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IDAC-ALPHA: AN ALPHA DOSIMETRY SOFTWARE FOR NORMAL ORGANS AND TISSUES

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Radiopharmaceuticals have been used for the treatment of various forms of cancer since the 1940s. In recent years, the advantages of alpha emitting radionuclides have emerged as a favourable treatment option. However, most alpha emitting radionuclides have long decay chains with long-lived daughter radionuclides. This leads to uncertainties in the dosimetry for normal organs and tissues, when established dosimetry models are employed. The aim of this project is to assign each progeny its own biokinetic behaviour. The novel dosimetry model was applied to ^{223}Ra-dichloride, frequently used for the treatment of patients with metastatic bone disease from castration-resistant prostate cancer. In this dosimetry model, individual biokinetics for each daughter radionuclide was included. This resulted in a decrease in absorbed dose to bone surfaces and red marrow and increased absorbed dose to liver and kidney, when compared with dosimetry models assuming that the daughter nuclides follow the biokinetics of the parent radionuclide.

INRODUCTION

Radiopharmaceuticals have been used for the treatment of various forms of cancer and benign diseases since the 1940s[1–3]. In recent years, the advantages of alpha emitting radionuclides have been included in the treatment arsenal. However, a problem from the dosimetry point of view is that some alpha emitting radionuclides have long decay chains, including daughter radionuclides with long half-lives and a biokinetic behaviour, which differ from that of the parent radionuclide.

The International Commission on Radiological Protection (ICRP) recommends that the use of radiopharmaceuticals for cancer treatment should be based on detailed, patient-specific dosimetry for the assessment of absorbed dose to normal organs and tumour tissues[4]. The calculation of absorbed dose to internal organs, tissues and the whole body is a fundamentally important aspect for successfully achieving clinical objectives. As radiopharmaceuticals are usually administered intravenously or orally, radionuclide therapy involves delivery of some radiation energy to all healthy organs and tissues. The amount of activity administered should be sufficient to treat the neoplasm effectively while minimising any detrimental dose to normal tissues[4]. However, when alpha emitting radionuclides are employed, a complete patient-specific dosimetry is challenging to perform, as most alpha emitters completely lack imageable photons. Where photons are present, administered activity doses (kBq to few MBq) mostly do not allow for adequate count statistics on imaging. Moreover, for the detection and measurement of alpha emitters in biological specimens dedicated equipment is necessary, which is not available in most clinical institutions. To overcome these problems, general reference parameters can be used to fill in where the data is missing or is not assessable. This strategy will allow a realistic absorbed dose estimation for patients treated with alpha emitting radionuclides and provide a more accurate absorbed dose calculation for critical organs of interest. A problem that should be addressed is that many assume the cumulated activity based on descriptive curve fitting, which means that each organ is treated independently and there is no way to include the different biokinetic models of progenies. The ICRP has in its computational framework of internal dosimetry[5] for radionuclides made changes, from descriptive to systemic models, which are based on full compartmental representation. All elements in the decay chain have separate biokinetic models including excretion and transfer rates between organs and blood and as the time integrated activities are calculated using a numeric differential equation, once the radionuclide has decayed, the calculations immediately follow the modelling of the daughter radionuclides. The calculations in this paper follow the computational framework of internal dosimetry given in ICRP Publication 130[5].

The aim of this project was to create a realistic dosimetry algorithm for alpha emitters relevant for molecular radiotherapy e.g. ^{225}Ac, ^{212}Bi, ^{213}Bi, ^{212}Pb, ^{223}Ra, ^{149}Tb and ^{227}Th[3], also taking into consideration the behaviour of their progenies. In particular, the algorithm was applied on a compartment model for $^{223}RaCl_2$ a radiopharmaceutical administered for treatment of patients with metastatic castration resistant prostate cancer (mCRPC)[6]. In the model presented herein the individual biokinetics of the progenies were included as opposed to the current common dosimetry method for radionuclides where radioactive progenies are assumed to follow the bio-distribution fate of the parent nuclide. The IDAC-Alpha, the software developed and presented herein, combines biokinetics and dosimetric models, integrating attributing biokinetic models from all progenies.

