Effect of image registration on 3D absorbed dose calculations in ^{177}Lu-DOTATOC Peptide Receptor Radionuclide Therapy

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1 **Running Title**

2 Effect of image registration in PRRT 3D absorbed dose calculation.

Abstract

Peptide receptor radionuclide therapy (PRRT) is an effective MRT (molecular radiotherapy) treatment, which consists of multiple administrations of a radiopharmaceutical labelled with ^{177}Lu or ^{90}Y. Through sequential functional imaging a patient specific voxel-based time-integrated-activity curve can be derived and used to calculate the cumulated activity. Multiple scans should be co-registered to allow accurate, patient specific 3D dosimetry. The purpose of this study is to measure the quality and to evaluate the impact of image registration algorithms on 3D absorbed dose calculation.

A cohort of 11 patients was extracted from the database of a clinical trial in PRRT. They were administered with a single administration of ^{177}Lu –DOTATOC. All patients underwent 5 SPECT/CT sequential scans at 1h, 4h, 24h, 40h, 70h post-injection that were subsequently registered using rigid and deformable algorithms. A similarity index was calculated to measure the quality of rigid and deformable registrations and to compare the two algorithms. 3D absorbed dose calculation was carried out with the Raydose Monte Carlo code.

The similarity analysis showed that deformable registrations provide superior results than rigid registrations ($p<0.001$).

Average absorbed dose to the kidneys calculated using rigid image registration was consistently lower than the average absorbed dose calculated using the deformable algorithm (90% of cases), with percentage differences in the range [-19;+4]%. Absorbed dose to lesions were also consistently lower (90% of cases) when calculated with rigid image registration with absorbed dose differences in the range [-67.2,100.7]%. Deformable image registration had a significant role in calculating 3D absorbed dose to organs or lesions with volumes smaller than 100mL.

Image based 3D dosimetry for ^{177}Lu-DOTATOC PRRT is significantly affected by the type of algorithm used to register sequential SPECT/CT scans. It is advisable to implement deformable image registration in clinical practice.

Introduction

Peptide receptor radionuclide therapy (PRRT) with radiolabelled somatostatin analogues is a specific type of molecular radiotherapy (MRT) and an effective treatment for patients with neuroendocrine tumours (NETs) [1]. It has been shown that three-dimensional (3D) voxel-based patient specific dosimetry is possible and allows to accurately assess the dose absorbed by the organs at risk (OARs) and by the different areas of the disease, as a measure of the potential therapeutic effect [2, 3, 4, 5].

Every methodology adopted for dosimetry is affected by a number of metrological issues and uncertainties as highlighted by D'Arienzo et al [6] and by Gustafsson et al [7]. These include, among others, measurement of administered activity, quantification of activity from imaging within a volume in the patient, construction and integration of the time-activity curve from imaging, and calculation of the absorbed dose. Moreover, patient specific pharmacokinetics and individual variations in anatomy determine unique three-dimensional radiopharmaceutical distributions inside the body as a function of time. For PRRT delivered with ^{177}Lu labelled somatostatin receptors the bio-distribution of the radiopharmaceutical may be assessed by performing multiple SPECT/CT scans. Through sequential SPECT/CT scans a patient specific voxel-based time-integrated activity curve can be derived and used to calculate the cumulated absorbed dose with either dose point kernel algorithms or Monte Carlo simulations or local energy deposition.

When dealing with sequential functional imaging, the misalignment of sequential scans is a critical aspect, by which the global accuracy of the dosimetry calculations can be strongly affected. Misregistration errors can derive from changes in patient repositioning, organ deformation, tumour progression/regression between different scans and

respiratory motion, as reported also by some critical works related to PET/CT diagnostics [8] and external beam radiotherapy [9, 10]. Whatever the source of these errors, they are likely to lead to a poor estimation of organ absorbed doses at the voxel level, and consequently to a sub-optimal treatment plan and to an erroneous prediction of MRT treatment response. On the other hand, several authors recommend to optimize MRT planning to limit the absorbed dose to OARs, while maximizing the tumour control in individualized MRT treatments [3]. Since only a series of 3D images may provide scientists for the possibility to apply all modelling and fitting methods to each voxel individually, approaching a totally personalized treatment, the registration of images should be as more adequate as possible.

