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Deliverable 3.3

Dosimetry protocol and software

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Abbreviations

Bq: Becquerel; MBq: Megabecquerel; GBq: Gigabecquerel

DTC: differentiated thyroid cancer

ICRP: International Commission on Radiological Protection

WB: Whole-Body

SPECT: Single Photon Emission Computed Tomography

CT: Computed Tomography

TAC: Time-Activity-Curve

ROI: Region of Interest

VOI: Volume of Interest

DVH: (Absorbed) Dose Volume Histogram

1. Introduction

Deliverable 3.3 is associated to Task 3.3 of the MEDIRAD project. The title, list of participants, timeline and content of Task 3.3 are listed below:

Task 3.3 Dosimetry calculations. (INSERM;** RMH/ICR, UKW**) M1-M48

The participant imaging centres will lead calculations of absorbed doses and related uncertainties. Protocols will be developed for each stage of image processing and dosimetry calculations and applied to the data collected. All anonymised raw and reconstructed patient image data from each imaging centre will be uploaded to each dosimetry site for processing. Tomographic image data will be reconstructed and corrected for scatter and attenuation. Image registration will be performed on all sequential image data with the CT acquired during hybrid imaging. Volumes of uptake will be identified and delineated. Normal organs will be identified and the absorbed doses calculated. In addition to mean dosimetry, 3D dosimetry will be performed for organs of uptake enabling production of dose volume histograms. Uncertainty analysis will be performed according to newly developed EANM guidelines. An inter-comparison of dose estimates obtained from all imaging centres will be made to identify discrepancies and to finalise and optimise a dose reconstruction protocol that is reproducible and applicable in clinical practice. A common software for the 3D dosimetry, incorporating uncertainty analysis, will be agreed upon. Recommendations will be produced in conjunction with WP6 to use this protocol and software for accurate patient-specific dosimetry.
Results will be fed at an early stage into Tasks 3.2 and 3.5 for initial development of a comprehensive biokinetic model and the epidemiological study and will continue to inform development as further data become available and are analysed.

Figure 1: Description of Task 3.3

Imaging and data collection protocols were reported in D3.1, whereas D3.2 is being prepared to report on the validation of centres selected for imaging and data network. D3.3 will therefore focus on image and data processing, from acquisition to absorbed dose calculation and reporting.

The type (format) of the deliverable is essentially that of a report, even though the mention “other” was selected to give account of the fact that we intend to select and discuss software for performing clinical dosimetry in the very specific context of MEDIRAD.

2. Clinical dosimetry

2.1 General context of clinical dosimetry

Clinical dosimetry consists of a chain of operations, as is summarized in Figure 2. Every step is conditioned by the previous one, and therefore these steps are not really independent.

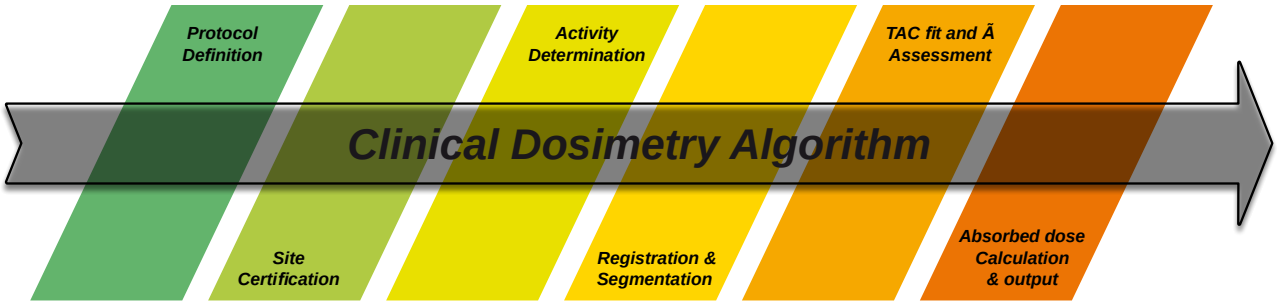

Figure 2. Clinical Dosimetry algorithm

In addition, the practical implementation of clinical dosimetry (how to?) is closely related to the intended clinical objective (what for?). Following the well-known MIRD formalism, the absorbed dose is obtained by determining the fate of the radiopharmaceutical in the patient (cumulated activity in the Source $\tilde{A}_{Source}$) and the way radiation energy propagates from the Source to be eventually absorbed in the Target (S Factor, or S Value $S_{(Target<-Source)}$).

