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Deliverable D2.3 - Methodological report on the development of a system for personalised dosimetry to account for in-field and out-of-field organ exposure from scatter dose during photon-based therapy, neutron radiation and imaging in proton therapy

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Abbreviations

CBCT	Cone Beam Computed Tomography
CT	Computed Tomography
DIBH	Deep Inspiration Breath Hold
DVH	Dose Volume Histogram
HL	Hodgkin's lymphoma
LET	Linear Energy Transfer
MC	Monte Carlo
MU	Monitor units
OAR	Organ at Risk
P3D	Periphocal 3D
RBE	Relative Biological Effectiveness
RS	Range Shifter
RT	Radiotherapy
TPS	Treatment Planning System

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1. Introduction

The current document presents the methodological report on the development of a system for personalised dosimetry to account for in-field and out-of-field organ exposure in photon- and proton-based radiotherapy (RT). This methodological report is based on the work performed in order to develop a comprehensive system for personalised dosimetry in RT which is part of the broader effort on developing novel patient dose estimation methods, and performing the risk assessment and the uncertainty evaluation for individual patients with suspected or diagnosed brain tumours and lymphomas undergoing radiological, nuclear medicine and radiation therapy procedures for diagnosis, staging, treatment, treatment response and follow-up.

The comprehensive methodology presented in this report includes measurement and simulation procedures developed to account for stray radiation dose in patients with lymphoma or/and brain tumours that received radiation therapy with photon or proton beams as well as personalised models of patients used with analytical algorithms to estimate dose distributions in out-of-field and partially exposed organs during photon radiation therapy. The methodology further considers the treatment protocols applied in the clinic together with machine-specific parameters to simulate dose delivery characteristics complemented by measurements and Monte Carlo (MC) simulations for the estimation of out-of-field and in-field dose distribution from stray radiation (neutrons) during proton therapy with the beam scanning technique. For both types of radiotherapy analysed in this work, organ-specific dose from stray radiation during radiotherapy exposures are complemented by dose distributions from radiotherapy-related imaging procedures hence the comprehensive character.

1.1 Background

The long-term survival of patients treated with radiotherapy is continuously increasing leading therefore to concerns, especially for young patients, regarding the risk of radiation-induced effects including second cancers (Yock et al 2014, Xu et al 2008). The quantification of the radiation burden to healthy tissues located both in proximity and outside the primary treatment field is therefore becoming an issue of key importance in modern radiotherapy as these doses can add up to substantiate their individual contributions to radiation-associated second cancer risks (Brenner and Hall 2008, Newhauser and Durante 2011).

The development of advanced radiotherapy techniques with the capacity of delivering highly conformal dose distributions to the targets involving steep dose gradients at the target periphery has improved the tumour volume conformity as well as the dose sparing of surrounding healthy tissues raising however new reasons of concern as they involve the use of image-guidance to a larger degree than ever before to ensure precise localization of both the tumour volume and surrounding healthy structures (Paganetti 2012, Stock et al 2012, Ardenfors et al 2014, Gudowska et al 2014, Landry et al 2015, Ardenfors et al 2018a).

The above considerations apply to any radiotherapy modality. Most of the patients are benefiting from photon radiotherapy. However, as proton therapy becomes available to a larger patient population and is given to younger patients that are expected to live longer after the treatment, concerns have been raised regarding the associated risk of radiation-induced second cancers, and the comparison to similar risks from photon therapy. Indeed, it has been suggested that the risk of radiation-induced second cancers from specific treatment techniques, could be used as a complementary criterion in the clinical decision process

(Dasu and Toma-Dasu 2017). Epidemiological studies have shown that radiation-induced tumours could appear both in field and out-of-field (de Gonzalez et al 2013). Furthermore, proton therapy makes increasing use of imaging as a tool to verify the positioning of the patient, potentially further increasing the radiation burden to the patients (Hyer et al 2010, Palm et al 2010, Bolsi et al 2018, Hvid et al 2018).

It is therefore essential that the contribution of all sources of radiation to the total risk is accurately accounted for and therefore it is essential to elaborate the methodological steps to assessing these doses in the treatment setting for individual patients.

1.2 General and specific issues to be addressed

The development of a comprehensive methodology to assess the doses to be considered in the risk appraisal for patients with lymphoma or/and brain tumours treated with photon or proton radiotherapy involves some common steps for the two irradiation modalities as well as some particular ones to proton radiotherapy.