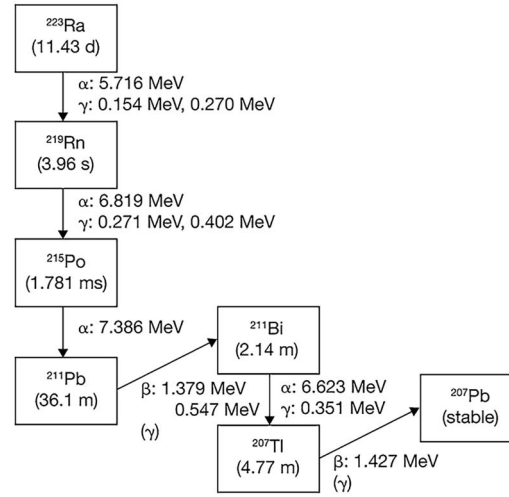

Figure 1: Nuclear decay data of 223Ra.

Radium-223 dichloride

Radium-223 dichloride ($^{223}RaCl_2$) is the first targeted alpha therapy used for therapeutic treatment of castration-resistant prostate cancer that has metastasized to[7–9] bone. The progenies of ^{223}Ra are ^{219}Rn, ^{215}Po, ^{211}Pb ^{211}Bi, ^{211}Po and ^{207}Tl, which decays to the stable nuclide ^{207}Pb. Halftimes and the dominant decay routes for each radionuclide are shown in Fig. 1. $^{223}RaCl_2$ is often routinely administered with a fractionated approach of treatment with six administrations of 55 kBq/kg body weight. $^{223}RaCl_2$ is not the first radiotherapeutic agent approved for this treatment. Radiopharmaceuticals like ^{32}P-orthophosphate, $^{89}SrCl_2$ and ^{153}Sm- EDTMP have since long been used in the treatment of bone metastases. However, $^{223}RaCl_2$ was the first alpha emitter to be approved in 2013 by the United States Food and Drug Administration and the first to demonstrate an overall survival advantage in the international ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) study[10].

For the biokinetics of $^{223}RaCl_2$ several biokinetic models and absorbed dose coefficients have been published based on healthy patient data. The most cited one is that by Lassmann and Nosske 2012[11]. In 2019 Taprogge *et al*.[6] published a specific biokinetic compartment model for $^{223}Ra\ Cl_2$ in patients with metastatic bone disease from mCRPC. This model was based on whole body measurements using a 5 cm (diameter) × 5 cm NaI(Tl)-detector placed 2 m over the patient bed. Measurements were performed every 2 h on Day 1, and additional (twice per day) readings were taken until the patient was discharged at approximately 48 h post administration. Further measurements were performed at 96 and 144 h post administration. Quantitative gamma-camera imaging was also performed using the 82 keV (20%) gamma photons from the ^{223}Ra decay. Planar whole-body images were acquired for approximately 30 min each. Image quantification was performed by calculating the geometric mean counts of anterior and posterior views using a predetermined sensitivity calibration coefficient and correcting for patient-specific attenuation.

This patient specific biokinetic model, based on data of four patients, shows that mCRPC patients have a higher initial bone uptake and a significantly faster washout in the first 50 h than the models predicted for healthy persons have shown[6]. The model suggests that ^{223}Ra-dichloride retention in the human skeleton requires two compartments one for the bone surface and one for incorporation into the bone matrix.