The absorbed dose (in Gy) in the Target is therefore:

$$\bar{D}_{Target} = \sum_{Source} \tilde{A}_{Source} \times S_{(Target \leftarrow Source)}$$

Table 1 presents the various contexts of implementation of clinical dosimetry, divided in 3 situations named Diagnostic, Therapy (1) and Therapy (2)

Context	$\tilde{A}_{Source}$	$S_{(Target \leftarrow Source)}$	$\bar{D}_{Target}$
Diagnostic	Group	Model	Model-based (ICRP reports)
Therapy (1)	Specific	Model ± adjusted	Model-based ± realistic
Therapy (2)	Specific	Specific	Patient-Specific Dosimetry

Table 1: Implementation of clinical dosimetry

- Diagnostic represents the situation of most radiopharmaceuticals, where the radiation delivered is limited and only stochastic effects are of interest. To that end, average pharmacokinetics obtained on a group of patients, healthy volunteers or sometimes extrapolated from animal data are used to calculate cumulated activities and together with S values derived from reference human models are used to compute the absorbed doses. This approach is usually implemented by following the recommendations of the ICRP.
- Therapy (1) is an intermediary situation, where cumulated activities are assessed for each patient, but S values are adapted from reference human models to the patient's geometry. This approach is usually sufficient to derive mean absorbed doses at the organ or tissue level, with a reasonable degree of accuracy, and most importantly is adapted to most clinical Nuclear Medicine department since adjustment of S Values is usually performed based on the ratio of organs/tissue volumes of the patient and reference model.
- Therapy (2) represents the ideal situation in therapy, where both cumulated activity and S values are computed specifically for each patient (actually, radiation transport and absorbed dose determination are usually performed in one pass, without the S value determination intermediary). This is the only possibility to assess a fully patient-specific dosimetry, compute absorbed dose gradients and absorbed dose volume histograms (DVHs) for specific volumes of interest rather than just mean absorbed doses. This approach usually requires tools and methodologies seldom encountered in clinical Nuclear Medicine Departments.

The context of MEDIRAD is somehow special in the sense that the focus will be in low absorbed doses delivered to normal (critical) organs or tissues in a context of therapy. This means developing and implementing a dosimetric approach that includes methodological aspects that belong to both Diagnostic and Therapeutic domains.

2.2 Global dosimetry framework in MEDIRAD

Clinical dosimetry will be performed on 100 patients treated for DTC with ^{131}I. The clinical protocol has been presented in MEDIRAD Deliverable D3.1.

From an organisational point of view, 4 clinical centres will acquire data from approximatively 25 patients each. An anonymisation process – still under discussion – will allow feeding a common database. The database will contain both raw and reconstructed/processed images/data, and will be accessible by all WP partners involved in clinical dosimetry (Figure 3). The database structure is being elaborated in conjunction with WP2 partners (LTSI-INSERM Rennes, France).

The objective is to make sure that:

- All centres involved in clinical dosimetry can process all available data, according to their requirements/tools:
  - All Dosimetry Centres that are also Imaging centres will *at least* process their own clinical data (but may also process all data).
  - INSERM/CRCT (Dosimetry-only centre) will perform dosimetry for *all* patients.
- A comparison of the results obtained by the different partners from the same raw data will be made possible,
- A comparison of various approaches proposed for clinical dosimetry will be performed.

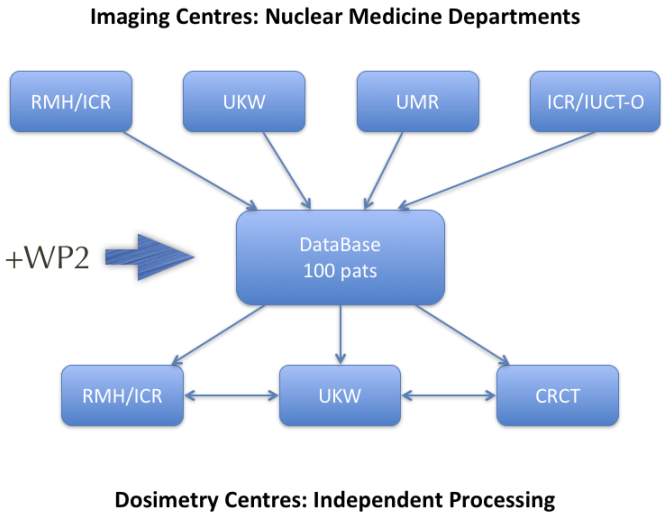

Figure 3: Database for clinical dosimetry processing

2.3 Dosimetric approaches

As presented above, the context of MEDIRAD is somehow special in the sense that both high absorbed doses delivered during the therapy to tumour targets and low absorbed doses delivered to critical/normal organs/tissues are of relevance. Even though the MIRD formalism applies to all situations, its practical implementation is different according to the context.

