

DOSE8: AN APPLICATION ENABLING THE TIME EFFICIENT DOSIMETRY CALCULATION ACCORDING TO THE MIRD-SCHEME

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Abstract

Dosimetry is the process of calculating the effective radioactive dose that is applied to tumors and organs respectively as a patient undergoes a peptide receptor radionuclide therapy. This work presents the novel application software 'DoSE8' that was developed from our group and that incorporates all necessary image processing steps (registration and segmentation) and data handling for (partly) automating and calculating complete dosimetries. 'DoSE8' significantly accelerates dosimetry calculation from six hours to only fifteen minutes per patient and, therefore, makes it possible to perform dosimetry in clinical routine at all. Furthermore, it enables the calculation of a sufficient amount of dosimetries to develop reliable prediction models that allow predicting the proper amount of radioactive substances to be injected directly from body indices and before the actual medical treatment takes place.

Keywords –*Dosimetry, Scintigraphy, MIRD, Registration, Segmentation*

1. Introduction

Peptide receptor radionuclide therapy using radiolabeled somatostatin analogues is a novel treatment option for patients with metastatic neuroendocrine tumors. In the course of therapy patients are intravenously injected with somatostatin analogues that dock on the tumors and destroy the cancer tissue by radioactivity. The challenge for this internal radiation therapy is to deliver the highest possible dose to the tumor while sparing normal organs from damage. [2, 5]

Up to now the applied patient dose is subjectively estimated by the physician based on indices such as body height and weight, blood parameters and tumor size. The actually effective dose on tumors and organs is calculated from scintigraphic image data captured by a gamma camera during the treatment process; i.e. after the dose has already been applied! Determining the effective doses at regions of interest (ROIs) is called internal dosimetry. [5]

In order to develop reliable models allowing for a correlation of body indices with actually absorbed doses, a high number of dosimetries must be calculated following the instructions given by

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the MIRD scheme (Medical Internal Radiation Dose scheme). Among other methods the MIRD scheme schedules a capture of a time series of planar ant (anterior, front view) and post (posterior, back view) scintigraphy images showing the radioactivity in the patient's body over a period of about 70 hours past injection (hpi) of the radiolabeled tracer, see *Figure 1*. Within these images relevant ROIs like tumors and endangered organs are encircled (masked) by a physician as accurately as possible at their greatest extension. By placing the masks in all corresponding ant and post images, the ROIs' mean radiation can be determined, see *Figure 2*. Further processing of these data allows for the calculation of the effective doses at the different ROIs over time. [6]

Currently, the described procedure is done manually for the most part, which is quite time consuming (about 6 hours per patient) and, thus, often not applicable in clinical routine. [8]

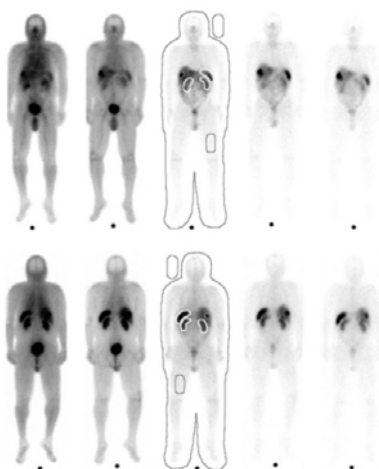


Figure 1: Planar anterior (top) and posterior (bottom) scintigraphies taken at 0.5, 3, 20, 44 and 68 hours (from left to right) past injecting a radiolabeled tracer. For the manually masked ROIs the effective doses are determined following the MIRD scheme. According radiation counts can be seen in Figure 2.

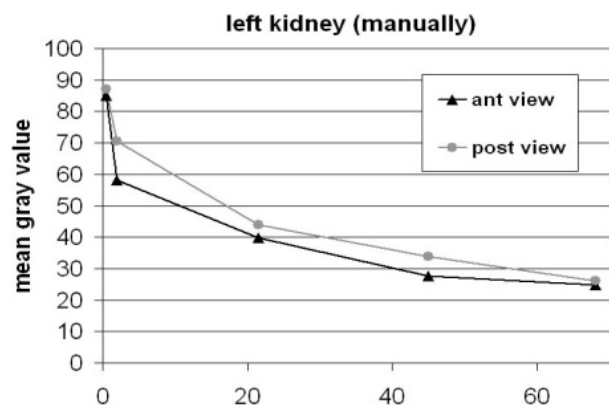


Figure 2: Mean radiation (gray values, counts) estimated from the ROI that corresponds to the kidney in anterior and posterior scintigraphy images shown in Figure 1 over time.

