncologica* **32** (1993) 807–817
- [47] Holmes, T., Mackie, T.R.: A Filtered Backprojection Dose Calculation Method for Inverse Treatment Planning. *Medical Physics* **21** (1994) 303–313
- [48] Larson, S.M., Divgi, C.R., Scott, A., Sgouros, G., Graham, M.C., Kostakoglu, L., Scheinberg, D., Cheung, N.K.V., Schlom, J., Finn, R.D.: Current status of radioimmunotherapy. *Nuclear Medicine and Biology* **21** (1994) 785–792
- [49] Strand, S.E., Ljungberg, M., Tennvall, J., Norrgren, K., Garkavij, M.: Radio-Immunotherapy Dosimetry with Special Emphasis on Spect Quantification and Extracorporeal Immuno-Adsorption. *Medical & Biological Engineering & Computing* **32** (1994) 551–561
- [50] Turner, J.H., Claringbold, P.G., Klemp, P.F.B., Cameron, P.J., Martindale, A.A., Glancy, R.J., Norman, P.E., Hetherington, E.L., Najdovski, L., Lambrecht, R.M.: Ho-166-Microsphere Liver Radiotherapy – A Preclinical Spect Dosimetry Study in the Pig. *Nuclear Medicine Communications* **15** (1994) 545–553
- [51] Giap, H.B., Macey, D.J., Bayouth, J.E., Boyer, A.L.: Validation of a dose-point kernel convolution technique for internal dosimetry. *Physics in Medicine and Biology* **40** (1995) 365–381
- [52] Giap, H.B., Macey, D.J., Podoloff, D.A.: Development of A SPECT-Based 3-Dimensional Treatment Planning System for Radioimmunotherapy. *J Nucl Med* **36** (1995) 1885–1894
- [53] Siegel, J.A., Zeiger, L.S., Order, S.E., Wallner, P.E.: Quantitative bremsstrahlung single-photon emission computed tomographic imaging – use for volume, activity, and absorbed dose calculations. *International Journal of Radiation Oncology Biology Physics* **31** (1995) 953–958
- [54] Furchang, E.E., Chui, C.S., Sgouros, G.: A Monte Carlo approach to patient-specific dosimetry. *Medical Physics* **23** (1996) 1523–1529
- [55] Tristram, M., Alaamer, A.S., Fleming, J.S., Lewington, V.J., Zivanovic, M.A.: Iodine-131-metaiodobenzylguanidine dosimetry in cancer therapy: Risk versus benefit. *J Nucl Med* **37** (1996) 1058–1063
- [56] Behr, T.M., Sharkey, R.M., Juweid, M.E., Dunn, R.M., Ying, Z.L., Zhang, C.H., Siegel, J.A., Goldenberg, D.M.: Variables influencing tumor dosimetry in radioimmunotherapy of CEA-expressing cancers with anti-CEA and antimucin monoclonal antibodies. *J Nucl Med* **38** (1997) 409–418
- [57] Behr, T.M., Sharkey, R.M., Juweid, M.E., Dunn, R.M., Vagg, R.C., Ying, Z.L., Zhang, C.H., Swayne, L.C., Vardi, Y., Siegel, J.A., Goldenberg, D.M.: Phase I/II clinical radioimmunotherapy with an iodine-131-labeled anti-carcinoembryonic antigen murine monoclonal antibody IgG. *J Nucl Med* **38** (1997) 858–870

- [58] Flux, G.D., Webb, S., Ott, R.J., Chittenden, S.J., Thomas, R.: Three-dimensional dosimetry for intraliesional radionuclide therapy using mathematical modeling and multimodality imaging. *J Nucl Med* **38** (1997) 1059–1066
- [59] Furfhang, E.E., Chui, C.S., Kolbert, K.S., Larson, S.M., Sgouros, G.: Implementation of a Monte Carlo dosimetry method for patient-specific internal emitter therapy. *Medical Physics* **24** (1997) 1163–1172
- [60] Koral, K.F., Lin, S.H., Fessler, J.A., Kaminski, M.S., Wahl, R.L.: Preliminary results from intensity-based CT-SPECT fusion in I-131 anti-B1 monoclonal-antibody therapy of lymphoma. *Cancer* **80** (1997) 2538–2544
