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Estimation of Patient Dose from Radiopharmaceuticals Using Voxel Models

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ABSTRACT

The aim of this study was to demonstrate the advantages of patient dosimetry using voxel models and to present sets of dose estimates for patients of different gender and size. These models offer greater realism with respect to organ shape and topology than the well-established Medical Internal Radiation Dose (MIRD)-type mathematical models. At the National Research Centre for Environment and Health (GSF), specific absorbed fractions have been previously calculated for 4 male and 3 female voxel models, representing different age and stature, for a wide range of source organs. For this study, estimates both for established and new radiopharmaceuticals were performed using biokinetic data from International Commission on Radiological Protection (ICRP). The above calculations allowed for comparison to the MIRD technique in relation to the resulting absorbed organ and effective doses. Furthermore, data sets representing a range of voxel phantoms were investigated. It was found that dose differences among the voxel models can amount up to a factor of 3.

Key words: voxel models, radiophamaceuticals, dosimetry, specific absorbed fractions

INTRODUCTION

Radiation-dose estimates are needed for patients receiving radiopharmaceuticals in diagnostic or therapeutic procedures. In diagnostic procedures, radiation dose estimates are required for the assessment of the risk to patients associated with the use of radiopharmaceuticals both for comparison with the possible benefit of an investigation and to help giving adequate information to the patient. For targeted radionuclide therapy, the dose to the tumor should be also estimated with accuracy and the need for patient-specific dosimetry is arising.

Internal dosimetry requires knowledge of both biological and physical parameters. With respect to the physical aspects, one of the most crucial requirements is to establish values of the so-called specific absorbed fractions (SAF) which specify the fraction of penetrating energy emitted by radioactivity in a given source region which is absorbed in a specified target tissue, divided by the mass of the target tissue. At the present time most available dosimetric parameters are based on Medical Internal Radiation Dose (MIRD)-type mathematical anthropomorphic phantoms, or to use another terminology, anthropomorphic models, and a whole range of data exists covering all ages.[1,2] The innovation of

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voxel models,[3–5] in which three-dimensional (3-D) images of the patient's body and organs are constructed with high resolution from medical images and segmentation techniques, presents a significant advance towards a more realistic representation of the human body. This follows from the ability of the procedure not only to localize organ voxels accurately in 3-D space but also to use the attenuation information inherent in each voxel to permit the estimation of tissue density. Since the late nineties, voxel models have been used for the calculation of SAFs, for example, from Jones,[6] Petoussi-Henss and Zankl,[7] Yoriyaz et al.,[8] Stabin and Yoriyaz,[9] and Zankl et al.[10]

The Voxel Models

The voxel models developed at the GSF until now are shown in Table 1. As it can be seen, they cover both sexes and a wide range of ages and statures. For this study, the adult models Donna, Helga, Irene, Golem, Visible Human, and Frank were employed. For comparison purposes, the adult voxel model of Zubal et al.[4] was used, a model available to several laboratories. More detailed description of the GSF voxel models is given elsewhere.[3,11–13] The Visible Human was segmented from the computed tomography (CT) pictures obtained from the National Library of Medicine's Visible Human Project. Another voxel model of the same individual exists, segmented from whole-body CT/magnetic resonance (MR)/color photographic images.[5] All other adult persons were patients who had to undergo whole-body CT for various reasons. The GSF voxel models contain a large number of organs and tissues, including almost all organs considered to be most radiosensitive and, therefore, "critical," except bone surface. They also have some tissues relevant to inhalation, such as extrathoracic airways (anterior nasal passages, larynx, pharynx), trachea and the main branches of bronchi.

Each organ or tissue was represented by those voxels identified as belonging to it from the CT slice images of the particular individual. Thus, the shape and location of organs were realistically simulated and mass was determined using tissue-density data from the International Commission on Radiation Units and Measurements (ICRU).[14] Furthermore, the percentage of hard bone and bone marrow in each voxel in the skeleton was estimated from the CT pictures and, thus, the distribution of red bone marrow in the whole skeleton was reconstructed with a high resolution (corresponding to the resolution of the CT scan). Segmentation for such a large number of organs was laborious and time-consuming—several weeks are needed to construct such a model, as full automation is still not possible and manual intervention is part of the procedure.