The common steps are the retrieve of the in-field doses from the dose distributions rendered by the treatment planning systems (TPSs) to the organs and the tissues not designated as Organs at Risk (OARs), the assessment of the dose distributions for the out-of-field organs using personalised patient models and the estimation of the dose distributions from diagnostic and radiotherapy-related imaging procedures (Kry et al 2017, Mazonakis and Damilakis 2021, Romero-Expósito et al 2022).

The particular issues related to the proton radiotherapy concern the estimation of the in-field and out-of-field dose distribution from stray and scattered neutrons during proton therapy (Mares et al 2022). While scattered radiation from the treatment machine or the patient contributing to radiation burden to organs far from the target is a common issue both for photon and proton treatments, the dose deposited by neutrons is specific to proton radiotherapy and therefore should receive a special attention as it is not a common source of concern for the type of radiotherapy involving photons most of the patients world-wide receive. Furthermore, neutrons are an additional concern in proton RT due to their increased biological effectiveness. Neutron dose equivalent determination is challenging due to variations in predicted or measured spectra (e.g., physics models or detector related) and the neutron kerma conversions used (Hägl et al 2020). Moreover, the beam line elements can modulate neutron production and spectrum, making, to some extent, the task of assessing them specific to each treatment machine and facility.

The present methodology includes therefore a description of the methodological specifications that are common to photon and proton RT and gives in-depth consideration to the ones that are proton-specific only.

2. Methodology

The dose contributors to be considered in the development of a comprehensive system for personalised dosimetry of patients with lymphoma or/and brain tumours treated with photon or proton radiotherapy are shown in a schematic manner in Figure 1. They are presented separately for photon and proton RT together with the most common modalities of assessing them as developed in the current project and/or found in the literature.

The methodological steps involved in their assessment are also separately presented for photon and proton RT. For the clarity of the presentation, the steps were detailed for each treatment modality even if they were identical for the two modalities.

Dose contributors		Photon RT		Proton RT	
In-field		Directly retrieved from the TPS		Directly retrieved from the TPS	
Out-of-field		**Doses from**	**Assessment methods**	**Doses from**	**Assessment methods**
		In-patient scattered photons	MC Measurement Analytical models	Neutrons	MC Measurement Analytical models
		Head scattered photons			
Imaging		**Type**	**Assessment methods**	**Type**	**Assessment methods**
	Planning and verification	CT	MC Analytical models	CT	MC Analytical models
	Set-up and IGRT	CBCT		CBCT	
		kV-planar DR		kV-planar DR	

Figure 1. Graphic overview of the dose contributors to be accounted in the development of a comprehensive system for personalised dosimetry in radiotherapy. Similarities between photon and proton RT are indicated by the use of the same background colour while differences are suggested by the use of different colours. It should be noted that the photon treatments employ low energy photons for which neutron production is negligible.

2.1 Methodological steps for personalised dosimetry in photon RT

Step 1. Assessment of the in-field doses

In order to assess the in-field doses one has to start by performing a review of the delineation of the organs of interest included in the treatment volume and, if needed, adjust their contouring using the drawing tools from the TPS. The doses delivered to these organs are subsequently determined directly from the treatment plans rendered by the TPS together with the relevant dosimetric and volumetric statistics. It should be noted that although different treatment planning systems are commercially available and employed at different clinics, type b class algorithms and higher (Knöös et al 2006, Ojala et al 2014) usually provide a dose calculation accuracy better than 3% (Howell et al 2010a). However, this accuracy decreases for locations beyond the border of the treatment field. Howell et al 2010b reported an overall underestimation of 40% for doses lower than 5% of the prescription dose. Therefore, doses calculated by TPS should be considered up to the 5% isodose. Analytical models, as described below, will complement the information from this isodose distribution.

Step 2. Assessment of the out-of-field doses

In order to assess the out-of-field doses accounting for the in-patient scattered photons and the head scattered photons a two-stage framework was developed:

- In the first stage, the planning CT is registered with the CT image of the ICRP110 phantom for the generation of a synthetic patient-specific whole-body CT. This could be achieved with dedicated image registration software, e.g. IS^{2}aR (Muñoz et al 2022) as in the present work. It should be noted that to enhance the patient-specificity of the phantom, the original CT scan could be employed to substitute the corresponding region within the synthetic phantom. This approach increases the accuracy of treatment plan modelling when conducting MC simulations.
- In the second stage, the synthetic CT is used together with dedicated algorithms or software implementing them, e.g. Periphocal 3D, P3D, (Sánchez-Nieto et al 2022) as in the present work, and treatment specific parameters like the number of monitor units (MU), the prescription dose and actual field size from individual treatment plans for the evaluation of peripheral photon doses.