For these reasons, and together with the need to implement more accurate 3D patient specific dosimetry calculation in MRT, a strong interest towards issues related to image registration has lately raised [11, 12]. Recently Jackson et al. [2] used sequential rigid and deformable registration to align SPECT/CT images in PRRT dosimetry calculations. They performed a CT to CT registration, due to the intrinsic variation in activity distribution of SPECT images, which makes SPECT to SPECT registration inadequate.

Although a full comparison between deformable and rigid registration methods was not carried out in that study, the authors concluded that registration accuracy and limited spatial resolution of the SPECT camera may preclude absorbed dose calculations to very small volumes and may have a low impact on estimated absorbed doses of large organs, especially if these organs exhibit homogenous uptake areas.

Ao et al [13], on the other hand, didn't present a complete study. They showed that deformable image registration can affect the accuracy of 3D dosimetry with ^{111}In-Zevalin, compared to rigid registration, but they based their study on a modelled phantom population. Therefore, important limitations were raised even by the authors: the respiratory

motion during SPECT/CT acquisitions was not modelled in the simulation; the study was basically on phantom, so any clinical reference on the realistic degree of deformation among different imaging time points was not considered; they unrealistically simulated uniform activity distributions in organs.

Furthermore, their study used only a single patient case (4 SPECT scanned at different time points and 1 CT scan acquired at 24h p.i. for attenuation correction) with the aim to prove that the clinical results were consistent with the simulations.

They focused on the impact of organ-by-organ deformable registration on quantitative SPECT images and investigated only the improvement in organ absorbed dose assessment.

In this study, instead, we systematically investigate the impact of using image registration within the context of an image based dosimetry trial in PRRT delivered with the administration of a therapeutical activity of ^{177}Lu-DOTATOC in patients suffering from metastasized NET with intense somatostatin receptor expression. Our clinical study included the acquisition of sequential quantitative SPECT/CT scans and the segmentation of both OARs and target lesions in the abdomen (mainly liver) and in the lung. With this work, we aim at demonstrating that it is feasible to implement a deformable image registration workflow in clinical MRT dosimetry and we hypothesize that the use of deformable image registration instead of rigid image registration (as defined by Brock et al [14]) delivers a significantly different representation of the 3D distribution in MRT for OARs and lesions different in size, shape and uptake level.

Material and Methods

Study protocol

A group of patients suffering from NET cancer was recruited for PRRT as part of a clinical trial (EUDRACT 2013-002605-65) at AUSL-IRCCS, Reggio Emilia, Italy. The study was conducted in accordance with the provisions of the Declaration of Helsinki and the ICH-GCP Guidelines. All patients entering the trial were asked to give written informed consent for research purposes. Patients were administered with a therapeutical dosage of the radiopharmaceutical ^{177}Lu -DOTATOC to perform the internal dosimetry study, according to the EANM guidelines [15]. The dosimetry study was performed only once after the first injection, though later in time patients received multiple fractions of radiopharmaceutical (^{177}Lu –DOTATOC or ^{90}Lu –DOTATOC). The first injected activity was chosen based on clinical conditions of patients, since the dosimetry study outcome had not been performed yet. The following injected activities were chosen based on more precise patient specific characteristics (general clinical state; presence of risk factors such as hypertension, diabetes, previous renal failure; one kidney resection). No injected activity was fixed or chosen based only on weight or body surface area, or similar approach, because the personalization of PRRT was the aim of the trial. The adopted administration protocol was described elsewhere [16].

A cohort of 11 clinical cases (in the following referred to as the cohort) was extracted from the clinical trial database and considered in this investigation. The choice of the clinical cases was led by the size of the lesions (typical volumes in the range [4mL, 150mL]) and by the anatomical area in which the lesions were located (e.g. different segments of the liver).

The mean administered activity for the cohort was 5.3 ± 0.9 GBq. Differences in administered activity were due to differences in patient's weight, height and other clinical parameters. After injection, 5 sequential SPECT/CT

abdominal scans (5 SPECT and 5 CT, i.e. one SPECT/CT for each time point; each CT image was used for attenuation correction of the relative SPECT image and for anatomical reference) were taken with the patient in supine position at 1, 4, 24, 44 and 72 hours post injection (p.i.). The standard imaging protocol required that patients kept their arms raised and placed above the head. However, no specific patient positioning protocol was adopted. Patients with special needs were provided with comfort devices such as knee fix or comfort cushions and the same devices were adopted in all sequential images.