- [61] Leichner, P.K., Akabani, G., Colcher, D., Harrison, K.A., Hawkins, W.G., Eckblade, M., Baranowska-Kortylewicz, J., Augustine, S.C., Wisecarver, J., Tempero, M.A.: Patient-specific dosimetry of indium-111- and yttrium-90-labeled monoclonal antibody CC49. *J Nucl Med* **38** (1997) 512–516
- [62] Tempero, M., Leichner, P., Baranowska-Kortylewicz, J., Harrison, K., Augustine, S., Schlom, J., Anderson, J., Wisecarver, J., Colcher, D.: High-dose therapy with (90)yttrium-labeled monoclonal antibody CC49: A phase I trial. *Clinical Cancer Research* **6** (2000) 3095–3102
- [63] Colnot, D.R., Quak, J.J., Roos, J.C., van Lingen, A., Wilhelm, A.J., van Kamp, G.J., Huijgens, P.C., Snow, G.B., van Dongen, G.A.M.S.: Phase I therapy study of Re-186-labeled chimeric monoclonal antibody U36 in patients with squamous cell carcinoma of the head and neck. *J Nucl Med* **41** (2000) 1999–2010
- [64] Van Laere, K., Koole, M., Kauppinen, T., Monsieurs, M., Bouwens, L., Dierck, R.: Nonuniform transmission in brain SPECT using Tl-201, Gd-153, and Tc-99m static line sources: Anthropomorphic dosimetry studies and influence on brain quantification. *J Nucl Med* **41** (2000) 2051–2062
- [65] Gonzalez, D.E., Jaszczak, R.J., Bowsher, J.E., Akabani, G., Greer, K.L.: High-resolution absolute SPECT quantitation for I-131 distributions used in the treatment of lymphoma: A phantom study. *Transactions on Nuclear Science* **48** (2001) 707–714
- [66] Thierens, H.M., Monsieurs, M.A., Brans, B., Van Driessche, T., Christiaens, I., Dierckx, R.A.: Dosimetry from organ to cellular dimensions. *Computerized Medical Imaging and Graphics* **25** (2001) 187–193
- [67] Ljungberg, M., Sjogreen, K., Liu, X.W., Frey, E., Dewaraja, Y., Strand, S.E.: A 3-dimensional absorbed dose calculation method based on quantitative SPECT for radionuclide therapy: Evaluation for I-131 using Monte Carlo simulation. *J Nucl Med* **43** (2002) 1101–1109
- [68] Dewaraja, Y.K., Wilderman, S.J., Ljungberg, M., Koral, K.F., Zasadny, K., Kaminski, M.S.: Accurate Dosimetry in ¹³¹I Radionuclide Therapy Using Patient-Specific, 3-Dimensional Methods for SPECT Reconstruction and Absorbed Dose Calculation. *J Nucl Med* **46** (2005) 840–849
- [69] Boucek, J.A., Turner, J.H.: Validation of prospective whole-body bone marrow dosimetry by SPECT/CT multimodality imaging in (131)I-anti-CD20 rituximab radioimmunotherapy of non-Hodgkin's lymphoma. *Eur J Nucl Med Mol Imaging* **32** (2005) 458–469
- [70] De Jong, M., Valkema, R., Van Gameren, A., Van Boven, H., Bex, A., Van De Weyer, E.P., Burggraaf, J.D., Korner, M., Reubi, J.C., Krenning, E.P.: Inhomogeneous localization of radioactivity in the human kidney after injection of [(111)In-DTPA]octreotide. *J Nucl Med* **45** (2004) 1168–1171
- [71] King, M., Farncombe, T.: An overview of attenuation and scatter correction of planar and SPECT data for dosimetry studies. *Cancer Biother Radiopharm* **18** (2003) 181–190
- [72] Ljungberg, M., Frey, E., Sjogreen, K., Liu, X., Dewaraja, Y., Strand, S.E.: 3D absorbed dose calculations based on SPECT: evaluation for 111-In-90-Y therapy using Monte Carlo simulations. *Cancer Biother Radiopharm* **18** (2003) 99–107.