Golem has the height and weight similar to the International Commission on Radiological Protection (ICRP) Reference Man, representing an average adult individual, while Irene is slimmer than the average female. The Visible Human and Frank are rather broadly built, the former being also very tall, and are probably more suitable to simulate bigger individuals. Similarly, the female phantoms Helga and Donna represent overweighted individuals. The organ and tissue masses of the voxel models of this study can be found in Zankl et al.[10] Figure 1 shows a 3-D representa-

Table 1. The GSF Voxel Models

Name	*Sex*	*Age*	*Weight (kg)*	*Height (cm)*	*Size of voxel (mm)^3*
Baby	female	8 weeks	4.2	57	2.9
Child	female	7 years	21.7	115	19.0
Donna	female	40 years	79	170	35.2
Helga	female	26 years	81	170	9.6
Irene	female	32 years	51	163	17.6
Laura	female	43 years	62	168	17.6
Frank	male	48 years	95	174	2.7
Golem	male	38 years	68.9	176	34.6
Otoko	male	unknown	65	170	9.6
Visible Human	male	38 years	103.2	180	4.3
Reference male	male	—	73	176	34.8
Reference female	female	—	60	163	15.1

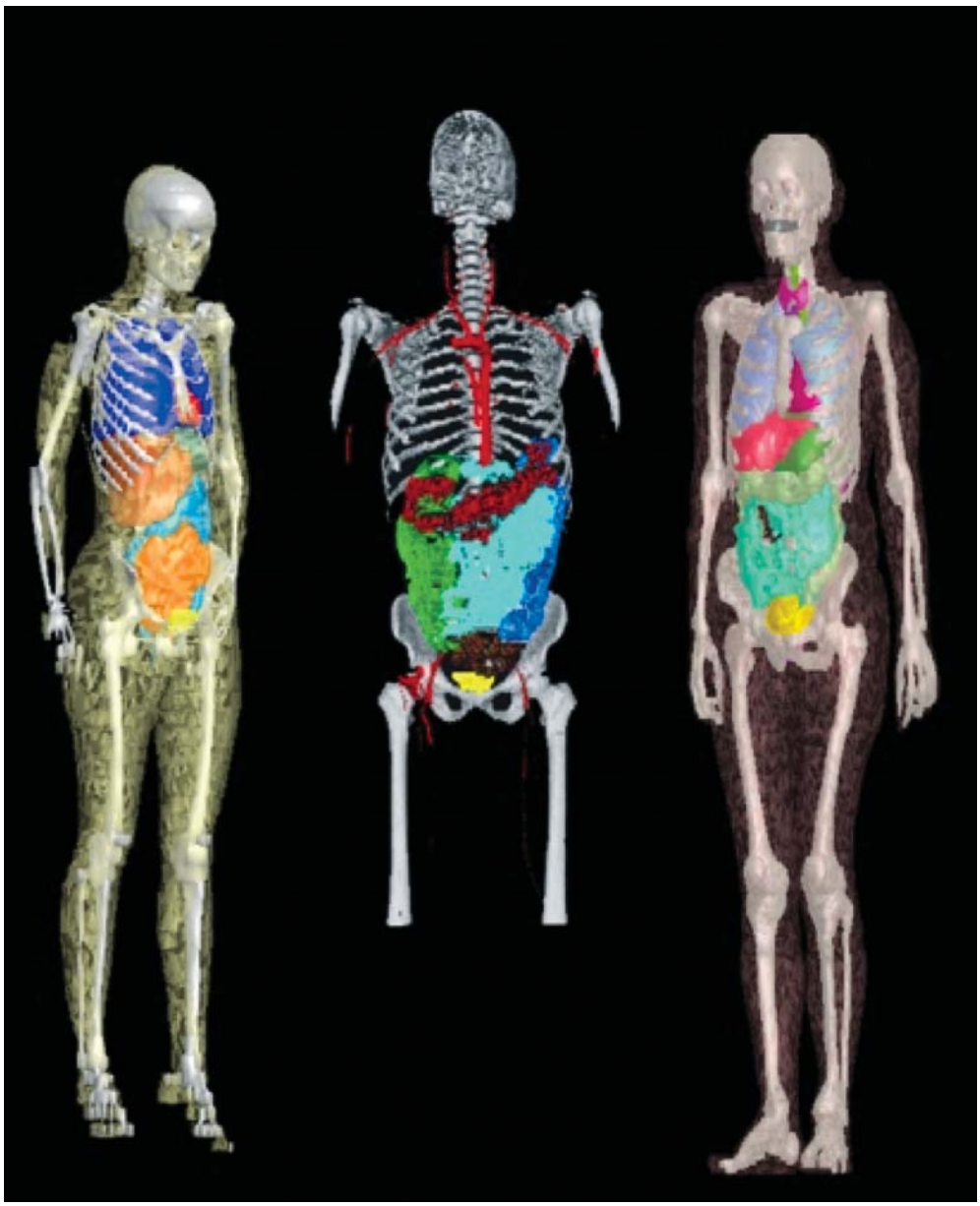

Figure 1. Three-dimensional representations of some organs of the voxel models Irene, Visible Human, and Golem (from left).

tion of some organs of the models Irene, Visible Human, and Golem and demonstrates the anatomical realism of this type of models.

Dosimetry Methods

In order to calculate the organ-dose estimates, the following formulation was used:

$$D_T = \Sigma A_s \; c \; \Sigma E_i Y_i (SAF_i)_{T \leftarrow S} + A_{REM} \left[(m_{TB} \; c \; \Sigma E_i Y_i (SAF_i)_{T \leftarrow TB} - \Sigma m_s \; c \; \Sigma E_i Y_i \; (SAF_i)_{T \leftarrow S}) \right] / m_{REM} \quad (1)$$

where D_T is the mean dose to a given target organ T; S, T is the source, target organs; TB is the total body; m is the mass, REM is the remaining tissues (m_{REM} is the $m_{TB} - \Sigma \; m_S$); A_S is the time integrated or cumulated activity and is equal to the total number of transformations in S (s); E_i is the mean energy (MeV) of radiation type i; Y_i is the yield of radiation type i per nuclear transformation; $(SAF_i)_{T \leftarrow S}$ is the specific absorbed fraction of energy of radiation type i; and c is a constant which converts units of MeV $\times$ g^{-1} $\times$ transformation^{-1} to units of mGy $\times$ MBq^{-1} $\times$ s^{-1}.

