Application of the EANM practical guidance on uncertainty analysis for MRT absorbed dose calculations on clinical cases

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Abstract

Background

Internal dosimetry evaluation consists of a multi-step process ranging from imaging acquisition to absorbed dose calculations. Assessment of uncertainty is complicated and, for that reason, it is commonly ignored in clinical routine. However, it is essential for adequate interpretation of the results. Recently, the EANM published a practical guidance on uncertainty analysis for molecular radiotherapy based on the application of the law of propagation of uncertainty. In this study, we investigated the overall uncertainty on a large sample of patient following the EANM guidelines. The aim of this study was to provide an indication of the typical uncertainties that may be expected from performing dosimetry, to determine parameters that have the greatest effect on the accuracy of calculations and to consider the potential improvements that could be made if these effects were reduced.

Results

Absorbed doses and the relative uncertainties were calculated for a sample of 49 patients and a total of 154 tumours. A wide range of relative dose uncertainty values was observed (14 - 102%). Uncertainties associated to each quantity along the dose calculation chain (i.e. Volume, Recovery Coefficient, Calibration Factor, Activity, Time-Activity Curve Fitting, Cumulated Activity and Absorbed Dose) were estimated. An equation was derived to describe relationship between the uncertainty in the absorbed dose and the volume. The largest source of error was the VOI delineation. By postulating different values of FHWM, the impact of the imaging system spatial resolution on the uncertainties was investigated.

Discussion

To the best of our knowledge, this is the first analysis of uncertainty in MRT based on a large sample of clinical cases. Wide inter-lesion variability of dose uncertainty was observed. Hence, a proper assessment of the uncertainties associated with the calculations should be considered as a basic scientific standard. A model for a quick estimate of uncertainty without implementing the entire error propagation schema, which may be useful in clinical practice, was presented. Ameliorating spatial resolution may be in future the key factor for accurate absorbed dose assessment.

Background

In recent decades, Molecular Radiotherapy (MRT) has been increasingly used for the treatment of neuroendocrine tumours (NETs). The use of somatostatin analogues labelled with radio-emitting isotopes has shown promising results [1–3] and it is expected that peptide receptor radionuclide therapy (PRRT) will become more widely used. Recently, the NETTER-1 trial [4] demonstrated that ^{177}Lu-DOTATATE-PRRT significantly improved progression-free survival. It has also been demonstrated that absorbed doses delivered to healthy organs and tumours have large inter-patient variability [5–8]. Moreover, many studies have provided evidence of dose effect correlations in PRRT [9–11]. For these reasons groups from

different hospitals and research institutes across Europe have proposed the use of dosimetry for PRRT in routine clinical practice [12]. Personalized medicine necessitates treatment to be optimized based on patient-specific dosimetry. Calculation of the absorbed doses delivered to organs at risk and tumours should ideally incorporate uncertainty analysis. This is particularly true in the case of tumour dosimetry that can be subjected to relatively high uncertainties due the wider range of absorbed doses delivered and the lack of standardised S-values [13–14].

To date, investigations into uncertainties of absorbed dose calculations in MRT have been mainly based on phantom measurements or simulated data [15–18]. However, uncertainty evaluation should ideally be considered for each individual case. Furthermore, the majority of studies have focused on one or only a few aspects of MRT absorbed dose measurements (for example on the calibration of gamma cameras [19] or on activity quantification [20–22]). However, internal dosimetry evaluation consists of a multi-step process with a specific uncertainty associated with each step [23]. Consequently, each step should be included into the overall dose uncertainty calculation.

Recently, the EANM published practical guidance on uncertainty analysis for molecular radiotherapy absorbed dose calculations [24]. This guide provides a detailed schema to determine uncertainties based on the application of the law of propagation of uncertainty (LPU) and was designed to be implemented using standard resources available in every clinic offering MRT. The published EANM paper also reports a patient example to support readers for implementation of the guidelines.

To the best of our knowledge, to date there are no published data to address uncertainty analysis that includes every aspect of the dosimetry calculation chain on a large sample of clinical cases.

In that context, this study shows the results of uncertainties in tumour dose calculations for a sample of patients treated at Azienda USL-IRCCS of Reggio Emilia (Italy). The scope of this paper is to give an indication of the typical uncertainties that may be expected from performing tumour dosimetry, to determine parameters that have the greatest effect on the accuracy of calculations, and to consider the potential improvements that could be made if these effects were reduced.

Materials And Methods

Patients

This study was carried out retrospectively on a sample of 49 patients enrolled in a clinical trial (EUDRACT 2015-005546-63) which received local institutional ethics committee approval at the Azienda USL-IRCCS of Reggio Emilia hospital.

All patients were affected by NETs and were treated with PRRT. According to the trial design, each patient underwent several ^{177}Lu- and ^{90}Y-DOTATOC administrations. Dosimetry was conducted at the first cycle of therapy after a therapeutic injection of ^{177}Lu-DOTATOC. A mean value of 4.2 ± 0.9 GBq of ^{177}Lu-

DOTATATE was administered to patients. A maximum of 5 lesions were analysed for each patient, with a total of 154.

Imaging

All examinations were performed using a hybrid Symbia T2 SPECT/CT (Siemens Healthineers, Germany). The SPECT gamma camera was equipped with a medium-energy, general purpose collimator (MEGP). The energy windows of ^{177}Lu photopeaks were set at 113 keV ± 7.5% and 208.4 keV ± 7.5%. SPECT projections were reconstructed using an iterative algorithm with compensations for attenuation from CT images, scatter and full collimator-detector response in the Siemens E-Soft workstation (Syngo, MI Application version 32B, Siemens Medical Solution, Germany) with Flash 3D iterative algorithm (10 iterations; 8 subsets; Gaussian filter). The reconstructed SPECT images were sampled on a matrix of 128 × 128 × 112 elements, resulting in a 4.8 mm cubic voxel size.