The abdomen SPECT images were acquired with a dual head gamma camera (SymbiaT2, Siemens Medical, Germany, 3/8" NaI(Tl)-detector) and the following settings: two medium energy (ME) collimators; matrix = 128 x 128; zoom = 1; views =32 x 2; time/view = 30 s; step and shoot mode; degree of rotation = 180°; non-circular orbit; detector configuration = 180°. The energy windows (EW) of ^{177}Lu photo-peaks used for imaging [17] were set at 113 keV ± 7.5% and 208.4 keV ± 7.5%. For the lower EW, the triple energy window (TEW) scatter correction was used (lower scatter window 87.58 – 104.53 keV, weight = 0.5; the upper scatter window 121.47 - 130.51 keV, weight= 0.9375). For the higher EW, the double energy window (DEW) scatter correction was used (lower scatter window 171.60 - 192.40 keV, weight = 0.75). The helical CT parameters were 130kV of voltage with care dose tool activated to optimise the anodic current for patient dose saving (maximum anodic current set at 90mAs for the first high quality CT at 1h p.i. and at 40mAs for CT acquired at 4h, 24h, 40h, and 70h p.i.), slice thickness 5mm.

The SPECT projections were reconstructed using an iterative algorithm with compensations for attenuation, scatter, and full collimator-detector response as implemented in the E-Soft workstation v32B (Syngo, Siemens Medical Solution, Germany) with the Flash 3D iterative algorithm (10 iterations; 8 subsets; Gaussian filter cut-off = 4.8 mm;

4.8 mm cubic voxel). The SPECT/CT acquisition and reconstruction protocols were previously validated by Grassi et al [18, 19].

Clinical practice of dosimetry in MRT requires the implementation of a specific calibration protocol allowing for the SPECT image to be expressed in units of Bq/mL [20], since this modality is not at present an intrinsically quantitative imaging technique. In our study a calibration factor (CF) in unit of Bq/counts was derived in reference conditions to convert the SPECT count data in absolute activity per voxel. We used a standard cylindrical plastic phantom of 5640 mL volume (Data Spectrum Corporation, Durham, USA) filled with a homogenous solution of ^{177}Lu (0.25 MBq/mL). The calibration protocol was described in detail elsewhere [18]. In brief, the reference phantom was scanned 5 times after preparation until the activity concentration reached a value of approximately 0.0078 MBq/mL (~ 5 half-lives of ^{177}Lu). As expected from the results about dead time obtained by Grassi et al [19], the CF was not affected by the count rate in the range of activity considered. The CF values calculated at different time points showed no significant deviation from a linear trend, and had a mean value of 28.5 Bq/counts and a standard error of 4%. This value was used to convert the clinical SPECT images in absolute activity distributions. Out scanner was characterized for Partial Volume Effect (PVE) [18,19] but contrast recovery was not considered here.

For each patient, both right and left kidneys were manually segmented on the first CT scan by a nuclear medicine physician together with a nuclear medicine physicist using the VoxelMed software [18]. This CT scan was acquired with no image contrast agent and with a high image quality protocol. In addition, target lesions were manually outlined with the same software on the same CT scan when possible or alternatively on a fused SPECT/CT scan. In the remainder of the manuscript these cases are referred to as ‘CT’ and ’SPECT/CT’ respectively. All volumes of

interest (VOI) were exported to file in the DICOM format for further analysis. All VOIs were validated by a physician.

Clinical dosimetry reporting was done in accordance with EANM guidelines [21].

Registration of sequential SPECT/CT images

In this study, we used both rigid and deformable image registration to bring, for each clinical case, the 5 sequential SPECT/CT scans in the same frame of reference of the first CT scan.

The rigid registration was manually performed using the Siemens E-Soft workstation. Each SPECT scan was registered to the reference CT scan using translations and rotations only, using an iterative process until the best match for the kidneys was visually found.

The deformable registration was performed with Velocity (Varian Medical Systems, Palo Alto, USA), which uses a modified B-spline deformable algorithm with mutual information-based matching [22]. This algorithm performs a 3-pass deformable registration (coarse, medium and fine resolution), that adds a very precise touch to the images. This kind of deformation is recommended generally used for CT to CT registration and, in general, to register high resolution images. Velocity's deformable image registration algorithm was found to be capable of considerably reducing the residual misalignment of anatomical structures by Hoffmann et al [23].