Extensive tables of specific absorbed fractions (SAF) are available for the voxel models mentioned above and photons of 10 keV–4 MeV, for up to 39 source organs and more than 30 target organs. These were calculated previously using a Monte Carlo code, simulating the radiation transport in these phantoms. For these calculations, the mass of the source organ was taken to be equal to the mass of the reference male and female. Details of these calculations can be found elsewhere.[10]

For particulate radiation, the absorbed fraction was assumed to be 1.0 for organ self-dose and otherwise zero, except for sources in the contents of walled organs, with the wall as the target tissue or when the source is in part of the skeleton. For sources in the contents of a walled organ, it was assumed that, for electrons, the dose to the walls is one half of the dose to the contents and for alpha particles 0.5% of the dose to the contents.

For sources in bone, the situation is considerably more complicated. We deliberately avoided presenting comparisons for bone-seeking radiopharmaceuticals, because such comparisons are extremely dependent on the adopted model for estimating dose to the sensitive cells on bone surfaces and the red marrow, which involve the complex geometry of the intermixture of these tissues in trabecular bone sites. In this study (Figs. 2 and 3), the dose to "bone" for the voxel phantoms refers to dose to total bone (mixture of hard bone and marrow). These values are not directly comparable with the MIRD values in which the dose to "bone" means dose to bone surfaces for the radiopharmaceuticals in this study. The dose to total bone should give a reasonable approximation to the dose to bone surfaces from γ-activity in other organs, and we have used this approximation in this study where bone itself is not a source organ. Similarly, the estimation of dose to marrow within the microstructure of trabecular bone depends on the model applied to determine absorbed fractions from path-length distributions in marrow cavities. In the present study, marrow