The FWHM of the system was measured by Grassi et al [25] and the result was 10.41 mm

The imaging protocol consisted of four sequential SPECT/CT scans of the abdomen typically at 1, 24, 44, 72 h p.i (post injection). If necessary, also the thorax area was scanned at 1, 24 and 72 h p.i.

A total of 141 lesions in the abdomen and a total of 13 lesions in the thorax were analysed.

Dosimetry workflow

At the first cycle a complete dosimetric evaluation of the selected tumours was performed based on SPECT/CT acquisitions. The SPECT/CT system was previously calibrated using a cylindrical Jasczcak phantom (Data Spectrum Corporation, USA) filled with a homogenous ^{177}Lu radioactive solution. A calibration factor (CF = 36.5 cps/MBq) was determined by the ratio between the known activity and the measured total counts, following the procedure described by Grassi et al [26]. A series of sequential multiple acquisitions of the phantom was performed. The standard uncertainty from repeating activity measurements was taken.

Subsequent to each SPECT acquisition, a CT image was acquired for attenuation correction. For radiation protection of patients, low resolution CT scans were acquired (90 mAs at the first scan and 30 mAs at the following acquisitions) and no contrast medium was used. As a consequence, most of the lesions were not visible on the CT image. For that reason, all tumours were manually segmented on the SPECT image. Contouring was performed in the Velocity Workstation (Varian Medical System, USA) using a variable threshold defined by a nuclear medicine physician. To avoid mis-registration errors, contours were outlined on the fused SPECT/CT image acquired 24 h p.i., duplicated, and manually translated to match them with the lesion volume on the other SPECT/CT images.

Activities were corrected for partial volume effects using recovery coefficients (RCs) previously determined based from phantoms with spherical inserts [27]. RCs as a function of insert volume were fitted with the following exponential curve:

$$RC(v) = A \cdot exp(-B \cdot v) + C \qquad (1)$$

where A, B and C are the fitting parameters and v (volume) is the independent variable.

Two different exponential curves were used to fit the time-activity points:

$$f_1(t) = A_0 \cdot exp\,(-\lambda_1 \cdot t) \qquad (2)$$

$$f_2(t) = A_0 \cdot ex\,p(-\lambda_1 \cdot t)\,[1 - exp\;\;(-\lambda_2 \cdot t)\,] \qquad (3)$$

Where A_0, λ_1 and λ_2 are the fitting parameters and t (time) is the independent variable. Eq. 2 was used in case of monotonically decreasing data-points or if only 3 time-points were available. Otherwise, Eq. 3 was used.

Cumulated activities were calculated by solving the integral of the exponential functions, based on the fitting parameters.

Tumour absorbed doses were calculated using the OLINDA1.1 sphere model. S-values derived from OLINDA1.1 were fitted against mass using a power function, as shown in Fig. 1. In this study, the absorbed dose after the first therapy cycle and the relative uncertainty were calculated.

Data analysis and statistics

All absorbed dose calculations and statistical analyses were performed in MATLAB R2019a (The MathWorks Inc., USA). A MATLAB script was developed and used to automatically calculate the uncertainty associated with each parameter based on the EANM guidelines [24]. Volume uncertainty $u(v)$ was calculated using the analytical expression given within the EANM document:

$$\left[\frac{u(v)}{v}\right]^2 = \left[3\frac{u(d)}{d}\right]^2 \qquad (4)$$

Where d is the equivalent diameter of the outlined lesion, with uncertainty:

$$\mathrm{u}^2(\mathrm{d}) = \frac{\mathrm{a}^2}{6} + \frac{(\mathrm{FWHM})^2}{4\ln 2} \qquad (5)$$

Where a is the voxel size and FWHM is the resolution of the imaging system, measured using a phantom with three capillary tubes filled with a radioactive solution, as described in [25].

Box-plots were used to visualize the distribution of standard uncertainty of each variable included in this analysis. Association between each variable and the dose uncertainties were qualitatively assessed graphically.

As discussed in the EANM guidance, uncertainty in the absorbed dose is expected to largely depend on the precision with which the lesion volume can be estimated. An absorbed dose uncertainty, u(D), curve against lesion volume (v) was determined by least squared fitting. A Power function of Eq. 6 was used to fit the empirical data points:

$$uD(v) = A \cdot v^{B} \qquad (6)$$

where A and B are the fitting parameters and v is the independent variable.

In this study, we further evaluated the expected improvement in absorbed dose uncertainty attainable with potential improvement in accuracy of the volume estimation. This was achieved by repeating all uncertainty calculations assuming a range of system spatial resolutions, such as the those typical of ^{68}Ga PET/CT and CT imaging.

Results

Forty-nine patients (22 males, 27 females, median age 62 years, range 36–79 years) were treated with PRRT. Among the 154 lesions analysed, 100 were situated within the liver (64.9%), 8 in the pancreas (5.2%), 5 in the lung (3.2%), 18 were bone lesions (11.7%), 18 were lymph nodes (11.7%) and 5 were in other locations (3.2%).

The median value of the contoured volumes on SPECT images was 6.9 mL, and the interquartile range was 4.68–17.24 mL.

The average uncertainty in absorbed dose was relatively high with a mean of 64.6% and median value of 72.8%. A wide range of uncertainty values were observed (14–102%). Figure 2 shows the distribution of the relative uncertainty for each parameter calculated along the dosimetry chain. The highest relative uncertainties were due to volumes and S-values. The absorbed dose uncertainty was plotted against the uncertainty associated with each of the parameters along the dosimetry workflows, as shown in Fig. 3. Different patterns were obtained for each variable, demonstrating the complex relationship that each quantity has on the estimate of absorbed dose.