- [73] Guy, M.J., Flux, G.D., Papavasileiou, P., Flower, M.A., Ott, R.J.: RMDP: a dedicated package for 131I SPECT quantification, registration and patient-specific dosimetry. *Cancer Biother Radiopharm* **18** (2003) 61–69
- [74] Sjogreen, K., Ljungberg, M., Strand, S.E.: Parameters influencing volume and activity quantitation in SPECT. *Acta Oncol* **35** (1996) 323–330
- [75] Beekman, F.J., Kamphuis, C., Frey, E.C.: Scatter compensation methods in 3D iterative SPECT reconstruction: A simulation study. *Physics in Medicine and Biology* **42** (1997) 1619–1632
- [76] Bruyant, P.P.: Analytic and iterative reconstruction algorithms in SPECT. *J Nucl Med* **43** (2002) 1343–1358
- [77] Wernick, M., Aarsvold, J.: *Emission Tomography: The Fundamentals of PET and SPECT*. Academic Press, 2004
- [78] Bailey, D.L.: *Transmission scanning in emission tomography*. *Eur J Nucl Med* **25** (1998) 774–787
- [79] Ljungberg, M., Strand, S.E.: Attenuation and scatter correction in SPECT for sources in a nonhomogeneous object: a monte Carlo study. *J Nucl Med* **32** (1991) 1278–1284
- [80] Damen, E.M., Muller, S.H., Boersma, L.J., de Boer, R.W., Lebesque, J.V.: Quantifying local lung perfusion and ventilation using correlated SPECT and CT data. *J Nucl Med* **35** (1994) 784–792
- [81] King, M.A., Tsui, B.M., Pan, T.S., Glick, S.J., Soares, E.J.: Attenuation compensation for cardiac single-photon emission computed tomographic imaging: Part 2. Attenuation compensation algorithms. *J Nucl Cardiol* **3** (1996) 55–64
- [82] Licho, R., Glick, S.J., Xia, W., Pan, T.S., Penney, B.C., King, M.A.: Attenuation compensation in 99mTc SPECT brain imaging: a comparison of the use of attenuation maps derived from transmission versus emission data in normal scans. *J Nucl Med* **40** (1999) 456–463
- [83] Zaidi, H., Hasegawa, B.: Determination of the attenuation map in emission tomography. *J Nucl Med* **44** (2003) 291–315
- [84] Zaidi, H.: Relevance of accurate Monte Carlo Modeling in nuclear medical imaging. *Medical Physics* **26** (1999) 574–608
- [85] Buvat, I., Castiglioni, I.: Monte Carlo simulations in SPECT and PET. *The quarterly Journal of Nuclear Medicine* **46** (2002) 48–61
- [86] Ljungberg, M., Strand, S.E., King, M.A.: *Monte Carlo Calculation in Nuclear Medicine: Applications in Diagnostic Imaging*. IOP Publishing, Bristol and Philadelphia 1998
- [87] Haidi, H., Sgouros, G.: *Therapeutic Applications of Monte-Carlo Calculations in Nuclear Medicine*. IOP Publishing, Bristol and Philadelphia 2003
- [88] Berger, M.J.: MonteCarlo calculation of the penetration and diffusion of fast charged particles. In: Alder, B., Fernbach, S., Rotenberg, M. (eds.): *Methods in computational physics Vol. 1*. Academic Press, New York 1963
- [89] Nelson, W.R., Hirayama, H., Rogers, D.W.O.: *The EGS4 code system*. Stanford Linear Accelerator Center report SLAC-265, 1985
- [90] Briesmeister, J.F. (Ed.): *MCNP – A General Monte Carlo N-Particle Transport Code*. Los Alamos National Laboratory report LA-12625-M, November 1993