A graphical illustration of the methodological step 2 for out-of-field dose assessment in photon RT is shown in Figure 2.

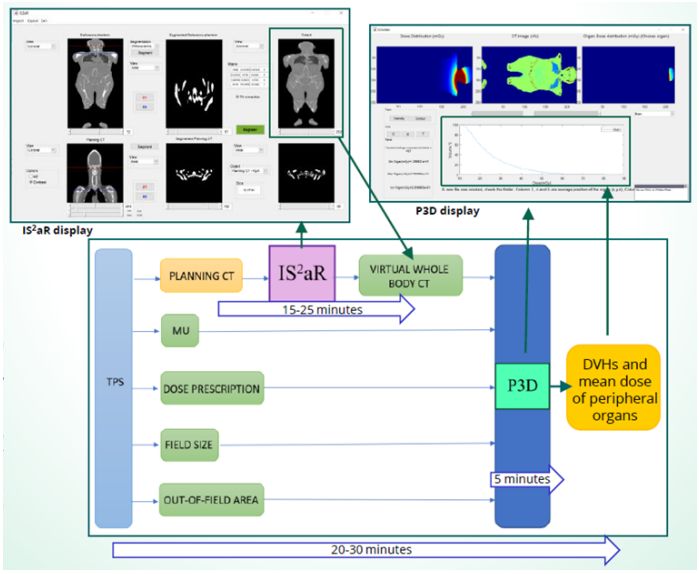

Figure 2. Graphic illustration of the framework for the calculation of out-of-field doses in photon RT using IS^{2}aR and P3D indicating the workflow and the time for executing the different stages, reproduced with permission from the authors (Romero-Expósito et al 2023a)

Step 3. Assessment of the imaging doses

In order to assess the imaging doses, one has first to collect all planning CTs as well as all images employed for patient set-up and position verification consisting of orthogonal images or, if employed, volumetric CBCTs.

- Doses from the planning CTs are determined using dedicated software applications for organ dose calculations, e.g., Virtual Dose (Ding et al 2015) as in the present work. These allow the calculation of individual organ doses based on a set of dose coefficients, as well as scanner specific and protocol specific parameters.

- Doses from the orthogonal images are obtained using organ dose conversion factors in planar radiography from the incident air kerma of individual images (Kelaranta et al 2016, Omar et al 2016).

Step 4. Summation of the doses

The total doses to organs are obtained by adding up the individual contributions from steps 1-3. For in-field and near-field organs, dose volume histogram (DVH) distributions are used for the summation while for peripheral organs receiving doses lower than approximately 2 Gy the mean dose can be used for the summation since these are in the linear region of the risk models for stochastic effects.

2.2 Methodological steps for personalised dosimetry in proton RT

Step 1. Assessment of the in-field doses

In order to assess the in-field doses one has to start by performing a review of the delineation of the organs of interest included in the treatment volume and, if needed, adjust their contouring using the drawing tools from the TPS. The doses delivered to these organs are subsequently determined directly from the treatment plans rendered by the TPS together with the relevant dosimetric and volumetric statistics. It should be noted that the commercially available TPSs for protons assume a relative biological effectiveness (RBE) of protons of 1.1, constant for all dose levels, fractional doses, linear energy transfer (LET) values and types of tissues, neglecting thus that the RBE of protons could vary depending on the factors listed above. This methodological step might therefore be revised in the future when the variable RBE will become available in the commercial TPSs.

Step 2. Assessment of the out-of-field doses

In order to assess the out-of-field doses accounting for the neutron contribution a two-stage framework was developed:

- In the first stage, the planning CT is registered with the CT image of the ICRP110 phantom for the generation of a synthetic patient-specific whole-body CT. This could be achieved with dedicated image registration software, e.g. IS^{2}aR (Muñoz et al 2022) as in the present work. To enhance the patient-specificity of the phantom, the original CT scan should be employed to substitute the corresponding region within the synthetic phantom. This approach increases the accuracy of treatment plan modelling when conducting MC simulations.
- In the second stage, the neutron doses were subsequently estimated at voxel level with Monte Carlo simulations of the individual treatment plan. In the present work, the Monte Carlo N-Particle (MCNP) code, version 6.2 (Werner 2017), was used to assess neutron production, together with the actual spatial distribution of the spots for each energy layer in the plan as described in Ardenfors et al (2018b). Alternatively, as the Monte Carlo simulations are resource and time demanding, analytical models could be considered.