A clear relationship was observed between absorbed dose uncertainty and volume uncertainty. A similar relationship was and therefore also seen between absorbed dose uncertainty and RC, counts and S-value uncertainty, which are strictly also dependent on the volume uncertainty.

The absorbed dose uncertainties against volume were fitted using the power function of Eq. 6. The fit coefficients are shown in Table 1, while the fit curve is shown in Fig. 4.

Table 1
Power curve best-fit parameters of absorbed dose uncertainty against volume.

	Value	Confidence interval (95%)
A	142.9	(135.9, 149.8)
B	-0.36	(-0.39, -0.34)

In order to assess if the number of data-points affects accuracy of TAC fitting, patients with four time-points and patients with three time-points were separately evaluated. A total of 141 four-points datasets and 13 three-points datasets were analysed, with average 12% relative uncertainty of TAC fitting on the former and average 16% on the latter.

The effect of different values of spatial resolution were investigated by hypothetically changing the value of FWHM given in Eq. 5. Figure 5 shows the relative absorbed dose uncertainty re-calculated for all the lesions, assuming three different values (0.5, 5 and 10 mm) of FWHM (note: the actual FWHM of the acquisition system was 10.41 mm). These values were chosen to represent the typical spatial resolution of CT, PET and SPECT acquisition systems, respectively. In Fig. 6 four lesions with very different volumes were considered and the absorbed dose uncertainty was estimated for a range of values of the system spatial resolution.

Discussion

Lack of knowledge of absorbed dose calculation uncertainties has been a factor that has impeded widespread uptake of dosimetry in MRT.

The EANM guidelines provide a schema of uncertainty propagation to evaluate the standard uncertainty in absorbed dose to a target. This schema was based on the recommendations described within the GUM [28] and necessarily involves formation of covariance matrices for several steps of the dosimetry process. In this work, we have applied the EANM guidelines to evaluate uncertainty of tumour dosimetry calculations in PRRT. This study carried out, for the first time, the uncertainty analysis of the entire process of dosimetry calculation on a large sample of clinical cases. A total of 154 lesions were analyzed.

As shown in Fig. 2, the fractional uncertainty associated with the considered quantities (volume, CF, S-factor, etc.) was widespread around the median value, incurring a high inter-lesion variability. Volume and S-values are the parameters with the highest uncertainty. These results confirmed that the uncertainty in absorbed dose is dominated by the uncertainty in the delineation of the VOI. For example, when contouring a volume, the uncertainty in edge definition due to the limited spatial resolution, together with the voxel width, involves errors in the assessment of the volume.

The uncertainty associated with the volume is then propagated to many of the other parameters (RC, Counts, Activity, Fitting, CA and Dose). The relationship between fractional absorbed dose uncertainty and tumour volume is evident in Fig. 4. The analytical power model for this relationship fitted the empirical data points well and this could be useful, in clinical practice, for a quick estimate of uncertainty without implementing the entire error propagation schema, which could be useful to select the lesions to be monitored for patient outcome assessment.

These results may be useful to provide the user with an indication about the typical expected uncertainty while performing dosimetry. Assuming an acceptable dose uncertainty of 40%, the cut-off tumour volume is around 33 mL. Consequently, it can be concluded that absorbed doses to lesions with volumes smaller than 33 mL cannot be determined to a significant level of confidence to make the result meaningful. However, it should be noted that this value depends on the spatial resolution of the imaging system and on the method used to contour the VOI. In this study, the VOIs were manually contoured on the SPECT images.

In this study, 128 lesions (out of 154) had a volume smaller than 33 mL. All 154 lesions were considered of clinical importance in the trial and were used in the treatment planning. It should be noted that for this analysis a tumour volume cut-off was not introduced (consequently also lesions with very small volumes were analysed) to provide worthy results in the whole clinical range of volumes.

Anyway exclusion of tumours below 33 mL is undesirable as they may be of clinical importance. The accuracy of VOI delineation may be improved by using the appropriate acquisition/reconstruction protocol (accounting for acquisition statistics, matrix, collimator type, reconstruction settings) to obtain images with a spatial resolution as high as possible. Lesions may be delineated using contrast enhanced CT or ^{68}Ga-PET where feasible, which are characterized by a better spatial resolution than SPECT imaging. Contouring on images with spatial resolution of 5 mm (typical of PET images) would provide a cut-off tumour volume of 4 mL (accepted dose uncertainty equal to 40%). Almost all the lesions provided dose uncertainty smaller than 40% if a spatial resolution equal to 0.5 mm (typical of CT images) was used. In that case, an absorbed dose uncertainty cut-off lower than 40% may be set in order to increase significance of dose calculations. For example, a cut-off volume of 4 mL would provide a confidence level of dose calculation around 20%. However, the possibility of using CT in place of SPECT or PET is to be evaluated, maybe combining both the morphological and functional information.

Uncertainty of volume evaluation might be further reduced by averaging VOIs delineated by different operators. However, this approach may be difficult to be applied in clinics.