2.3.1 Clinical dosimetry in MEDIRAD

The dosimetry scanning schedule is presented in Table 2. Since the clinical protocol includes 4 WB planar scans and one SPECT/(CT), planar (organ-based) dosimetry will be implemented in all patients. Optional WB acquisitions (6 ± 2 h and 168 ± 24 h) will increase the degree of confidence in pharmacokinetics parameters derived from the dosimetric analysis. Optional extra SPECT(/CT)

acquisitions will allow implementing a 3D dosimetric approach. Calibration factors will be obtained for each dataset from clinical departments. In addition, in a subset of centres (UKW, UMR) multiple blood samples will be drawn after therapy. The time points of sampling will be specified in the corresponding clinical protocols.

Hours post-^{131}I admin.	Mandatory	Optional
6 ± 2 h		WB planar and/or SPECT(/CT)*
24 ± 4 h	**WB planar**	SPECT(/CT)*
48 ± 4 h	**WB planar and SPECT(/CT)***	
72 ± 12 h	**WB planar**	SPECT(/CT)*
96 ± 12 h	**WB planar**	SPECT(/CT)*
168 ± 24 h		WB planar and/or SPECT(/CT)*

Table 2: Post-therapeutic patient dosimetry scanning schedule (from Imaging Protocol Summary)
* SPECT(/CT) range: base of skull to top of thigh

2.3.2 Methodology for planar dosimetry

Anterior and Posterior WB planar scans will be downloaded from the common database. Image fusion of planar scans obtained at different time-points will be performed using rigid transformations. The geometric mean approach will be implemented. Segmentation of relevant source organs/tissues (i.e. those with a significant uptake) will be made on the most adapted time-point, but if possible the 48±4h time point will be favoured, as this corresponds to the SPECT(/CT) acquisition time. Background subtraction will be based on ROIs defined on the same time-point.

All ROIs will be copied/pasted on all images acquired at different time-points. Time-activity curves for all ROIs will be obtained after BKG subtraction. TAC (time-activity-curve) fitting will be performed using computing tools available in each participating centre, and all relevant parameters insuring traceability will be recorded.

Organ/tissues masses will be derived from the CT of the SPECT/CT acquisition or a corresponding CT scan . Absorbed doses will be computed using local energy deposition approximation as a first order estimate. Computing software such as OLINDA (v1 and V2)[1] or IDAC[2] can also be used for that purpose, by adapting the masses of the reference computing models organs to that of the patient (Therapy (1) approach in Table 1).

2.3.3 Methodology for 3D dosimetry

3D dosimetry will be implemented for patient datasets that include several SPECT/CT (Table 2). The processing of 3D dataset essentially follows the same steps as for 2D (Figure 2). Still the necessity to correct for activity superposition in the projections disappears, thereby decreasing the uncertainties associated with operator-dependent BKG subtraction.

Depending on the registration process, activity determination at the voxel level can be considered, even though the time integration to provide cumulated activity at the voxel level remains challenging. Several approaches of TAC fit and integration at the voxel or VOI level will be compared to assess the variability associated with each procedure.

[1] http://www.doseinfo-radar.com/OLINDA.html
[2] http://www.idac-dose.org

Absorbed dose calculations will be performed using *ad hoc* tools (local energy deposition, convolution in homogeneous or heterogeneous media, Monte Carlo modelling of radiation transport) and commercial solutions (PlanetDose, Stratos) available at INSERM/CRCT. Other dosimetry centres (Figure 3) may use different approaches, in order to assess the variability of dosimetric approaches.