Step 3. Assessment of the imaging doses

In order to assess the imaging doses, one has first to collect all planning and verification CTs as well as all images employed for patient set-up and position verification consisting of orthogonal images or, if employed, volumetric CBCTs.

- Doses from the planning CTs are determined using dedicated software applications for organ dose calculations, e.g., Virtual Dose (Ding et al 2015) as in the present work. These allow the

calculation of individual organ doses based on a set of dose coefficients, as well as scanner specific and protocol specific parameters.

- Doses from the orthogonal images are obtained using organ dose conversion factors in planar radiography from the incident air kerma of individual images (Kelaranta et al 2016, Omar et al 2016).

Step 4. Summation of the doses

The total doses to organs are obtained by adding up the individual contributions from steps 1-3. The radiobiological effect of proton and neutrons must be considered to perform a proper summation with the imaging photon doses. Thus, the in-field proton doses should be given as RBE-weighted dose and the neutron out-of-field dose, as dose equivalent (in Sv). For in-field and near-field organs, dose volume histogram (DVH) distributions are used for the summation while for peripheral organs receiving doses lower than approximately 2 Gy (RBE) (or 2 Sv) the mean dose can be used for the summation since these are in the linear region of the risk models for stochastic effects.

3. Results

The above presented methodology was applied on two cohorts of brain and lymphoma patients according to the SINFONIA objectives.

For all the patients the therapeutic doses, i.e. the in-field doses, determined as described in Step 1 of the presented methodology, were below the tolerance doses for deterministic effects, as expected following the optimisation of the treatment plans clinically delivered.

Research efforts were therefore focused on the determination of the secondary and imaging doses for individual patients in the considered cohorts. Thus, they covered the three main sources of secondary doses in RT: scattered radiation (including neutrons for proton therapy) that can travel far from the treatment site, planning (and verification for proton RT) CTs, and set-up imaging doses (planar images and/or CBCT).

As previously mentioned, scattered radiation from the treatment machine or the patient can contribute to radiation burden to organs far from the target and this is an issue both for photon and proton treatments, and thus it has to be determined as detailed in Step 2 of the methodology.

As neutrons pose additional concern in proton RT due to their increased biological effectiveness extensive focus was put on determining their contribution to the total dose burden for individual patients. The Monte Carlo N-Particle (MCNP) code was used to assess the neutron production in a primary proton beam based on commissioning data from the Skandion Clinic and benchmarked against neutron dose measurements.

An example of the influence of the RS on the neutron dose is shown in Figure 3 for a brain case.