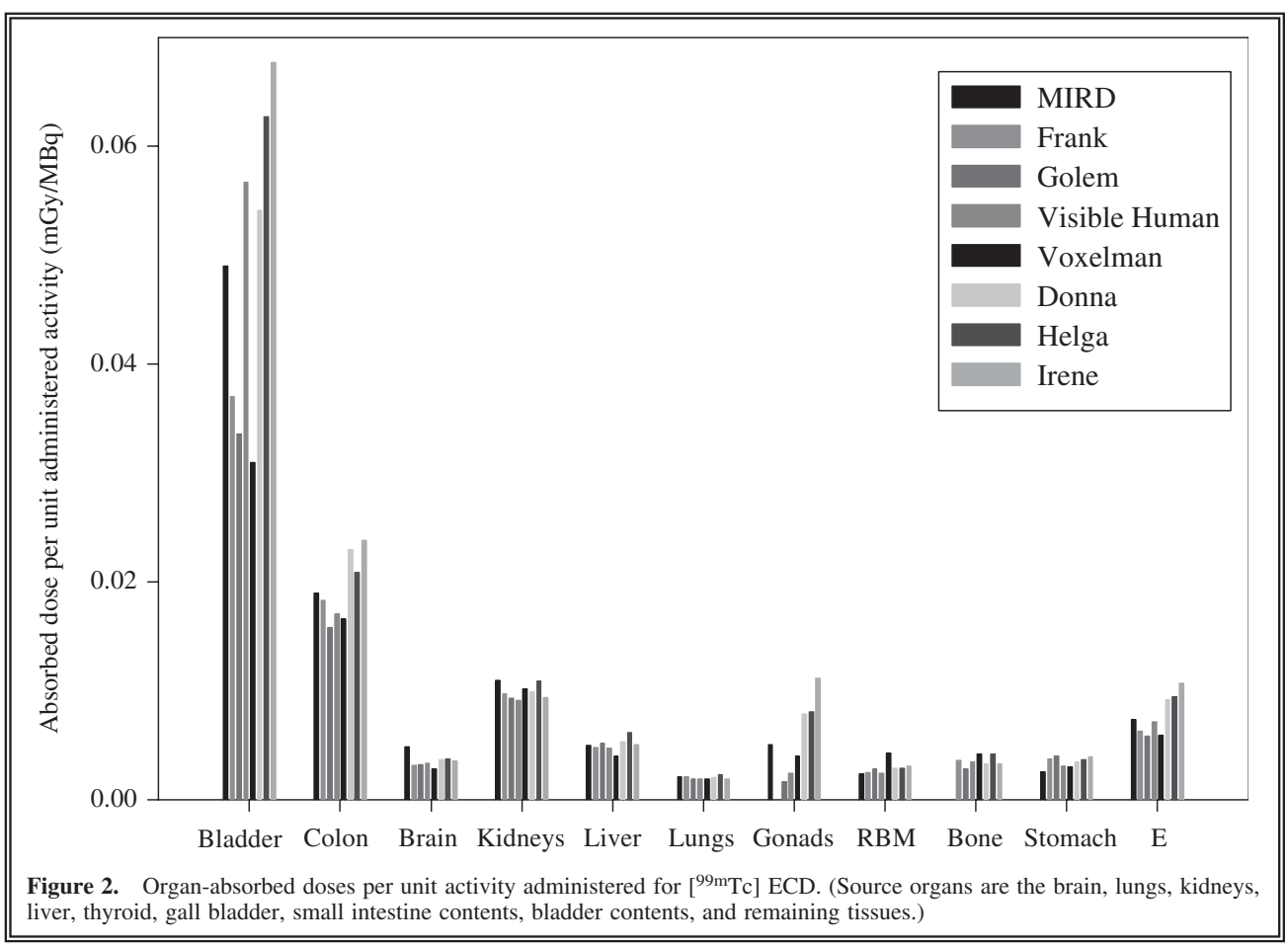

Figure 2. Organ-absorbed doses per unit activity administered for [^{99m}Tc] ECD. (Source organs are the brain, lungs, kidneys, liver, thyroid, gall bladder, small intestine contents, bladder contents, and remaining tissues.)