The model presented herein is using biokinetic data for $^{223}RaCl_2$ from Taprogge *et al*.[6]. The biokinetics for each progeny (^{219}Rn, ^{215}Po, ^{211}Pb, ^{211}Bi, ^{211}Po, ^{207}Tl) are considered individually[5]. The calculations are performed in two steps. First, a biokinetic model is created for each organ of interest based on the biokinetic data of the parent radionuclide. Secondly, the software modifies the data to a compartmental model creating a full biokinetic model, covering all decays from progenies and can therefore be solved numerically. For comparison, absorbed doses are also calculated by using a conventional established dosimetry tool where all progenies' decays follow the same biokinetic as the parent radionuclide ^{223}Ra.

METHOD

Biokinetic models and assumptions

The software code of IDAC-Alpha is based on two assumptions. Firstly, the kinetic energy emitted due

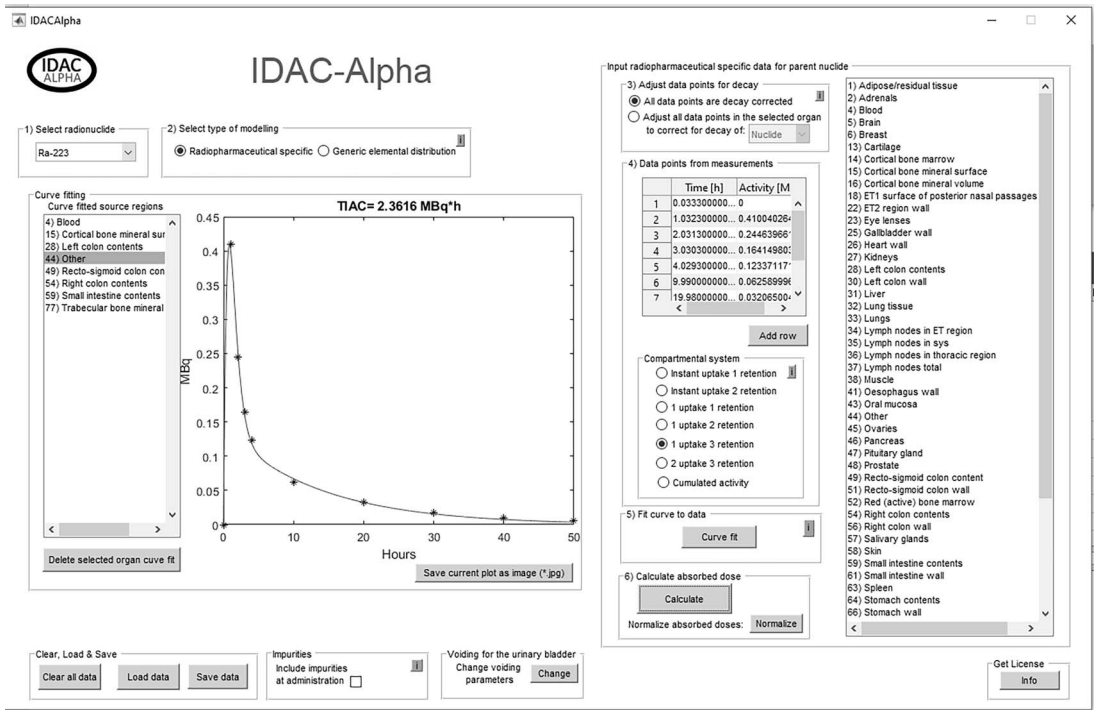

Figure 2: The graphical interface of IDAC-Alpha. The blue stars are the time activity data of the model of mCRP patients and the red line is the corresponding compartmental representation for the source region Other/Rest of the body which are used in the biokinetic modelling for the transport of daughter nuclides.