In this work, the CT component of each SPECT/CT scan was first manually registered to the reference CT scan to match the bony anatomy and then the Velocity deformable multi-pass registration algorithm was applied for optimal

image fusion over the whole image. Images registered with the Velocity deformable registration algorithm were visually assessed and considered to be clinically acceptable. The deformable registration was carried out between the CT scans, and the resulting deformation map was applied to the corresponding SPECT scan. The temporal scan sequence is reported in Figure 1 (a). Both rigid and deformable registration workflows are depicted in Figure 1 (b) and Figure 1 (c). An example of a rigid and a deformable registration is shown in Figure 2 with the relevant VOIs.

The quality of the image registration was evaluated using the Structural Similarity Index (SSIM) [14] as implemented in the MATLAB (The Mathworks, Natick MA) platform. SSIM was designed to provide an objective metric for comparing a distorted image to a distortion-free (reference) image and is calculated as a combination of pixel intensity, contrast and structural information [24]. In this work, SSIM was calculated in the range [0,100] where 100 indicates a perfect match between the images. For all the clinical cases, the SSIM values were calculated between the first CT scan (used as reference) and the sequential CT scans registered using both rigid and deformable algorithms. Differences between SSIM values for the deformable and rigid registration were compared with paired samples Wilcoxon tests (two-sided, significance level 0,05) of the four comparison (images acquired at T2, T3, T4 and T5 compared to the CT acquired at T1). Statistical analysis was performed using R 3.3.3 (R Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria, 2017).

Dosimetry calculations

For each patient, all registered images and VOIs were imported in Raydose [25], a full 3D Monte Carlo based application for dosimetry calculations in MRT. Raydose is based on the general purpose Geant4 toolkit and can

transport all particles on a virtual phantom generated from a patient specific CT scan. Raydose can replicate the decay of ^{177}Lu using data taken from the evaluated nuclear structure database (ENSDF available at: www.nndc.bnl.gov/ensdf), and simulates beta-decay spectra and correct intensity photon emission in the subsequent daughter nuclei which contributes to the overall absorbed dose [26]. Each SPECT scan, representing a voxel-by-voxel snapshot of activity at a given time point, was used by Raydose to calculate a total absorbed dose map following the method described by Marcatili et al [25]. 3D absorbed dose calculations using Raydose were carried out for both rigidly and deformably registered scans (cf. Figure 1 (b) and (c) respectively) on two 20 core Dell PowerEdge rack server (Intel Xeon E5-2670 @ 2.5GHz) with each machine equipped with 64 Gb RAM. Full patient absorbed dose calculation, including 5 scans per patient, was carried out in approximately 9 hours. For each scan, 150 million events were simulated giving a MC uncertainty < 5% in the total absorbed dose distribution map. Other sources of uncertainty related for instance to activity calibration were not relevant to this work and were not included. The total absorbed dose distribution calculated with Raydose was exported to file in the DICOM RTDOSE format.

Data Analysis

Standard radiotherapy tools such as Dose Volume Histograms (DVH) were used to assess the quality of the absorbed dose distribution in all clinical cases and for both rigid and deformable image registration. Furthermore, minimum, maximum and average absorbed dose to OARs and lesions were also calculated. A dosimetric comparison between the two registration methods was carried out using the percentage difference (P.D.) figure of merit, calculated using mean absorbed dose values in the VOIs:

$$P.D.=(D_{rig}-D_{def})/D_{def} \times 100 \qquad \text{Eq 1}$$

where D_{rig} and D_{def} are the mean absorbed doses calculated on rigidly registered images and deformably registered images respectively. The deformable image registration method was arbitrarily chosen as a reference given the longitudinal nature of the study. A positive P.D. indicates an overestimation of the average absorbed dose as calculated using rigid registration, while a negative P.D. indicates an underestimation of absorbed dose from rigid registration compared to absorbed dose from deformable image registration.

Results

Figure 3 shows the SSIM values for the deformable registration (straight line) and for the rigid registration (dotted line). All the differences between SSIM values were highly statistically significant ($p < 0.001$).

Single values for SSIM are reported in Table 1 for each patient and for each CT image (acquired at T2, T3, T4 and T5), in comparison with the CT acquired at T1. Standard deviations for rigid and deformable registrations were also calculated. It can be noted that the quality of the registration is higher in the case of deformably registered volumes.