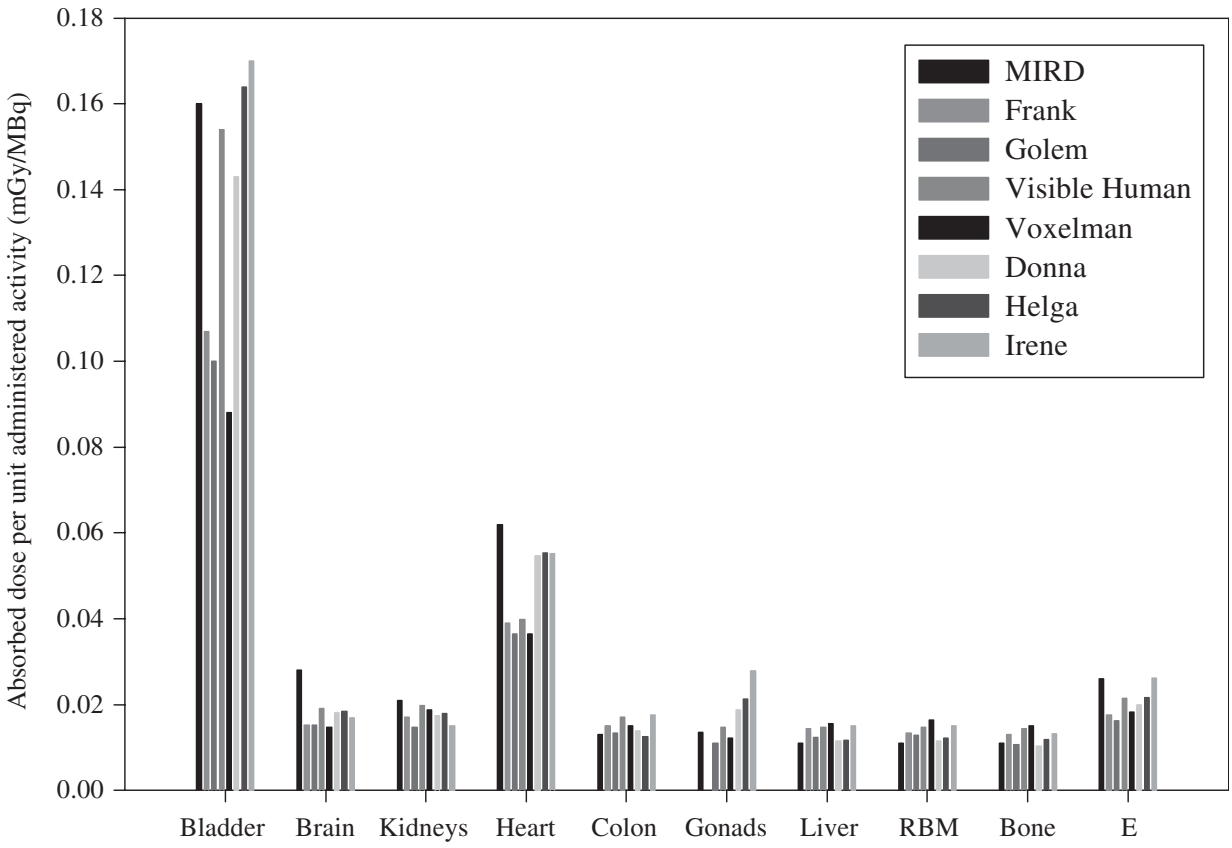

Figure 3. Organ-absorbed doses per unit activity administered for [^{18}F] FDG. (Source organs are the brain, heart wall, kidneys, bladder contents, and remaining tissues.)

dose is estimated by the voxel method, allowing for the specification of the relative amounts of bone and marrow at any skeletal site, as a mean dose to the red marrow mass and, again, the comparison to the MIRD system is not strictly valid when the marrow is a source organ.

If the values of cumulated activity are known, the organ-absorbed doses can be estimated by applying the formula (1). To facilitate this procedure, software was developed at the GSF which incorporates SAF values, biokinetic data, and nuclear transformation data.