2.3.4 Methodology for blood-based dosimetry

The activity in the blood samples will be quantified with a calibrated well counter. The corresponding time-activity curves will be fitted and integrate in order to obtain time-integrated absorbed dose coefficients per ml of blood. The absorbed dose calculation will be performed as described by the EANM Dosimetry Committee standard operational procedures for blood and bone marrow dosimetry in differentiated thyroid cancer therapy.

2.4 Model-based vs. patient-specific dosimetry

Since MEDIRAD is focussed on low absorbed doses, WP3 will consider not only (elevated) absorbed doses delivered to source organs/tissues, but also absorbed doses delivered to target-only organs/tissues that may be located at a distance from radiation emissions points.

In that context, following the recommendations proposed by the ICRP is wise. ICRP 103 is still not fully implemented in nuclear medicine dosimetry practice. A recent code, IDAC, allows the calculation of absorbed doses based on ICRP 110 models and SAFs published in ICRP 133. However, reference S Values based on the ICRP 110 models are yet to be published. We will compare approaches recommended in ICRP 60 and 103. This will not only imply using a different set of radiation weighting factors, but also to consider different computing models and associated reference S Values.

A list of target organs/tissues of interest with associated weighting factors (according ICRP 60 and 103) is presented in Table 3.

Tissue weighting factor (w_T)			
Tissue	**ICRP 26 (1977)**	**ICRP 60 (1991)**	**ICRP 103 (2007)**
Bladder	…	0.05	0.04
Bone	0.03	0.01	0.01
Brain	…	…	0.01
Breasts	0.15	0.05	0.12
Colon	…	…	0.12
Oesophagus	…	0.05	0.04
Liver	…	0.05	0.04
Lower Large Intestine	…	0.12	…
Lungs	0.12	0.12	0.12
Ovaries/testes	0.25	0.20	0.08
Red marrow	0.12	0.12	0.12
Salivary glands	…	…	0.01
Skin	…	0.01	0.01
Stomach	…	0.12	0.12
Thyroid	0.03	0.05	0.04
Remainder	0.30	0.05	0.12

Table 3: list of tissues and tissue weighting factors considered in ICRP recommendations

OLINDA V1 will be used to derive absorbed doses according to ICRP 60 recommendations. OLINDA V2 and IDAC will be used to derive absorbed doses according to ICRP 103 recommendations. A comparison of effective doses obtained from the different approaches will be made.

In addition, a comparison of effective doses obtained from direct, patient-specific calculation and from the conventional ICRP approach (averaged cumulated activities and reference computational model, both according ICRP 60 and 103 recommendations) will be made, as presented in Figure 4.

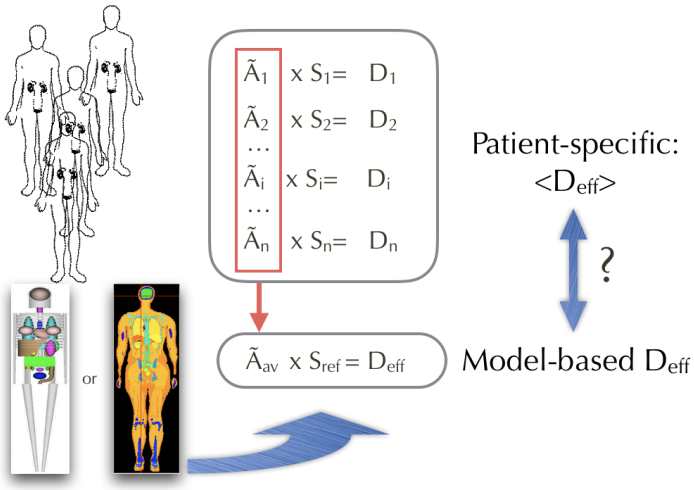

Figure 4: Comparison of patient-specific and model-based approaches

3. Conclusion

The report presented here is a summary of actions that will be implemented during the activity phase of the clinical dosimetry protocol.

- Clinical images/data acquired in *Imaging centres* will be uploaded to a centralized database for further use by partners involved in clinical dosimetry (*Dosimetry centres*).
- *Dosimetry centres* will perform dosimetric calculations according to available data (2D and/or 3D) and tools available locally, at least for the patients acquired in their centre.
- A comparison between model-based (2D) and patient-specific (3D) dosimetry will be performed by INSERM/CRCT on a subset of clinical data acquired using both 2D and 3D quantitative imaging.
- At the end of Task3.3, recommendations will be written and disseminated via EANM and EFOMP.

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