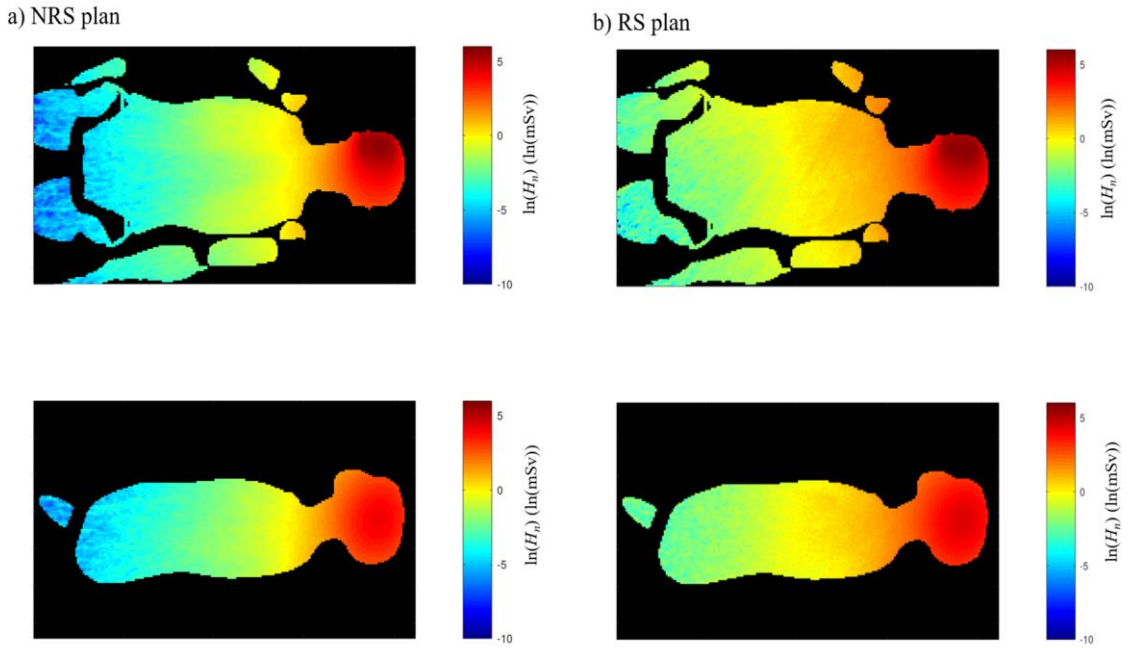

Figure 3. Neutron dose equivalent distribution inside the phantom for the plan without RS (NRS plan) (a) and with RS (b) (RS plan). Coronal and sagittal view at the depth of isocenter, from top to bottom, reproduced with permission from the authors (Romero-Expósito et al 2023b)

The target for the example shown in Figure 3 was situated at 3 cm depth in brain and the treatment involved 30 fractions of 1.82 Gy per fraction to the target volume (an absorbed dose to the target of 54.6 Gy (60 Gy(RBE) assuming RBE_{proton}=1.1). The RS plan led to 4-5 times higher doses. Beam line elements modulate neutron production, but absolute dose levels are low (below 1% of the prescription dose). During the simulation, the secondary photon doses were also evaluated. The results showed that photon absorbed doses are between 5 up to 37 times lower than proton doses.

The overall results on the out-of-field doses determined following Step 2 of the methodology indicate that scattered doses from photon treatments to out-of-field organs may be significant and therefore accounting for these doses is warranted. Thus, scattered doses up to 3 or 4 Gy have been found for distant organs for which the TPS predicted less than 1 Gy. For proton treatments, neutron doses on the level of 1.5-2 mSv/Gy to target were found for near-field organs, decreasing to 2-100 µSv/Gy for more distant organs. It is important to notice that lower levels of neutron doses have been determined from proton treatments, than corresponding scattered doses from photon treatment. These findings indicate the general benefit of modern proton delivery techniques and the low absolute contribution of neutrons, in contrast to historically used passive scattering techniques (Romero-Exposito et al 2022).

In addition, analytical models could be used as alternative to resource demanding MC approaches, the dosimetric accuracy provided being better than 20-30% for distant organs and thus comparable to the dosimetric accuracy available for imaging doses of comparable magnitude.

Regarding the planning and verification CTs, the Hodgkin's lymphoma (HL) treatments proven to be more CT-intensive in comparison to brain treatments, particularly for proton treatments, as CT simulation is seldom repeated in photon treatment. Thus, brain patients had about three CT scans acquired during their proton treatment, while up to 3 times as many are acquired for complex treatments for HL, such as those employing deep inspiration breath hold (DIBH) techniques. These exhibit large variations in protocols and

purposes such as planning free breathing or DIBH scans as well as standard dose or low dose protocols for verification CTs.

Following thus the methodology presented in this report (Step 3), employing the scan parameters obtained from the DICOM files as conventionally done in diagnostic radiology, the individual dose calculations using the VirtualDose software have shown that in-field and near-field organs have the largest radiation burden from repeated CTs. In addition, the inclusion of normal tissues among the in-field and near-field organs largely depends on target extension. Nevertheless, the in-field and near-field organs receive total doses from CT scans in the interval 10-200 mGy, which typically represents less than 1% of the prescription dose. Individual organ doses were extracted using VirtualDose software and scan specific parameters. Few more detailed examples of the in-field and near-field organ doses are given in Table 1. The corresponding doses from CT scans in photon RT are 3-10 times lower.