In order to speed up the process of dosimetry and enabling its calculation in clinical routine at all, several image handling and processing algorithms for (partly) automating the dosimetry are supported by the in-house developed dosimetry software 'DoSE8', that is presented in this article.

The challenge is to provide user-friendly software that supports the medical experts in the tedious process of masking the ROIs (segmentation problem) and placing the masks within all corresponding images of a series (registration problem). The segmentation as well as the registration is demanding due to the fact that scintigraphy images are very noisy (Poisson noise) and the relevant object boundaries appear very fuzzy in the images. Although several dosimetry tools currently exist (e.g. 'Olinda/EXM'), none of them support automatic registration and segmentation capabilities for time efficient data collection that significantly reduces the total time requirement for dosimetry calculation. Existing tools only support the calculation of the applied dose mainly by implementing data fitting functionality and lookup tables. [3]

In this work we introduce the new software tool 'DoSE8' that supports the segmentation task as well as the registration task and, hence, accelerates the entire dosimetry process significantly, producing a nearly complete dosimetry calculation and report. The required functionality and optimization of the usability of the software have been developed in cooperation with the Department of

Nuclear Medicine at the PET center in Bad Berka, Germany. All implementations are realized in Matlab™.

2. Methods

In the following the developed software including the implemented functionality for image registration and segmentation, the results of algorithm evaluation as well as the incorporated dosimetry calculation are presented.

2.1. Graphical user interface

The designed graphical user interface (GUI) provides a variety of functionality allowing the medical expert to easily collect dosimetric data, which mainly consist of radioactive counts being characterized by mean gray values per ROI over time, see *Figure 3* [6].



Figure 3: Graphical User Interface of proprietary software ‘DoSE8’ for computer aided dosimetry based on a series of planar anterior and posterior scintigraphy images. The software includes several, partly automated options for dosimetric data collection [3].

All anterior and posterior scintigraphy images belonging to one series are displayed simultaneously. The medical expert can (i) interactively switch between images of different capturing time, (ii) create and name new ROIs, (iii) delete or manipulate any existing ROI. Additionally, the medical expert is supported by (i) registration functionality that semi-automatically corrects for an offset in the ant and post view images as well as a fully-automatic registration of all images in the time series as well as (ii) a segmentation tool that allows for a comfortable semi-automatic segmentation of the structures in question. Finally, the user is provided with information such as actually effective half-times, uptake and residence time of radiation in different ROIs, but has also access to intermediate results like their size (number of pixels) and their mean gray value progressions (counts) over time in ant and post view. These data as well as all images, ROI masks and further required patient information can be exported in common file formats (*.mat, *.csv, *.png) and serve as input for the very last and brief consecutive processing step in the dosimetry software ‘Olinda/EXM’ used to finish calculations of the dose distribution [6].

2.2. Image registration

Since scintigraphy images belonging to one series are taken at different time points, image data are not registered a priori and, therefore, correct alignment of corresponding image regions cannot be assumed. Furthermore, ant and post images cannot be assumed to be registered to each other in general. In order to support the medical expert in placing the ROI masks in all ant and post images, a rigid registration based on template matching has been implemented.

Corresponding ant and post images are registered from the software using the dose marker that is always visible in both images (small high-contrast circular region). Due to this pre-registration, the registration of the time series can be restricted to either all ant images or all post images.

The normalized cross correlation (NCC) is known to be reasonably robust against global intensity offsets and contrast variations, which strongly occur since the radiation dose decreases constantly with time. Although the change of contrast in the image series is, up to a certain degree, most likely to be non-linear over time, Sjögren et al. demonstrated good results using the NCC as distance measurement feature for matching scintigraphy images [7]. We also successfully adopted this approach to our problem.