to the alpha decay of the parent nuclide releases the radionuclide from the chemical binding of the pharmaceutical. Secondly, each progeny will act individually as its own simple ion transferred between organs and tissues through the blood. For the dosimetry the mean organ absorbed dose calculations are based on ICRP reference data and assumes that the activity is uniformly distributed through the whole tissue. The biokinetic software includes separate biokinetic data for nuclides for seven parent radionuclides ^{225}Ac, ^{211}At, ^{212}Bi, ^{213}Bi, ^{212}Pb, ^{223}Ra, ^{149}Tb and ^{227}Th. The idea is to create an algorithm where the biokinetic models of any new radiopharmaceutical based on these radionuclides could be used and the biokinetic models for progenies will be attached to the parent model creating a unique compartmental model for every radiopharmaceutical, depending on parent nuclides and the specific organ uptakes. The graphical interface of IDAC-Alpha is shown in Figure 2. The generation of the model is done in three steps: (1) selection of parent nuclide, (2) select source organs and insert activity data at different time points following administration and (3) from the selected radionuclide, compartmental models are created which are connected with the compartmental model of each progeny. Once activity data and compartment fitting based on the inserted data points are included into the code, a unique full compartment model will be created. Based on this generated model, the activity distribution is followed until only an negligile amount of activity is left in the body. Based on this activity the absorbed dose is calculated with an integrated version of IDAC-Dose2.1[12]. The time required for the biokinetic modelling and the dosimetric calculations is less than 2 s. Once the biokinetic and dosimetric calculations are preformed the total absorbed dose coefficients are presented for each source organ separately for both male and female. The software also presents separately for each nuclide the absorbed dose coefficients for all radiation or each type of radiation (photons, electrons, alphas). An effective dose coefficient is also calculated as defined in ICRP Publication 103[13] excluding the target region for the treatment. The results can be stored in a PDF format report or in a CVS-file.

Applying the $^{223}RaCl_2$ biokinetic model for mCRPC patients

A biokinetic compartment model specific for mCRPC patients was published by Taprogge et al.[6]. The model was based on activity retention data for