- [91] Agostinelli, S., Allison, J., Amakoe, K. et al.: Geant4 – a simulation toolkit. *Nuclear Instruments and Methods in Physics Research, NIM A* **506** (2003) 250–303
- [92] Jan, S., Santin, G., Strul, D., Staelens, S., Assie, K., Autret, D., Avner, S., Barbier, R., Bardies, M., Bloomfield, P.M., Brasse, D., Breton, V., Bruyndonckx, P., Buvat, I., Chatzioannou, A.F., Choi, Y., Chung, Y.H., Comtat, C., Donnarieix, D., Ferrer, L., Glick, S.J., Groiselle, C.J., Guez, D., Honore, P.F., Kerhoas-Cavata, S., Kirov, A.S., Kohli, V., Koole, M., Krieguer, M., van der Laan, D.J., Lamare, F., Largeron, G., Lartizien, C., Lazaro, D., Maas, M.C., Maigne, L., Mayet, F., Melot, F., Merheb, C., Pennacchio, E., Perez, J., Pietrzyk, U., Rannou, F.R., Rey, M., Schaart, D.R., Schmidlein, C.R., Simon, L., Song, T.Y., Vieira, J.M., Visvikis, D., Van de Walle, R., Wieers, E., Morel, C.: GATE: a simulation toolkit for PET and SPECT. *Phys Med Biol* **49** (2004) 4543–4561
- [93] Dewaraja, Y.K., Ljungberg, M., Bose, A., Majumdar, A., Koral, K.A.: parallel Monte Carlo code for planar and SPECT imaging: implementation, verification and applications in I-131 SPECT. *Comp Meth Progr Biomed* **67** (2002) 115–124
- [94] Zaidi, H., Montandon, M.L., Slosman, D.O.: Magnetic resonance imaging-guided attenuation and scatter corrections in three-dimensional brain positron emission tomography. *Med Phys* **30** (2003) 937–948
- [95] Akbari, R.B., Ott, R.J., Trott, N.G., Sharma, H.L., Smith, A.G.: Radionuclide purity and radiation dosimetry of ¹²⁴I used in positron tomography of the thyroid. *Phys Med Biol* **31** (1986) 789–791

- [96] Ott, R.J., Batty, V., Webb, B.S., Flower, M.A., Leach, M.O., Clack, R., Marsden, P.K., McCready, V.R., Bateman, J.E., Sharma, H., et al.: Measurement of radiation dose to the thyroid using positron emission tomography. *Br J Radiol* **60** (1987) 245–251
- [97] Flower, M.A., Irvine, A.T., Ott, R.J., Kabir, F., McCready, V.R., Harmer, C.L., Sharma, H.L., Smith, A.G.: Thyroid imaging using positron emission tomography – a comparison with ultrasound imaging and conventional scintigraphy in thyrotoxicosis. *Br J Radiol* **63** (1990) 325–330
- [98] Westera, G., Reist, H.W., Buchegger, F., Heusser, C.H., Hardman, N., Pfeiffer, A., Sharma, H.L., von Schulthess, G.K., Mach, J.P.: Radio-immuno positron emission tomography with monoclonal antibodies: a new approach to quantifying in vivo tumour concentration and biodistribution for radioimmunotherapy. *Nucl Med Commun* **12** (1991) 429–437
- [99] Pentlow, K.S., Graham, M.C., Lambrecht, R.M., Cheung, N.K., Larson, S.M.: Quantitative imaging of I-124 using positron emission tomography with applications to radioimmunodiagnosis and radioimmunotherapy. *Med Phys* **18** (1991) 357–366
- [100] Larson, S.M., Pentlow, K.S., Volkow, N.D., Wolf, A.P., Finn, R.D., Lambrecht, R.M., Graham, M.C., Di Resta, G., Bendriem, B., Daghighian, F., et al.: PET scanning of iodine-124-3F9 as an approach to tumor dosimetry during treatment planning for radioimmunotherapy in a child with neuroblastoma. *J Nucl Med* **33** (1992) 2020–2023