The thorax region taken from the middle image in the time series serves as template image in the NCC containing meaningful information. For an automatic extraction of the NCC template the minimum whole body bounding box is estimated applying the ‘whole body detection’ algorithm explained in section 2.3. From this bounding box the thorax area lying between 1/7 (upper limit) and 2/5 (lower limit) in the vertical direction is cropped. The given limits were empirically determined by Sjögren et al. [7].

2.3. ROI segmentation

The image registration is followed by a segmentation step in which the relevant structures such as the whole body region and the organs and tumors of interest are being segmented. In order to considerably speed up the segmentation process we support a fully automatic segmentation algorithm for the whole body segmentation and a second, semi-automatic algorithm that allows the medical expert to fine-tune the segmentation result of organs and tumors. The segmentation algorithms should work robustly in quite noisy scintigraphy images, enable the user to interactively influence the segmentation process and provide closed contours as segmentation output.

In order to calculate organ doses in respect to the initially applied dose, it is necessary to determine the whole body counts in the first image of a time series as reference. Therefore, the whole body region is fully automatically detected by a region growing approach which is applied on the background region, see *Figure 1* (boundaries in the middle scintigraphy). Before the region growing, the image is Gaussian filtered and gray-scale opening and closing operations [1] are applied to remove radiation scatters outside the body. The region growing algorithm's homogeneity criterion is defined as the region mean intensity, and neighbor pixels are added to the region if their gray value difference to the current mean intensity is below a certain threshold. The largest region of the complement of the segmentation result represents the wanted body region.

The semi-automatic algorithm for organ and tumor segmentation is based on parametric B-spline snakes as introduced by Sekhar et al. [4]. The medical expert has to initialize a B-spline by either placing knot points around the object that should be segmented or can likewise instantiate an organ

shape from a data base and adjust it to the actual data. The required amount of points varies depending on organ complexity and size; usually 10-20 knot points are sufficient. Then the algorithm calculates a B-spline of the given points and optimizes the result iteratively according to the scheme of the snake optimization algorithm explained by Sekhar et al.. If necessary, the user can easily readjust knot points and restart the snake optimization to improve the segmentation result further.

2.4. Dosimetry calculation

The underlying dosimetry calculation method for ‘DoSE8’ is the ‘Individual patient dosimetry for radio receptor therapy using ^{177}Lu DOTA-TATE and ^{177}Lu DOTA-NOC’ method developed by and used at the PET center Bad Berka, Germany. This method, which is based on the MIRD scheme [6], consists of the following steps:

(i) ROI analysis of a time series that consists of at least five planar scintigraphies is performed, (ii) size and radiation counts for each ROI are determined, (iii) additionally a geometric based background subtraction is calculated on the basis of patient and source region thickness, (iv) activity distributions and time characteristics in interesting regions are calculated, (v) uptake of organs and tumors is then fitted to exponential curves of first or second order. The resulting parameters describe the actually effective half-times (resulting as a composition of physical and biological half-times) as well as initial activity and residence time in important regions. (vi) Finally, the mean absorbed doses are estimated with the help of s-value charts, which were developed by the MIRD committee. They include types and dimensions of emitted energies, geometrical aspects like size, shape, and distance of source and target regions as well as composition of absorbing and intermediate tissue. All described steps except the very last that is done with the software Olinda/EXMTM are incorporated in ‘DoSE8’. [8]

3. Results

14 whole body scintigraphy image series ($K = 14$) taken from patients treated with ^{177}Lu -DOTA-TATE were used as basis for the evaluation. Each dataset consisted of five ($K = 5$) manually segmented ROIs (organs and tumors) in average, resulting in approximately 70 regions at all. The manual segmentation data are generated by a medical expert using ‘DoSE8’.