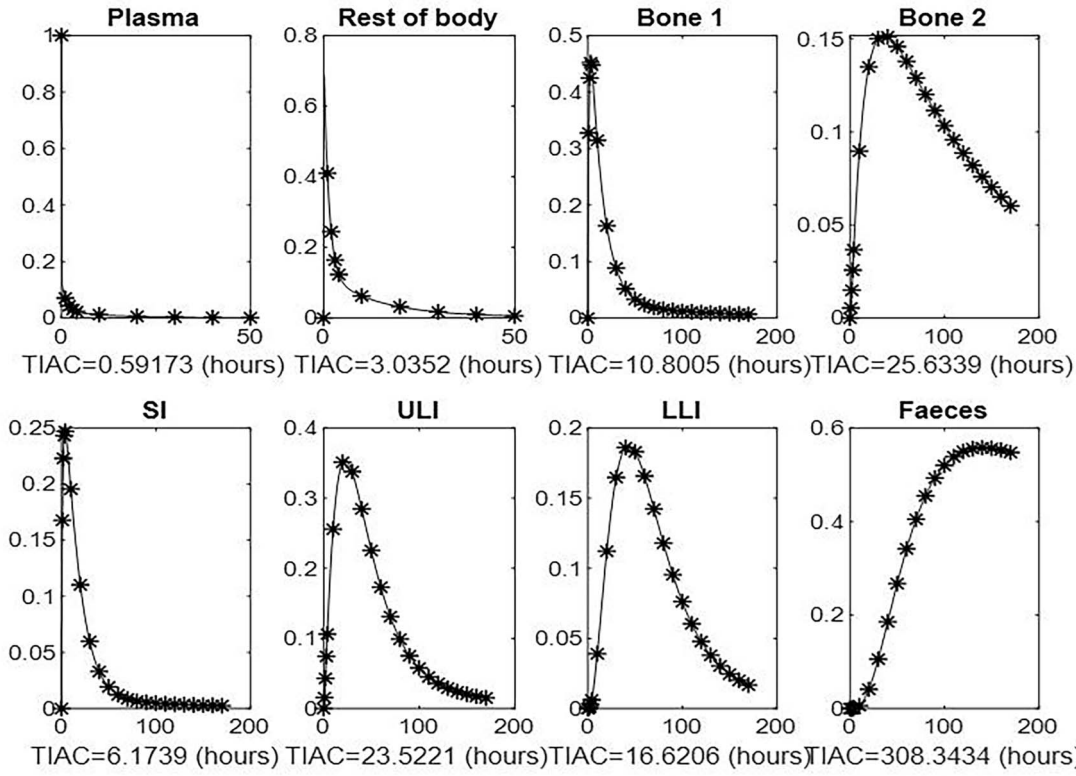

Figure 3: Time integrated activity coefficients curves for the seven source organs, bone represented with two different compartments given in the biokinetic model for mCRP patients[6].

plasma, bone surfaces, small intestines, large intestines and excretion through the gastrointestinal tract from six mCRPC patients. The time integrated activity coefficients (TIAC) curves for all source organs in the biokinetic model for mCRPC patients are presented in Figure 3. From the TIAC, time activity points were generated and from these data points, a compartment configuration was created for each source organ. The compartment configurations for the source region 'rest of the body' used in the biokinetic and dosimetric calculations are shown if Figure 3. From the time dependent $^{223}RaCl_2$ mCRPC compartment model the parent nuclide could in this case be integrated with generic biokinetic models for all the Ra-223 progenies. This allows element specific transport of all daughter nuclides, as the activity for all radionuclides both progenies and parent at each time point are known. After the TIAC for all radionuclides and source organ are modelled, the absorbed dose and effective dose are calculated. The absorbed dose calculations are also performed based on the alternative assumption that the progenies are following the decay biokinetic model of the parent radionuclide in the same source organs. The code keeps track of every decay and follows each decay through the whole chain. To illustrate this better, the biokinetic models for the first four decay chains of Ra-223 are shown below. For instance, if Ra-223 decays in bone, yielding for that specific decay a Rd-219 in the bone, in which compartment the radon decay starts and subsequently follows that biokinetic model before decaying into Po-215. If radon-219 decays in the kidneys, then Po-215 will start in the kidneys compartment following the biokinetic model for polonium. So, each decay of each progeny is individually followed and simulated through the whole decay chain during 1 year of transport in the body.

Absorbed dose and effective dose calculations

The mean absorbed dose to a target region (D) was calculated by[14]

$$D(r_T, T_D) = \sum_{r_S} \int_{T=0}^{T=1\ \text{year}} A(r_s, t) * S(r_T \longleftarrow r_s, t)\, dt\,[\text{Gy}],$$