Table 2 reports the absorbed dose volume statistics for kidneys normalized to the administered activity, and the percentage difference, as defined in Eq 1. It can be noted that P.D. is negative for 10 out of 11 patients and ranges from +4% down to -19% (mean=-5,1%; median=-5,2%; 25th percentile=-7,6; 5th percentile=-8,9%). This indicates that the average absorbed dose calculated using rigid image registration (D_{rig}) is consistently lower than the average

absorbed dose calculated using the deformable algorithm (D_{def}). It is also worth noting that in some cases (e.g. patient 3 and 10) there is a large difference (>5%) in P.D. between left and right kidney for the same patient, mainly due to a difficult rigid registration, caused by patient's twisting or tilting.

Table 3 reports the absorbed dose volume statistics for lesions, normalized to the administered activity, and the percentage differences. In this case P.D. ranges from -67.2% to 100.7% (mean=-15.0%; median=-17.11%; 25th percentile=-6.25%; 5th percentile=+0.10%). The image modality used for the segmentation of the lesion is also reported.

The DVHs calculated for rigid and deformable registration are depicted in Figure 4a (kidneys) and Figure 4b (lesion) for clinical case No. 5 (cf. Figure 2).

Figure 5 depicts the P.D. as a function of volume for all VOIs. The imaging modality used to contour the lesions is also reported.

Discussion

The analysis of the similarity index showed that the deformed CT scans are more similar to the reference CT than the rigidly registered CT scans. The deformation matrices, or the rigid registration matrices are the same applied to NM scans, so similarities in CT images are translated to similarities in NM scans. CT images are only taken as reference for both registration algorithms, since NM scans are not adequate showing a time variant distribution of activity in sequential NM imaging.

Hence, the deformable registration algorithm has a higher degree of improvement than the rigid registration, providing an image more similar to the reference one. Furthermore, the standard deviations reported in Table 1 show also that the deformable registration images produce a SSIM index much more stable than the rigid registration. This may be expected, since the rigid registration may be more or less complex depending on the patient repositioning for acquisition or patient movement during acquisitions. While rigid registration is intrinsically 'locally' accurate, deformable image registration is 'globally' accurate as it succeeds in accounting for multiple internal organ movement simultaneously.

The mean absorbed dose calculated with deformable image registration (D_{def}) was found to be in general higher than the mean absorbed dose calculated with rigid registration (D_{rig}). This was expected, since the deformable registration of images causes a change in the quantification of the activity inside VOIs after realignment. The negative value of P.D. in most cases show that deformable registration provides a gain in activity quantification in the VOIs with a consequently higher absorbed dose estimation. In our investigation, in 10 out of 11 cases, D_{rig} for kidneys was lower than D_{def} by up to 19% as shown in Table 2. In 20 out of 22 cases, D_{rig} for lesions was lower than D_{def} by up to 67% as shown in Table 3. An interesting correlation between P.D. and imaging modality in which the lesion was outlined ('CT' or 'SPECT/CT') is also shown in Table 3. Indeed, it can be noted that when the lesion was outlined on a fused scan (i.e. 'SPECT/CT') and the corresponding mass used in absorbed dose calculations, the P.D. for D_{rig} compared to D_{def} was higher than 20%, in 80% of the cases. On the other hand, when the contour was based on CT and the corresponding mass used in absorbed dose calculations, the P.D. was lower than 20%, in 75% of cases. This suggests that the choice of the imaging modality used for target delineation is an additional important factor to consider when

the aim is to evaluate the effect of the deformable algorithm on the absorbed dose calculation. These results could be helpful in informing volume segmentation protocols in future clinical trials in PRRT and other kind of MRT.

Figure 4 clearly shows that while the effect of the image registration algorithm on the absorbed dose statistics extracted from relatively large OARs might be negligible, it can have a large impact on the absorbed dose calculation for target lesions with underestimations of the absorbed dose to 50% of the volume that can be as large as 60% and an underestimation of the maximum absorbed dose to the lesion up to 70%. This can have important consequences in absorbed dose prescription and in the evaluation of the effectiveness of therapy.

Figure 5 shows a clear dependence of P.D. with lesion volume: larger volumes correspond to smaller P.D. In our study, lesion volumes were in the range [4, 166] mL with a mean value of 34 mL. The same dependence is not so evident for the kidneys (range [125, 346] mL, mean 214 mL). For larger lesions with a volume comparable to that of the kidneys, the P.D. was lower than 5%, which is in line with the mean P.D. calculated in the analysis of the kidney absorbed dose distribution. Our data indicates that deformable registration affects organ absorbed dose calculation mainly when volumes are smaller than 100mL. This volume interval is in our experience the range of volume of lesions in PRRT.