Conclusion

In conclusion, this study provided the first analysis of uncertainties of absorbed dose calculations on a sample of clinical cases treated with PRRT. Assessment of uncertainties provides the degree of consistence of the data and allows to adequately weigh results in treatment planning. For that reason, it is firmly recommended to include the analysis of uncertainty for any measured or calculated parameters in clinical routine. However, such analyses in MRT are rarely performed. The application of uncertainty analysis in clinical practice may help clinicians to select tumours for treatment response evaluation and may help to identify parameters that more affect accuracy of calculation. Such analysis may increase the validity of dosimetry and, in turn, it would encourage physicians to use dosimetry in treatment planning. In research field, it may facilitate determination of dose-response relationship and it may allow to compare results among different clinical sites. This study showed volume delineation to be one of the parameters which more affect accuracy of dose calculations and it most likely is the easiest side to ameliorate in the clinical practice. Using PET or CT imaging would reduce the amount of uncertainty by a factor between 50% and 70% in comparison to use SPECT images, based on these results. The ability to improve accuracy of absorbed dose calculations might be crucial to optimize treatment efficacy in internal radionuclide therapy.

Abbreviations

CA: Cumulated activity; **CF:** Calibration factor; **CT:** Computed tomography; **EANM:** European Association of Nuclear Medicine; **FWHM:** Full width at half maximum; **LPU:** Law of propagation of uncertainty; **MRT:** Molecular radiotherapy; **NET:** Neuroendocrine tumours; **PET:** Positron emission tomography; **PRRT:** Peptide receptor radionuclide therapy; **RC:** Recovery coefficient; **SPECT:** Single photon emission computed tomography; **TAC:** Time-activity curve; **VOI:** Volume-of-interest

Declarations

Ethics approval and consent to participate

This study involves human partecipants. All partecipants were enrolled in a clinical trial (EUDRACT 2015-005546- 63) at Azienda USL-IRCCS of Reggio Emilia (Italy). The study was approved by the ethics committee of Azienda USL-IRCCS of Reggio Emilia (Italy) and each patient gave written informed consent for the study conduction.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

DF, FF, EG conceived and designed the study; DF, JG, GF analysed and interpreted the data; DF drafted the manuscript; JG, FF, GF, EG reviewed the manuscript. All authors read and approved the manuscript and consented to its publication.

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Not applicable.