Table 1. In-field and near-field organ doses from repeated CTs for 65 HL patients treated with proton RT

Organ	Dose range (mGy)	Median dose (mGy)	% of prescribed dose to the target
Breasts	7-127	67	0.1-0.7
Lungs	33-151	69	0.1-0.8
Heart	12-162	63	0.1-0.9
Thyroid	14-203	39	0.1-1-0

Imaging practices for daily target localisation represent the other major contributor of radiation burden for imaging during the radiation therapy process as emphasised by the presented methodology. A broad array of imaging techniques could be employed for this purpose to allow 2D/2D, 2D/3D and even 3D/3D image registrations and calculations of correction vectors for patient positioning. The Skandion Clinic has not used 3D/3D for any of the treatments considered in SINFONIA (brain and HL). 2D/2D and 2D/3D approaches are least dose intensive as they employ orthogonal imaging of the treated volumes. The dose contributions determined through the use of organ dose conversion factors (step 3 in the present methodology) and are in the order of 0.1-0.5 mSv per image to in-field and near-field organs, similar to those from planar images in diagnostic radiology. The frequency of imaging depends on many factors, including the mobility of the treated area, the use of patient immobilisation devices and their performance, the need for verification imaging. Analyses carried out in SINFONIA have shown that between 15 and 110 planar images (median 39) are taken for the relatively short treatment protocols of HL treatments. Similar variations have also been seen for brain treatments. The cumulative dose from these images however does not exceed 0.4% of the prescription dose for in field and near field organs. It therefore appears that these imaging doses represent a low contribution to the total radiation burden of brain cancer and HL patients, typically in the range of clinically acceptable dose variations.

Regarding the final step of the methodology, Step 4, an example is presented in Figure 4. For the summation of the individual contributions, attention should be paid to the in-field and near-field organs as the actual dose distribution are needed for the overall assessment. Figure 4 shows the differential and cumulative DVHs for the right lung of one HL patient receiving photon RT (47 Gy prescribed in 22 fractions). The imaging doses were due to a daily CBCT and 4 CT scans. In the differential plot, the contribution from out-of-field and imaging lies on the low dose region on the left. The global effect produces a shift to higher doses in the cumulative DVH. In terms on mean dose in lung, the addition of out-of-field and imaging doses to the in-field data from TPS entails an increase of almost 10%, from 11.15 to 12.25 Gy. Regarding the prescription dose, this increase represents a 2.3 %.

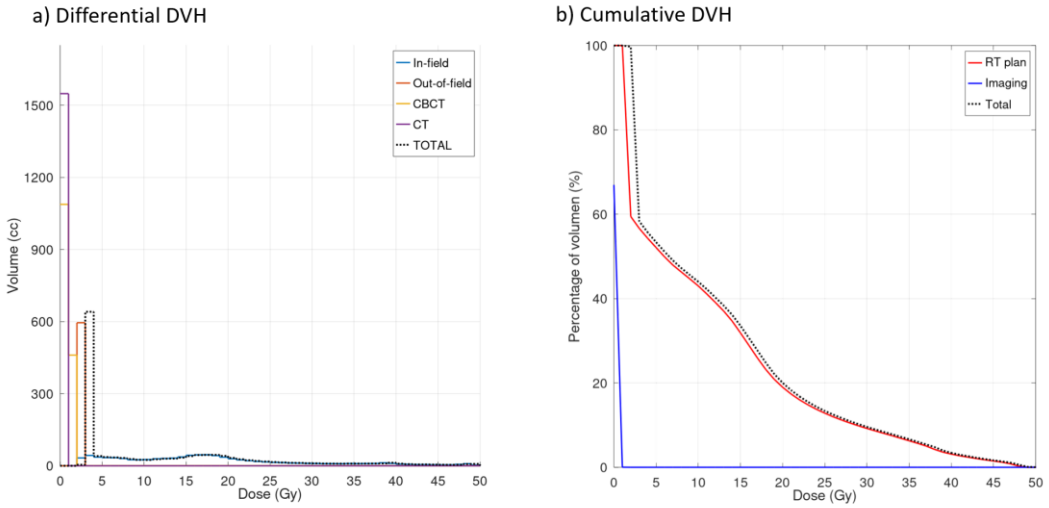

Figure 4. Differential (a) and cumulative (b) DVH of the right lung of a HL photon RT patient. Comparison between the different contributions and the global result.

4. Conclusions

Within SINFONIA we have developed methodological approaches to evaluate doses from all the major contributors to secondary doses to satisfactory accuracy. The major contributor to secondary doses from RT appears to be the scattered radiation. The neutron contribution from modern proton delivery techniques is lower than the corresponding scattered radiation from photon treatments indicating the general benefit of modern proton therapy techniques. Future studies would have to be dedicated to dose evaluations from hypothetical scenarios employing CBCT for patient position verification in proton therapy.

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