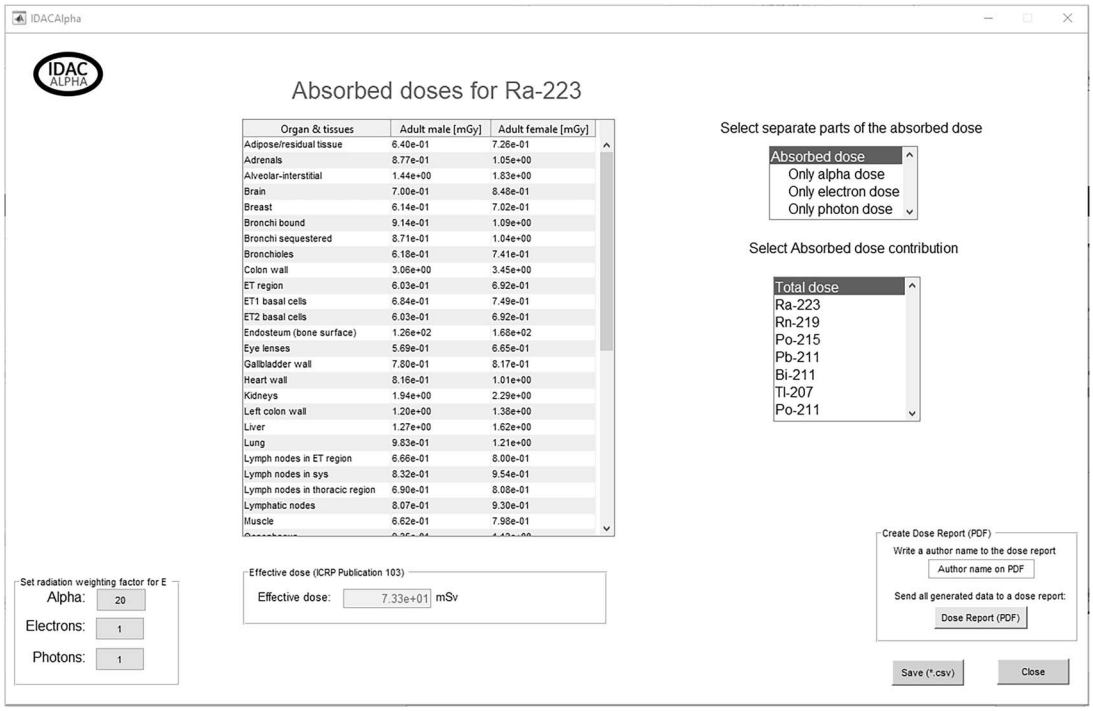

Figure 4: The absorbed dose and effective dose given for the biokinetic model for mCRP patients using IDAC-Alpha. The calculations are for a 1 MBq intravenous administration and the absorbed doses are given in mGy and the effective dose in mSv.

where $A(r_s, t)$ is the time dependent activity at time t, in source region r_s for 1 year after administration e.g. 1 year corresponds to ∼30 half-lives for ^{223}Ra. $S(r_T \longleftarrow r_s, t)$ is the mean absorbed dose in target r_T per nuclear transformations in source region r_s at time t. The $S(r_T \longleftarrow r_s, t)$ is generated using the radionuclide decay scheme and the Monte Carlo simulated specific absorbed fractions by simulating every source-target combination.

$$S\left(r_T \longleftarrow r_s\right) = \sum_i \Delta_i \Phi\left(r_T \leftarrow r_s, E_i\right)\left[\mathrm{Gy/Bq}\right],$$

where $\Phi(r_T \leftarrow r_s, E_i)$ is the absorbed fraction from the source region to the target region r_T divided by the mass in kilograms of the target region r_T of the ith components in the decay scheme and $\Delta_i = E_i Y_i$ is the energy yield, where Y_i is the yield and E_i is the mean energy of the ith nuclear transition of the radionuclide expressed in Joule.

The effective dose (E), which is the sum of sex average radiation weighted equivalent dose from radiosensitive organs is calculated by

$$E = \sum\nolimits_T w_T H_T = \sum\nolimits_R \frac{w_R D_{T,R_{\mathrm{Ref.male}}} + w_R D_{T,R_{\mathrm{Ref.female}}}}{2}\ [Sv],$$

where w_R is the radiation weighting factor of radiation R, w_T is the tissue weighting factor representing the relative organs and tissues detrimental effects. $D_{T,R_{Ref.male}}$ and $D_{T,R_{\mathrm{Ref.female}}}$ is the mean absorbed dose of target region T of the reference male and female person, respectively. In the calculations performed here the radiation weighting factors are set to 1 for photons and electrons and 20 for alpha decay. The tissue weighting factors for red marrow, colon, lung, stomach, breast and remainder tissues are set to 0.12, for gonads set to 0.08 for urinary bladder, oesophagus, liver and thyroid set to 0.04 and for bone surface, brain, salivary glands, skin 0.01, giving a total fraction of 1[13].