- [101] Ott, R.J., Tait, D., Flower, M.A., Babich, J.W., Lambrecht, R.M.: Treatment planning for ¹³¹I-mIBG radiotherapy of neural crest tumours using 124I-mIBG positron emission tomography. *Br J Radiol* **65** (1992) 787–791
- [102] Pentlow, K.S., Graham, M.C., Lambrecht, R.M., Daghighian, F., Bacharach, S.L., Bendriem, B., Finn, R.D., Jordan, K., Kalaigian, H., Karp, J.S., Robeson, W.R., Larson, S.M.: Quantitative imaging of iodine-124 with PET. *J Nucl Med* **37** (1996) 1557–1562
- [103] Lubberink, M., Lundqvist, H., Westlin, J.E., Tolmachev, V., Schneider, H., Lovqvist, A., Sundin, A., Carlsson, J.: Positron emission tomography and radioimmunotargeting – aspects of quantification and dosimetry. *Acta Oncol* **38** (1999) 343–349
- [104] Crawford, D.C., Flower, M.A., Pratt, B.E., Hill, C., Zweit, J., McCready, V.R., Harmer, C.L.: Thyroid volume measurement in thyrotoxic patients: comparison between ultrasonography and iodine-124 positron emission tomography. *Eur J Nucl Med* **24** (1997) 1470–1478
- [105] Eschmann, S.M., Reischl, G., Bilger, K., Kupferschlag, J., Thelen, M.H., Dohmen, B.M., Besenfelder, H., Bares, R.: Evaluation of dosimetry of radioiodine therapy in benign and malignant thyroid disorders by means of iodine-124 and PET. *Eur J Nucl Med Mol Imaging* **29** (2002) 760–767
- [106] Sgouros, G., Kolbert, K.S., Sheikh, A., Pentlow, K.S., Mun, E.F., Barth, A., Robbins, R.J., Larson, S.M.: Patient-specific dosimetry for ¹³¹I thyroid cancer therapy using ¹²⁴I PET and 3-dimensional-internal dosimetry (3D-ID) software. *J Nucl Med* **45** (2004) 1366–1372
- [107] Rosch, F., Herzog, H., Stolz, B., Brockmann, J., Kohle, M., Muhlen-siepen, H., Marbach, P., Muller-Gartner, H.W.: Uptake kinetics of the somatostatin receptor ligand [Y-86]DOTA-DPhe(1)-Tyr(3)-octreotide ([Y-86]SMT487) using positron emission tomography in non-human primates and calculation of radiation doses of the Y-90-labelled analogue. *Eur J Nucl Med* **26** (1999) 358–366
- [108] Forster, G.J., Engelbach, M.J., Brockmann, J.J., Reber, H.J., Buchholz, H.G., Macke, H.R., Rosch, F.R., Herzog, H.R., Bartenstein, P.R.: Preliminary data on biodistribution and dosimetry for therapy planning of somatostatin receptor positive tumours: comparison of (86)Y-DOTATOC and (111)In-DTPA-octreotide. *Eur J Nucl Med* **28** (2001) 1743–1750
- [109] Jamar, F., Barone, R., Mathieu, I., Walrand, S., Labar, D., Carlier, P., de Camps, J., Schran, H., Chen, T., Smith, M.C., Bouterfa, H., Valkema, R., Krenning, E.P., Kvols, L.K., Pauwels, S.: ⁸⁶Y-DOTA(0)-D-Phe1-Tyr3-octreotide (SMT487) – a phase 1 clinical study: pharmacokinetics, biodistribution and renal protective effect of different regimens of amino acid co-infusion. *Eur J Nucl Med Mol Imaging* **30** (2003) 510–518