3.1. Image Registration

The NCC gives a 2D-translation vector $\mathbf{r}_k = (x_k \ y_k)^T$ between the template (extracted from the medial image) and every of the remaining $k = \{1, \dots, K - 1\}$ images belonging to the image time series. These automatically determined image shifts are compared to the median translations $\mathbf{m}_k = \text{Median}_M(\mathbf{u}_k)$ of the M_k ROI masks of the k^{th} time series image in the n^{th} data set that have been manually shifted by the corresponding shift vectors \mathbf{u}_k . The *mean shift difference* $\mu_d = E_k\{d_k\} = (d_{d,x} \ d_{d,y})^T$, with $d_k = \mathbf{r}_k - \mathbf{m}_k$, over all time series images serves as criterion for the evaluation of the registration approach. In order to confirm the applicability of such a simple rigid registration approach (translation via template matching), we evaluated two additional criteria: the patients’ *vertical body orientation* α_k in each image and the standard deviation of the *manual ROI shifts* $\sigma_{\text{int}} = \text{Std}_{M,K}(\mathbf{u}_k) = (\sigma_{d,x} \ \sigma_{d,y})^T$ over all $K - 1$ time series images, again excluding the medial reference image. σ_{int} serves as a measure for organ or tumor movements relative to each other over time (inter organ variability) and inaccuracies in the manual shift estimation. It allows for exclud-

ing the necessity of a non-rigid transformation. For the purpose of estimating the vertical body orientation, the physician additionally provided manually drawn body triangles (base of the neck and the middle of the crouch) for each scintigraphy from which we calculated vertical body orientation angles α_{α} as well as their mean values μ_{α} and standard deviations σ_{α} over all time series images.

The absolute value of the *mean shift difference* μ_d lies in a range between 0.16 px and 5.72 px. The average mean difference for all considered data sets and independent of the direction is about 1.91 px. Comparing these results to the average patient body size of about 230×750 px, the registration results are quite acceptable. The mean variations μ_{α} in the *vertical body orientation angles* of all images belonging to one series are less than 1° for all N evaluated data sets; the corresponding standard deviations σ_{α} are between 0.16° and 1.85°. Thus, adding the rotation as third transformation parameter would not significantly improve the quality of the image registration, but would unnecessarily decrease the robustness and performance of the algorithm. The standard deviation σ_{int} of the *mean manual ROI shift* for the evaluated data sets are in a range of 0.92 px to 4.41 px, showing a total average of 2.08 px. Compared to the typical size of an organ or tumor of about 50 px, such low shift variations confirm the assumption of only very slight organ and tumor movement inside the upper body. Thus, a rigid translation as applied appears to be sufficient for registering scintigraphy images.

3. 2. Image segmentation

The segmentation accuracy was assessed by comparing the segmented region boundaries of manually segmented and automatically segmented tumors and organs resulting in a total of 70 compared segmentations. The mean segmentation error concerning the absolute contour difference was 1.94 px for all ROIs and merely 1.54 px for tumors. The corresponding standard deviation of the segmentation errors was 1.91 px for all ROIs or 1.21 px for tumors respectively. Overall, this is not a bad result, especially when keeping in mind the very poor image quality and the significantly accelerated segmentation process. The inter-observer variability that was assessed by comparing multiple segmentations of five medical experts showed quite the same order of magnitude.

3. 3. Time requirement

In order to assess the gained speed up, full dosimetries of fourteen representative datasets were calculated using ‘DoSE8’. Due to the integrated automatic registration, the semi-automatic segmentation and the built-in calculation the current software reduces the typical required time for a dosimetry, as it is known from traditional examinations, from approximately 5-6 hours to less than 15 minutes on average for the fourteen processed datasets in these study, thus a total time reduction of about 96% is achieved.

4. Conclusions

The proposed software ‘DoSE8’ supports image handling and processing functionalities which significantly speed up the process of dosimetry and, therefore, makes dosimetry calculation in clinical routine possible at all. Furthermore, subjective errors due to human exhaustion and misinterpretation can be reduced and precision as well as quality of segmentation is improved. The evaluation results of the used registration and segmentation algorithms are quite promising. In order to evaluate the system as a whole, the next step in the project will be to compare final dosimetry results obtained with DoSE8 to dosimetry results obtained with the traditional method.

5. References

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