The following additional observations can be made: (a) in patient No. 5 (cf. Figure 2), ‘liver lesion 1’ (volume 8 mL, ‘CT’ contouring modality) is characterized by a large negative P.D. of -67.2% (figure 2 to see the area of the liver). This value can be explained by the presence of a motion artefact in the abdomen hugely corrected using deformable image registration, and by the modality of contouring; (b) in patient No. 9, ‘liver lesion 3’ (volume 26 mL, ‘CT’ contouring modality) is characterized by a large positive P.D. value of 100.7%. This was due to a significant motion

artefact affecting the superior abdominal region causing a large mismatch between the reference CT image and the sequential SPECT images. The deformable registration algorithm was unable to correct for the mismatch; (c) in patient No. 6, 'liver lesion 4' (volume 4 mL, 'SPECT/CT' contouring modality) is characterized by a small P.D. of 0.3; in this case, the performance of both registration algorithms was equally good due to the reproducibility of the location of the lesion across scans together with the limited spatial resolution of SPECT images.

In our experience, deformable image registration was a useful tool in accounting for misregistrations due to respiratory motion and patient repositioning. The extent and the effect of the correction depended on many factors including the location of the anatomical volume that needed to be registered, the anatomical position of the organ or lesion and on the volume of the VOIs. Whereas several works about the deformable registration in external radiation therapy have been published with plenty of results (e.g. in the work of Pukala J et al [27]), in MRT only few papers are available [2, 13]. Also, a recent work shows the superiority of deformable registration of PET/CT to planning CT by multiple positional metrics, compared to rigid registration [28].

Jackson et al. [2] reported that the accuracy of the CT to CT deformable image registration of SPECT/CT studies and the limited spatial resolution of the SPECT camera may have a low impact on the estimated absorbed dose calculation of large organs and of lesions down to 2-3cm in diameter (corresponding to spherical volumes between 4 and 14 mL). This is true, because the exact voxel-to-voxel alignment have a marginal impact on estimated absorbed dose. In our study, all lesions had a volume larger than 4mL and 16 out of 22 had a volume larger than or equal to 14 mL. In our experience, deformable registration could be successfully used across the range of VOIs considered in this study. Even if the differences between D_{rig} and D_{def} were found to be smaller for kidneys than for lesions, deformable image

registration proved to have a key role in the 3D absorbed dose calculation process as it took into account variations in patient specific anatomical characteristics.

The differences between D_{rig} and D_{def} observed in our study are on average smaller than those observed by Ao et al [13] in their study. This may be due to the fact that Ao et al used one single CT image acquired at 24h p.i. for the attenuation correction in the reconstruction of each sequential SPECT image acquired at different time points. In addition, they outlined VOIs on the SPECT scans, that in many cases are larger than VOIs contoured on CT images. On the other hand, we acquired a different CT scan for each SPECT scan and used this information in both attenuation correction and image registration. This approach makes quantitative imaging more accurate and more adequate for a PRRT trial. Our image registration workflow was based on anatomical imaging and VOIs were outlined in the majority of cases on the first CT scan.

In particular, in this study we also considered the contribution of 'CT' contouring modality in SPECT quantification on big down to small clinical volumes (i.e. organ down to lesion size).

The 'CT' contouring modality may be a more accurate criterion to define the morphological size of tumours. Also, Uribe et al [29] studied the CT guided segmentation of SPECT images in phantoms, compared to 40% fixed threshold segmentation and to a complex segmentation algorithm developed by Grimes et al. [30]. They concluded that the 'CT' contouring modality performed better than SPECT 40% fixed threshold segmentation for objects with volume larger than about 8.5ml, but depending on the shape of the inserts. For smaller volumes, they stated that the 'CT' contouring modality in SPECT quantification is strongly affected by partial volume effect. The strong need for partial volume

effect correction (by calculation of recovery coefficient for missing activity) for small volumes obtained with a 'CT' contouring was reported also by Grassi et al [19].

Unfortunately, the 'CT' contouring modality may be difficult to use in clinical SPECT exams sometimes, since tumours are not always clearly visible in CT images. A way to deal with this problem may be to adopt a contouring based on SPECT images, which performs similarly to 'CT' contouring modality for small volumes [29]. This was observed in this work as well.

In conclusion, three-dimensional image based dosimetry for ^{177}Lu-DOTATOC peptide receptor radionuclide therapy is significantly affected by the type of algorithm used to register sequential SPECT/CT scans. We have shown that it is feasible to implement in the clinical practice a workflow based on deformable image registration. This could have important implications in the design of future trials in PRRT.