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Figures

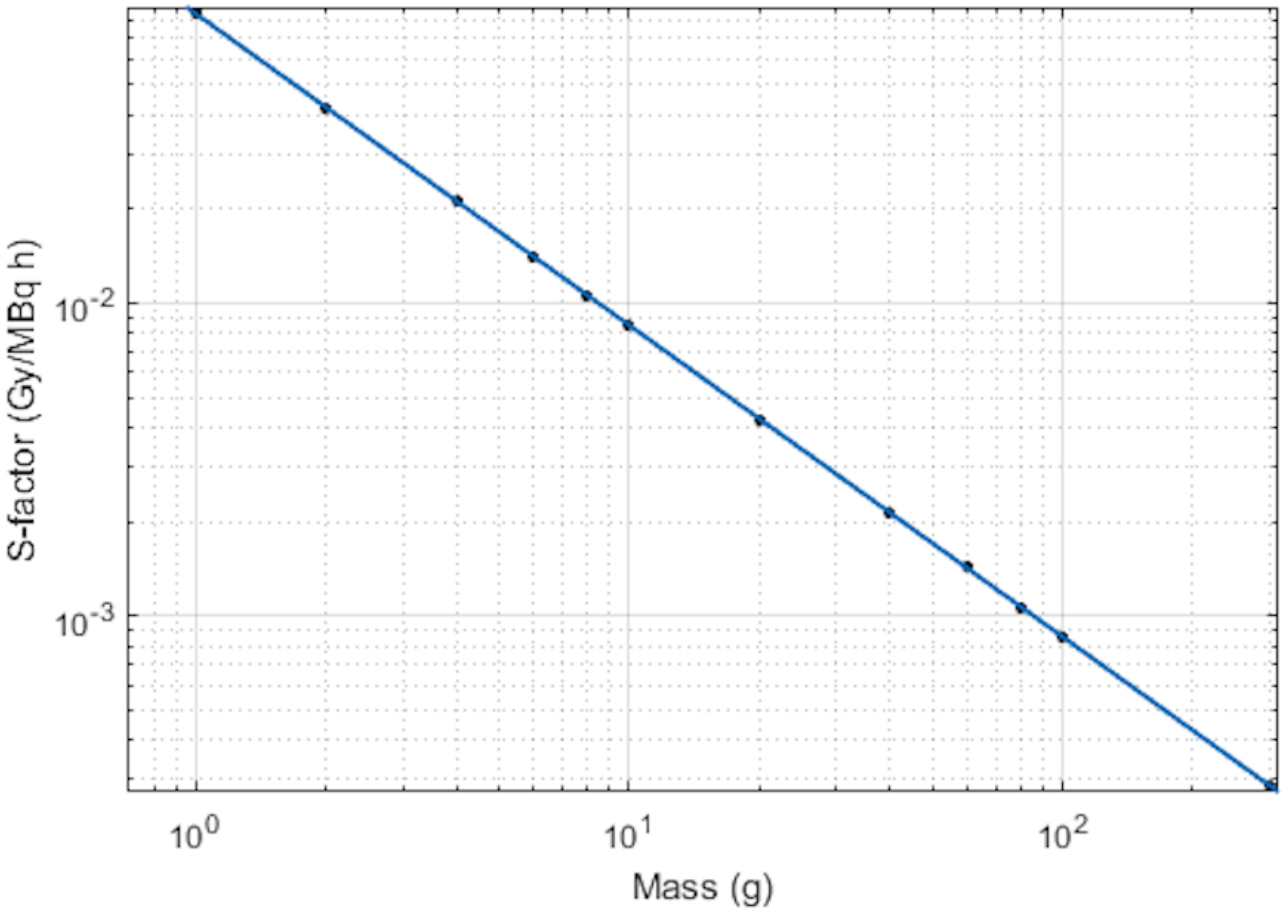

Figure 1

S-factors against mass for unit density spheres

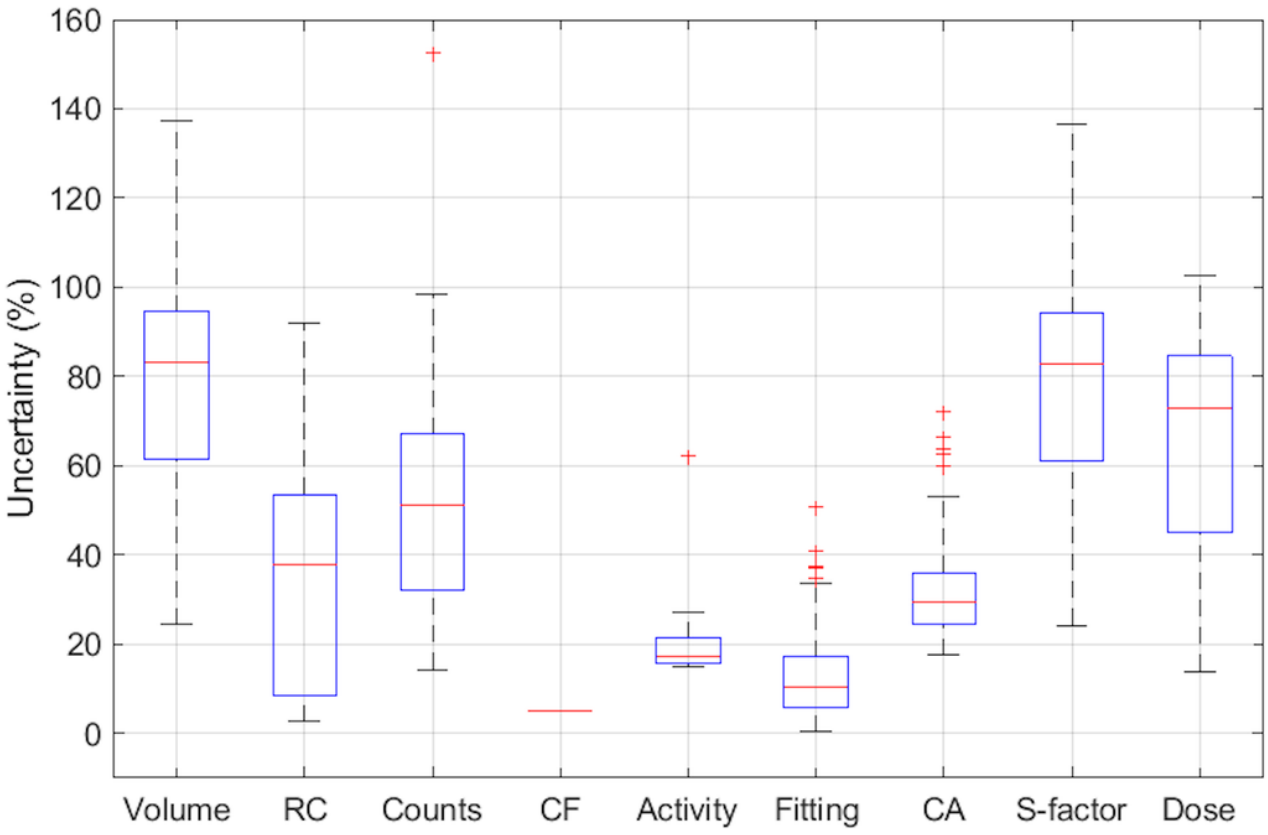

Figure 2

Distribution of uncertainty (%) for each step of the dose calculation schema.