Effective dose E was calculated for all models from the estimated organ doses and tissue weighting factors, according to the formula set out in ICRP 60.[15] However, it should be noted that the values of effective dose shown here are model-specific and, therefore, should be considered with caution, as they do not really correspond to the correct definition of effective dose, which is a quantity defined using simultaneous organ doses for both male and female.[15] The E for the male models is lower than the E of the female ones, because for the former ones, there is no breast dose considered. Dose to the gonads was taken as the dose to the ovaries for the female and to the testes for the male ones. Clearly, the male models did not have a uterus dose (contributing to the so-called remainder), which was simply ignored.

RESULTS

As an example of the results, Figs. 2 and 3 show comparative values of some organ doses and effective doses for the 7 voxel models and for the radiopharmaceuticals technetium-labeled ethyl cysteinate dimer, [^{99m}Tc] ECD and for 2-fluoro-2-deoxy-d-glycose, [^{18}F]-FDG. The biokinetic data were taken from ICRP.[15,16] For comparison purposes, the respective organ doses for the

MIRD model stemming from ICRP[16,17] are also shown. The accuracy of these values is determined by physical factors, including radionuclide emission data; mass, shape, and geometric location of simulated organs; and the estimation of specific absorbed fractions. The error in the Monte Carlo estimation of SAF values is generally between 1% and 5%,[10] and the contribution from all other physical errors is considered to be of similar magnitude. The effects of biological uncertainty (i.e., the variation in the uptake and distribution of the radiopharmaceutical among the organs) reflects uncertainties in the cumulated activity, which can amount up to a factor of 3.[16]

It can be seen that dose differences among the MIRD and voxel systems are occasionally significant owing to substantial differences in SAF values between the two methods. It was shown in other studies that the SAFs to the voxel models may be greater or less than to the MIRD-type models by factors up to 1000 for low-energy gamma radiation and small organs;[7,10] however, the low-energy emissions are usually not very important to the total dose picture. The main reason for the differences in SAFs at these low energies is the different geometries of the models, leading to different interorgan distances and different proximity of certain organs to source organs.

Furthermore, dose differences among the voxel models can amount up to a factor of 3. Because for the evaluation of organ-absorbed doses all source organs were assigned reference masses, these results show that there is a significant influence of organ topology from individual to individual on the resulting organ doses. In the case of the effective dose, E for the male models is lower than the E of the female ones because for the former ones (except for Frank) there is no breast dose considered. Furthermore, the values of E for the various models do not differ to the same extent as the individual organ doses. Findings supporting these tendencies were reported from Petoussi et al.,[7] Zankl et al.,[10] Smith et al.[18] and Smith et al.[19]

CONCLUSIONS

The improved realism of the voxel models with respect to the organ shape and location introduces for some organs deviations between voxel and MIRD organ doses, as well as between the various voxel models which, however, are mostly not reflected so strongly at the effective dose. Individual anatomy leads to dose deviations from person to person; thus, individual dosimetry is required, a fact recognized already by the nuclear medicine community. Clearly, the need for personal dosimetry—and accuracy—is more stringent in targeted radionuclide therapy than for diagnostic applications.

For performing individual dosimetry in nuclear therapy, a model—partial or whole body—for every patient is necessary, and the biological data should be measured directly on the patient. The first requirement is, at the moment, very difficult and will be practically feasible when the segmentation procedures have improved so much so that the creation of a model can be completed in a couple of hours or days. Measuring the biological data of every patient also requires extra effort from the nuclear medicine department, as well as the patient. Furthermore, for therapeutic applications, the tumor dose has to be calculated, as well as the organ doses, and this requires dose calculations for the "real" patient data.

However, until the day when individual dosimetry is common practice, patient dosimetry using various voxel models of different sex, age, and stature is the best solution. Using these models, and the appropriate dosimetric procedures, a large number of organ doses can be calculated and included in a database; the most suitable can be then chosen, fitting closer to the anatomy and age of the patient. If "representative" organ doses are required—for example, for the radiation protection of a "standard" patient—the new voxel reference models should be used (i.e., standardized voxel models with "representative" organ masses and locations).

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