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Conflicts of interest

The authors have no relevant conflicts of interest to disclose.

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Table 1

Brief Title for Table 1: SSIM values

	CT(T2) versus CT(T1)		CT(T3) versus CT(T1)		CT(T4) versus CT(T1)		CT(T5) versus CT(T1)	
Case Number	**Deformable**	**Rigid**	**Deformable**	**Rigid**	**Deformable**	**Rigid**	**Deformable**	**Rigid**
1	99,58%	98,53%	99,59%	97,18%	99,44%	96,44%	99,62%	96,44%
2	99,66%	98,95%	99,62%	98,16%	99,60%	98,47%	99,62%	98,17%
3	99,62%	97,86%	99,38%	98,30%	99,56%	98,01%	99,30%	97,98%
4	99,62%	98,49%	99,66%	96,99%	99,55%	97,71%	99,62%	98,54%
5	99,61%	98,60%	99,59%	98,76%	99,71%	98,63%	99,37%	97,81%
6	99,53%	98,71%	99,40%	98,27%	99,48%	97,14%	99,38%	97,97%
7	99,66%	97,35%	99,55%	97,08%	99,43%	97,11%	99,55%	95,32%
8	99,73%	97,04%	99,65%	97,09%	99,69%	97,97%	99,67%	98,25%
9	99,65%	97,32%	99,65%	97,92%	99,62%	98,61%	99,55%	98,03%
10	99,57%	98,95%	99,49%	98,34%	99,40%	98,12%	99,42%	97,61%
11	99,49%	97,67%	99,36%	96,98%	99,37%	96,53%	99,44%	96,88%
Standard deviation	**0,07%**	**0,70%**	**0,11%**	**0,67%**	**0,12%**	**0,79%**	**0,13%**	**0,96%**

Table 1 SSIM values calculated for each patient and for each CT image (acquired at T2, T3, T4 and T5) in comparison with the CT acquired at T1. Index values were used to investigate the similarity of deformbly and rigidly registered images with the reference CT acquired at T1.

Table 2

Brief Title for Table 2: Absorbed dose volume statistics for kidneys

Case number	VOI		Absorbed dose (mGy/MBq) Deformable registration			Absorbed dose (mGy/MBq) Rigid registration			P.D.
	Name	Vol (mL)	Min	Mean	Max	Min	Mean	Max	
1	right kidney	268	0.03	0.51	1.25	0.04	0.49	1.18	-4.7
	left kidney	210	0.01	0.50	1.30	0.03	0.49	1.52	-0.4
2	right kidney	135	0.13	0.82	3.21	0.06	0.76	3.23	-7.9
	left kidney	144	0.00	0.65	1.29	0.00	0.59	1.24	-8.9
3	right kidney	138	0.10	0.73	1.40	0.07	0.67	1.40	-8.1
	left kidney	125	0.07	0.65	1.58	0.05	0.64	1.55	-2.6
4	right kidney	283	0.01	0.37	1.14	0.02	0.37	1.13	-0.5
	left kidney	282	0.02	0.39	1.21	0.01	0.37	1.14	-5.6
5	right kidney	156	0.22	1.08	2.04	0.20	1.05	1.86	-2.6
	left kidney	156	0.10	1.01	2.07	0.09	0.94	2.04	-6.9
6	right kidney	346	0.01	0.73	1.80	0.01	0.72	1.75	-1.3
	left kidney	252	0.07	0.84	1.98	0.05	0.80	1.86	-4.6
7	right kidney	198	0.06	0.76	1.71	0.05	0.71	1.71	-6.1
	left kidney	196	0.04	0.69	1.69	0.04	0.65	1.89	-6.4
8	right kidney	241	0.09	0.77	1.58	0.07	0.71	1.37	-7.9
	left kidney	254	0.03	0.74	1.43	0.02	0.67	1.38	-8.8
9	right kidney	203	0.01	0.84	1.93	0.02	0.87	1.77	4.2
	left kidney	174	0.06	0.90	2.10	0.06	0.89	2.01	-0.4
10	right kidney	234	0.03	0.47	0.95	0.02	0.38	0.99	-19.0
	left kidney	232	0.02	0.47	0.98	0.03	0.45	1.32	-4.0
11	right kidney	243	0.05	0.58	1.20	0.05	0.55	1.28	-5.1
	left kidney	246	0.02	0.56	1.24	0.02	0.53	1.24	-5.3

Table 2 Absorbed dose volume statistics for kidneys normalized to the administered activity and percentage difference on mean Absorbed dose values (cf. Eq 1) between rigid and deformable registration.