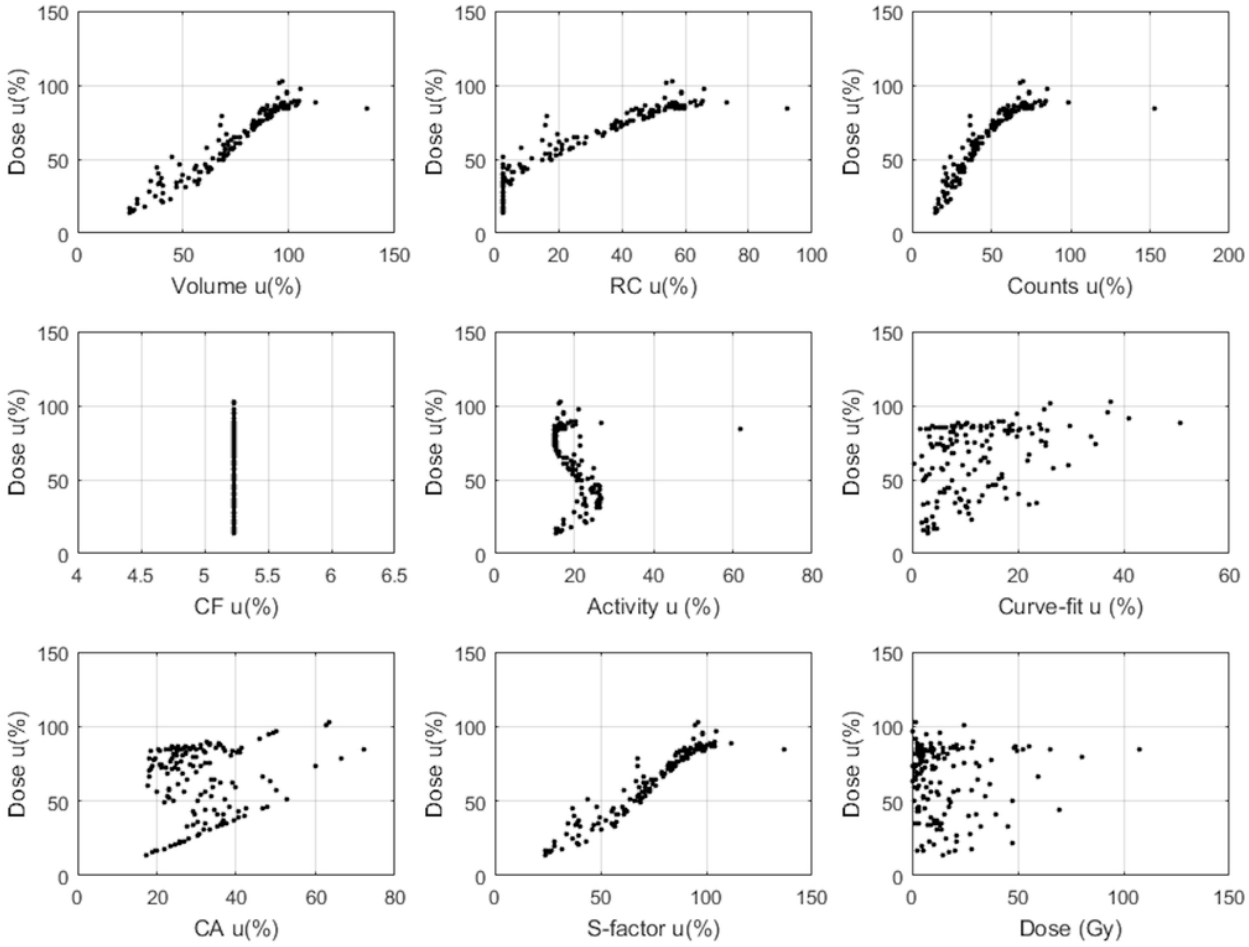

Figure 3

Relationship between dose uncertainty (y-axis) and volume, RC, counts, CF, activity, curve fitting parameters, cumulated activity and S-factors uncertainties (x-axis). The graph at the bottom right shows absorbed dose (Gy) against the dose uncertainty.

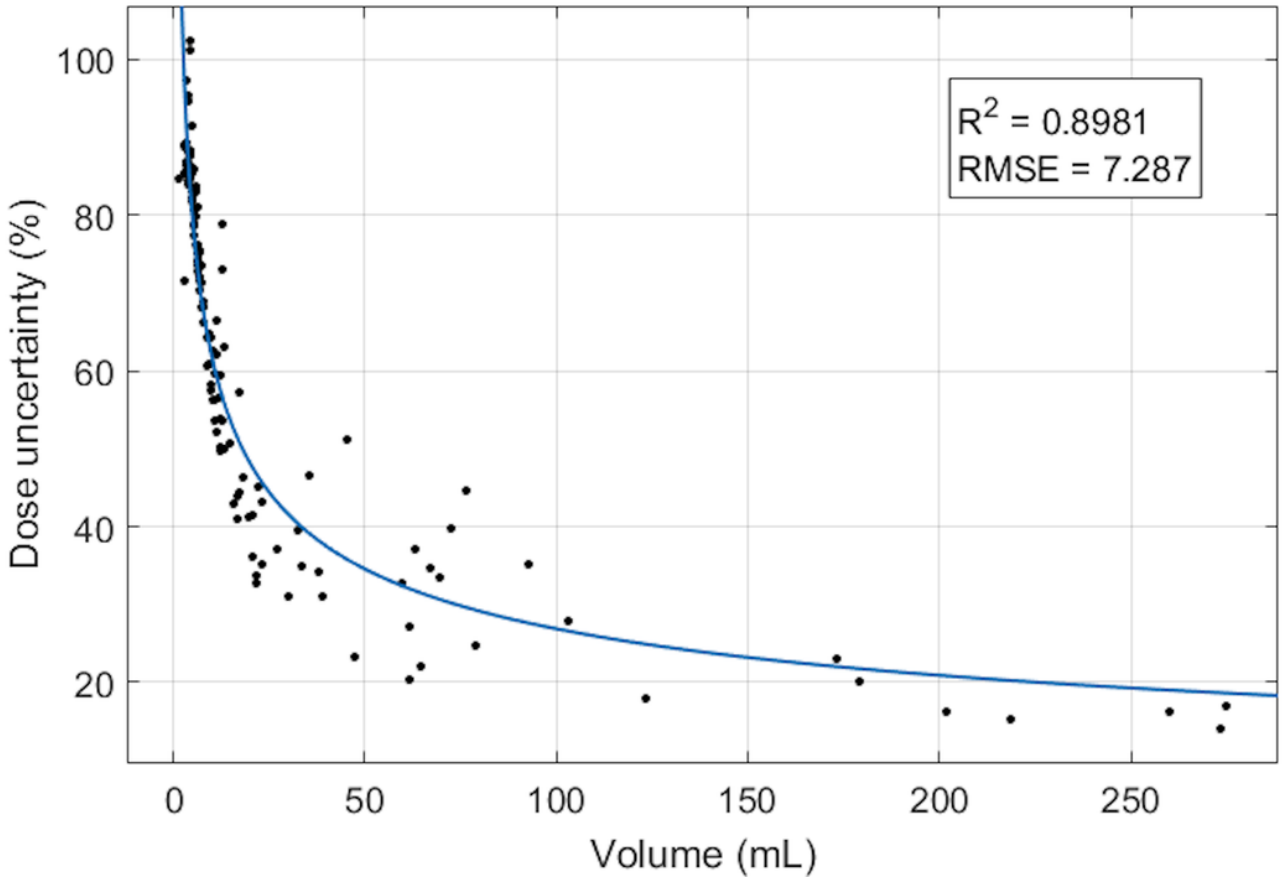

Figure 4

Dose uncertainty (%) against volume (mL). Points were fitted with a power function. R2 and RMSE are reported into the graph.