- [110] Palm, S., Enmon, R.M. Jr, Matei, C., Kolbert, K.S., Xu, S., Zanzonico, P.B., Finn, R.L., Koutcher, J.A., Larson, S.M., Sgouros, G.: Pharmacokinetics and Biodistribution of (86)Y-Trastuzumab for (90)Y dosimetry in an ovarian carcinoma model: correlative MicroPET and MRI. *J Nucl Med* **44** (2003) 1148–1155
- [111] Buchholz, H.G., Herzog, H., Forster, G.J., Reber, H., Nickel, O., Rosch, F., Bartenstein, P.: PET imaging with yttrium-86: comparison of phantom measurements acquired with different PET scanners before and after applying background subtraction. *Eur J Nucl Med Mol Imaging* **30** (2003) 716–720
- [112] Helisch, A., Forster, G.J., Reber, H., Buchholz, H.G., Arnold, R., Goke, B., Weber, M.M., Wiedenmann, B., Pauwels, S., Haus, U., Bouterfa, H., Bartenstein, P.: Pre-therapeutic dosimetry and biodistribution of ⁸⁶Y-DOTA-Phe1-Tyr3-octreotide versus ¹¹¹In-pentetreotide in patients with advanced neuroendocrine tumours. *Eur J Nucl Med Mol Imaging* **31** (2004) 1386–1392
- [113] Barone, R., Borson-Chazot, F., Valkema, R., Walrand, S., Chauvin, F., Gogou, L., Kvols, L.K., Krenning, E.P., Jamar, F., Pauwels, S.: Patient-specific dosimetry in predicting renal toxicity with (90)Y-DOTATOC: relevance of kidney volume and dose rate in finding a dose-effect relationship. *J Nucl Med* **46** (2005) 99S–106S
- [114] Pauwels, S., Barone, R., Walrand, S., Borson-Chazot, F., Valkema, R., Kvols, L.K., Krenning, E.P., Jamar, F.: Practical dosimetry of peptide receptor radionuclide therapy with (90)Y-labeled somatostatin analogs. *J Nucl Med* **46** (2005) 92S–98S
- [115] Ugur, O., Kothari, P.J., Finn, R.D., Zanzonico, P., Ruan, S., Guenther, I., Maecke, H.R., Larson, S.M.: Ga-66 labeled somatostatin analogue DOTA-DPhe1-Tyr3-octreotide as a potential agent for positron emission tomography imaging and receptor mediated internal radiotherapy of somatostatin receptor positive tumors. *Nucl Med Biol.* **29** (2002) 147–57
- [116] Lubberink, M., Lundqvist, H., Tolmachev, V.: Production, PET performance and dosimetric considerations of Ce-134/La-134, an Auger electron and positron-emitting generator for radionuclide therapy. *Physics in Medicine and Biology* **47** (2002) 615–629
- [117] Sgouros, G., Barest, G., Thekkumthala, J., Chui, C., Mohan, R., Bigler, R.E., Zanzonico, P.B.: Treatment planning for internal radionuclide therapy – 3-dimensional dosimetry for non-uniformly distributed radionuclides. *J Nucl Med* **31** (1990) 1884–1891
- [118] Bolch, W.E., Bouchet, L.G., Robertson, J.S., Wessels, B.W., Siegel, J.A., Howell, R.W., Erdi, A.K., Aydogan, B., Costes, S., Watson, E.E.: MIRL pamphlet No. 17: The dosimetry of nonuniform activity distributions – Radionuclide S values at the voxel level. *J Nucl Med* **40** (1999) 11S–36S
- [119] Hasegawa, B., Tang, H.R., Da Silva, A.J., Wong, K.H., Iwata, K., Wu, M.C.: Dual-modality imaging. *Nuclear Instruments & Methods in Physics Research Section A – Accelerators Spectrometers Detectors and Associated Equipment* **471** (2001) 140–144

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