Table 3

Brief Title for Table 3: Absorbed dose volume statistics for lesions

1

Case	Lesion			Absorbed dose (mGy/MBq) Deformable registration			Absorbed dose (mGy/MBq) Rigid registration			P.D.	Modality
	Type	No.	Vol (mL)	Min	Mean	Max	Min	Mean	Max		
1	liver	1	166	0.18	2.52	5.21	0.05	2.20	5.05	-12.6	CT
	liver	2	148	0.09	1.60	4.04	0.10	1.53	3.71	-4.7	CT
2	liver	1	23	0.21	2.79	8.03	0.37	2.36	7.52	-15.6	CT
	liver	2	20	1.06	4.46	6.83	0.66	4.15	6.72	-7.0	CT
3	liver	1	10	0.24	0.78	1.71	0.20	0.61	1.69	-21.5	SPECT/CT
4	bone	1	39	0.00	0.18	0.85	0.01	0.14	0.61	-21.6	SPECT/CT
5	liver	1	8	0.22	0.76	1.74	0.07	0.25	0.59	-67.2	CT
6	lung	1	20	0.05	2.37	7.26	0.11	1.93	6.79	-18.6	CT
	liver	2	15	0.30	1.64	4.44	0.25	1.29	3.92	-21.5	SPECT/CT
	liver	3	25	0.18	1.45	3.41	0.05	0.96	3.45	-33.5	SPECT/CT
	liver	4	4	0.19	0.61	1.37	0.05	0.61	1.40	0.3	SPECT/CT
7	abdomen	1	6	0.16	0.36	0.50	0.14	0.34	0.50	-6.1	CT
	abdomen	2	38	0.10	0.52	1.19	0.12	0.49	1.09	-6.1	CT
8	liver	1	11	0.13	0.86	2.72	0.07	0.48	2.66	-44.2	SPECT/CT
	liver	2	6	0.12	0.58	1.35	0.07	0.32	1.13	-43.9	SPECT/CT
	liver	3	14	0.12	0.73	2.86	0.10	0.70	2.55	-3.8	SPECT/CT
9	abdomen	1	44	0.08	2.26	10.07	0.13	2.11	7.77	-6.7	CT
	abdomen	2	16	0.25	5.29	16.73	0.34	4.77	16.30	-9.9	CT
	liver	3	26	0.19	1.50	9.54	0.20	3.01	10.95	100.7	CT
10	abdomen	1	56	0.04	0.98	2.64	0.07	0.71	2.81	-27.0	CT
	liver	2	47	0.09	0.77	1.59	0.14	0.57	1.66	-26.4	SPECT/CT
	liver	3	26	0.15	0.76	2.82	0.12	0.51	1.96	-32.8	SPECT/CT

Table 3 Absorbed dose volume statistics for lesions normalized to the administered activity and percentage difference (cf. Eq 1) between rigid and deformable registration. The imaging modality used for VOI segmentation is also reported.

Captions

Figure 1 Temporal sequence (a), rigid registration (b) and deformable registration (c) of SPECT/CT scans acquired in this study. Identity registrations are represented by the double line connector (=). Rigid and deformable registrations are represented by the straight ( ) and curved line connectors (∗) respectively. All transformation matrices operating on a given scan, can also be applied to all other scans that are in the same frame of reference (i.e. identity registered).

Figure 2 Example of rigid (a, b, c, d) and deformable (e, f, g, h) registration for clinical case No. 5. Kidneys are visible in the transverse axis (a, e) while the lesion is shown in the transverse (b, f), coronal (c, g) and sagittal axis (d, h).

Figure 3 SSIM value calculated for deformable registrations (solid line) and rigid registrations (dotted line). CT images acquired at T2, T3, T4 and T5 were separately compared with the CT acquired at T1 ($p<0.001$ for each plot).

Figure 4 DVHs for kidneys (a) and lesions (b) calculated on rigidly (dashed line) and deformably (solid line) registered SPECT/CT scans for clinical case No. 5 (cf. Figure 2).

Figure 5 Percentage Difference on mean organ absorbed dose as a function of volume for all clinical cases considered in this study.