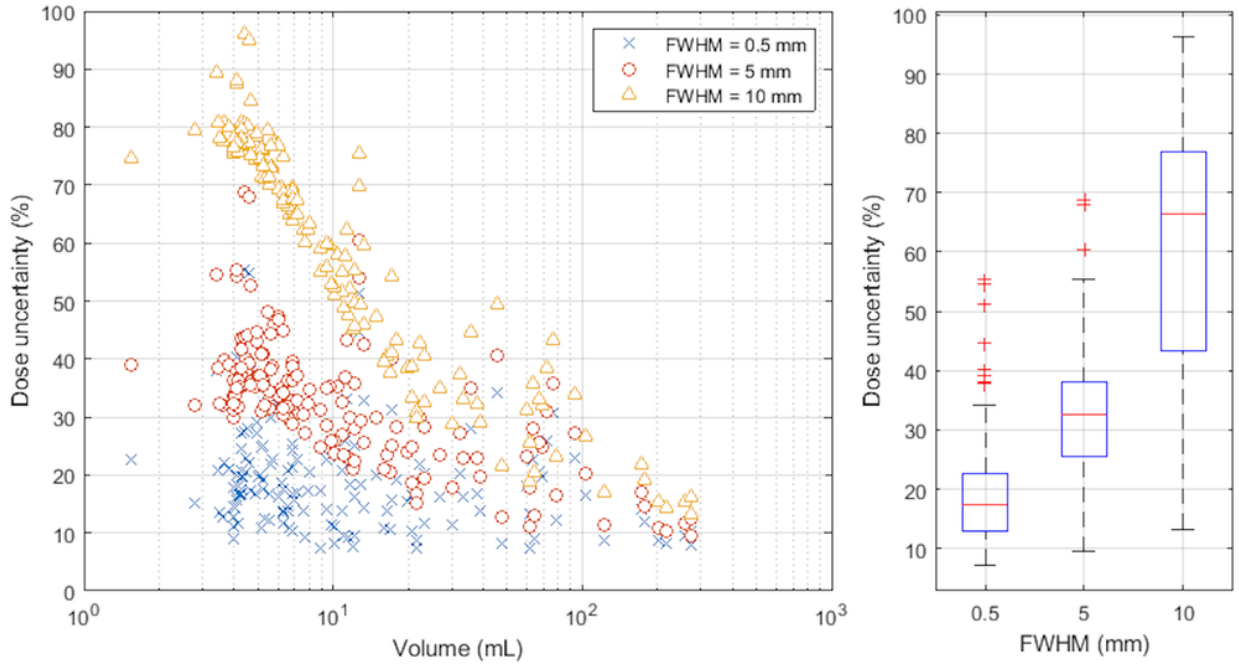

Figure 5

On the left, dose uncertainty (%) against volume (mL) calculated for all the lesions, postulating imaging systems with FWHM equal to 0.5, 5 and 10 mm (representative of CT, PET and SPECT systems, respectively). On the right, distributions of dose uncertainty (%) for each value of the FWHM.