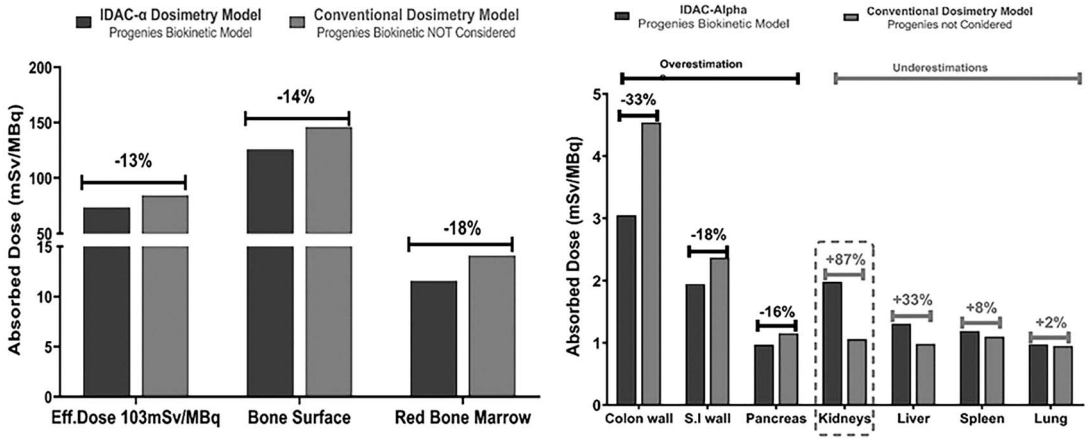

Figure 5: Absorbed dose and effective dose comparison when including transfer of progenies or not.

RESULTS AND DISCUSSION

The absorbed doses calculated using the IDAC-Alpha software, including transfer of daughter nuclides based on the biokinetic model of mCRP patients are shown in Figure 3. Figure 4 shows the results of a $^{223}RaCl_2$ calculations. For a selected absorbed dose to the skeletal metastases, the program also provides the necessary administered activity and absorbed dose to non-target organs and tissues. The effective dose calculation, based on the established biokinetic model, where the daughter nuclides are following that of the parent nuclide, showed an effective dose per unit administered activity of 83.4 mSv/MBq and by applying the IDAC-Alpha model, daughter nuclides are following their individual biokinetic model, the effective dose was calculated to 73.4 mSv/MBq, which is 12% lower. The dosimetry of ^{223}Ra calculated by IDAC-Alpha, resulted in a decreased absorbed dose (D) in critical organs/tissues such as bone (bone surface −14% decreased D & bone marrow −18% decreased D) due to decreased bone uptake of daughter radionuclides. At the same time, the D in the liver and in the kidneys increased by 33% and 87%, respectively, due to the different retention and excretion of the daughter radionuclides. The results are shown in Figure 5. Hence, the proposed novel software addresses dosimetric overestimations or underestimations in critical organs, when calculated with established models used for radionuclides decaying into stable isotopes. It is worth mentioning that the impact of including biokinetic models of daughter nuclides in the absorbed dose calculations will be greater when one or more have long half-lives. A limitation in the present estimates of the $^{223}RaCl_2$ doses is that the ^{223}Ra biokinetics is based on only four individuals. A general limitation of all types of dosimetry calculation using mean absorbed dose to organs and tissues is that it does not necessarily reflects clinical responses for short-range alpha-emitting radionuclides, as only a subpopulation of cells in the organ might be affected.

The established models will significantly overestimate the self-dose to the source organs and therefore also underestimate the absorbed dose to the rest of the body, as the transport of daughter radionuclides out of the source region is ignored.

CONCLUSION

IDAC-Alpha is a biokinetic, user friendly software with a graphical interface, developed to perform realistic alpha dosimetry calculations for normal organs and tissues. The software includes separate transfer of the various progenies. Including the biokinetics of the progenies will give improved absorbed dose estimates and an improved prediction of the normal tissue radiotoxicity.

CONFLICT OF INTEREST

AK, TM and EK work for ABX-CRO, MA have made consulting works for ABX-CRO, and SM have no conflict of interest.

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