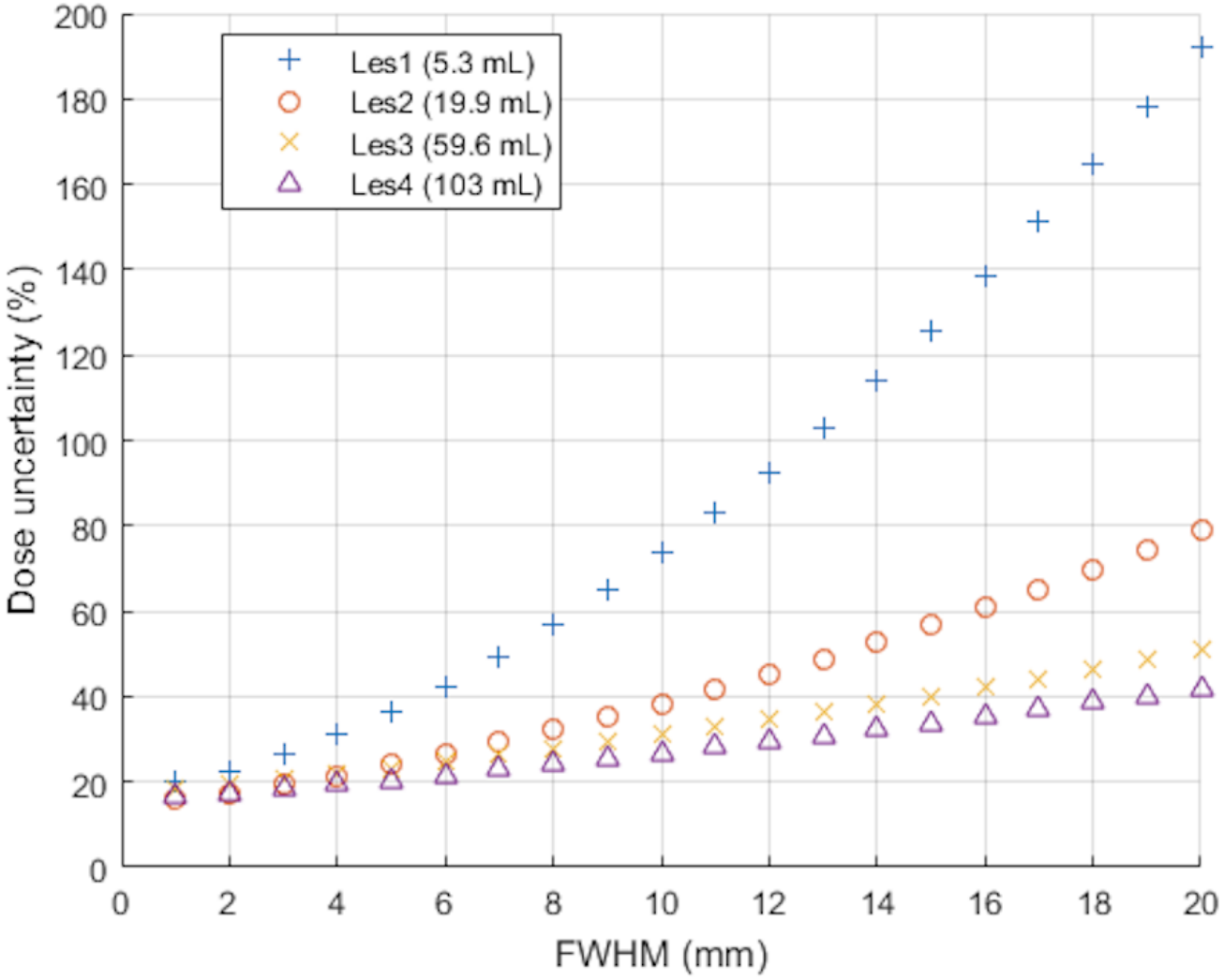

Figure 6

Dose uncertainty (%) as a function of the imaging system spatial resolution (FWHM in mm) in four lesions. Lesions were chosen to fill a range of different values of volume.

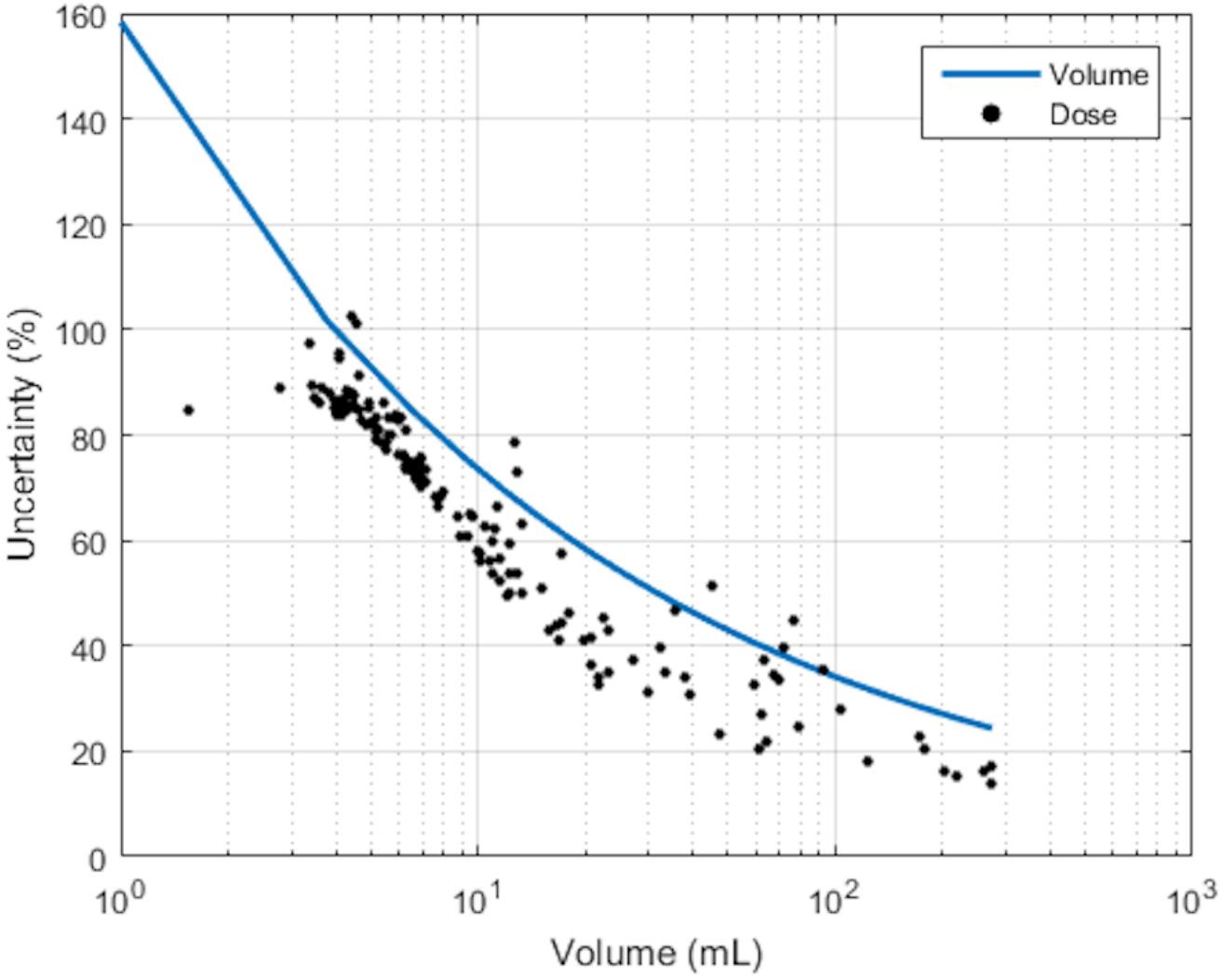

Figure 7

Dose uncertainty (black points) and the volume uncertainty (blue line) as a function of the delineated VOI volume.