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► To cite this version:

David Bondesson, Arturs Meijers, Guillaume Janssens, Simon Rit, Moritz Rabe, et al.. Anthropomorphic lung phantom based validation of in-room proton therapy 4D-CBCT image correction for dose calculation. *Zeitschrift fur Medizinische Physik*, 2022, 32 (1), pp.74-84. 10.1016/j.zemedi.2020.09.004 . hal-03029930

HAL Id: hal-03029930

<https://hal.science/hal-03029930>

Submitted on 1 Dec 2020

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1 Anthropomorphic lung phantom based 2 validation of in-room proton therapy 4D- 3 CBCT image correction for dose 4 calculation

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1 **Abstract**

2 **Purpose:** Ventilation-induced tumour motion remains a challenge for the accuracy of proton
3 therapy treatments in lung patients. We investigated the feasibility of using a 4D virtual CT
4 (4D-vCT) approach based on deformable image registration (DIR) and motion-aware 4D
5 CBCT reconstruction (MA-ROOSTER) to enable accurate daily proton dose calculation using
6 a gantry-mounted CBCT scanner tailored to proton therapy.

7 **Methods:** Ventilation correlated data of 10 breathing phases were acquired from a porcine ex-
8 vivo functional lung phantom using CT and CBCT. 4D-vCTs were generated by (1) DIR of
9 the mid-position 4D-CT to the mid-position 4D-CBCT (reconstructed with the MA-
10 ROOSTER) using a diffeomorphic Morphons algorithm and (2) subsequent propagation of
11 the obtained mid-position vCT to the individual 4D-CBCT phases. Proton therapy treatment
12 planning was performed to evaluate dose calculation accuracy of the 4D-vCTs. A robust
13 treatment plan delivering a nominal dose of 60 Gy was generated on the average intensity
14 image of the 4D-CT for an approximated internal target volume (ITV). Dose distributions
15 were then recalculated on individual phases of the 4D-CT and the 4D-vCT based on the
16 optimized plan.

17 Dose accumulation was performed for 4D-vCT and 4D-CT using DIR of each phase to the
18 mid position, which was chosen as reference. Dose based on the 4D-vCT was then evaluated
19 against the dose calculated on 4D-CT both, phase-by-phase as well as accumulated, by
20 comparing dose volume histogram (DVH) values (D_{mean} , $D_{2\%}$, $D_{98\%}$, $D_{95\%}$) for the ITV, and
21 by a 3D-gamma index analysis (global, 3% / 3mm, 5 Gy, 20 Gy and 30 Gy dose thresholds).

22 **Results:** Good agreement was found between the 4D-CT and 4D-vCT-based ITV-DVH
23 curves. The relative differences ($(\text{CT-vCT})/\text{CT}$) between accumulated values of ITV D_{mean} ,
24 $D_{2\%}$, $D_{95\%}$ and $D_{98\%}$ for the 4D-CT and 4D-vCT-based dose distributions were -0.2%, 0.0%, -
25 0.1% and -0.1%, respectively. Phase specific values varied between -0.5%-0.2%, -0.2%-0.5%, -
26 -3.5%-1.5% and -5.7%-2.3%. The relative difference of accumulated D_{mean} over the lungs was
27 2.3% and D_{mean} for the phases varied between -5.4% and 5.8%. The gamma pass-rates with 5
28 Gy, 20 Gy and 30 Gy thresholds for the accumulated doses were 96.7%, 99.6% and 99.9%,
29 respectively. Phase-by-phase comparison yielded pass-rates between 86%-97%, 88%-98%
30 and 94%-100%.

1 **Conclusions:** Feasibility of the suggested 4D-vCT workflow using proton therapy specific
2 imaging equipment was shown. Results indicate the potential of the method to be applied for
3 daily 4D proton dose estimation.

4 Keywords: tomography, cone-beam, proton therapy, 4D-vCT, motion, thorax

5 **1. Introduction**

6 Ventilation-induced tissue motion remains a major challenge for accuracy in
7 proton therapy of lung cancer, which is however deemed effective [1–3]. Optimal proton
8 therapy treatment for lung cancer entails accounting for several sources of uncertainty, such
9 as imaging artefacts (e.g. due to metal implants), organ motion, setup and anatomical
10 variations and dose range uncertainties [4–8]. One of the challenges to precise treatment of
11 lung cancer patients is ventilation motion, which can cause significant errors in imaging,
12 patient alignment or, via interplay effects among others, in the delivered dose distribution [9].
13 These errors can lead to issues such as tumours not receiving the expected dose, or the heart
14 (or other sensitive organs) receiving excessive radiation dose, having severe effects on both
15 patient survival and complications [10]. To monitor and manage these issues, methods for
16 monitoring and managing ventilation motion are being developed to create a treatment plan
17 robustly optimized with respect to motion [11]. One important step has been to utilize a
18 planning 4D-CT to establish a motion robust treatment plan. Complementing the planning
19 CT, several studies have shown that CBCTs can yield further advantages by significantly
20 reducing set-up errors and increasing radiotherapy (RT) accuracy [12–14]. Thus, daily on-
21 board imaging and adaptive radiotherapy based on in-room 4D-cone beam CT (CBCT) has
22 been suggested as an alternative [15]. However, to enable CBCT-based proton dose
23 calculations for adaptation and/or plan re-optimization, accurate Hounsfield unit (HU) values
24 are required [16, 17]. To this end, correction strategies must be applied to CBCTs since their
25 native image quality is severely degraded by, among others, scatter effects.

26 Also, 4D-CBCTs are not yet part of clinical proton therapy workflows since technical factors
27 generally delayed CBCT's adoption compared to photon therapy [18]. Additionally, low
28 image quality and thus poor soft tissue contrast have limited motion modelling. However,
29 considerable progress has been made with novel motion-aware/-compensating image
30 reconstruction methods [19–25]. These methods can be divided into ventilation-correlated or
31 motion compensated approaches, where the former may suffer from streaking artefacts due to
32 a low number of projections in each reconstructed motion state and the latter only yields a
33 static final image. To find a trade-off that would yield a more stable, yet still motion-aware

1 reconstruction, a new method was recently introduced called motion-aware spatial and
2 temporal regularization (MA-ROOSTER) [26]. It reconstructs a 4D-CBCT image from a
3 motion averaged CBCT scan and the initial planning 4D-CT by performing spatial and
4 temporal regularization, considering also that the voxel trajectories are curved based on the
5 estimated ventilation motion of the 4D-CT. MA-ROOSTER has been shown to yield streak-
6 free reconstructions and robust information on tumour location throughout the breathing
7 cycle. Since direct accurate dose calculation on the obtained CBCT images is currently not
8 feasible for proton therapy due to the previously mentioned downsides causing inaccurate HU
9 values [27–29], it has instead been suggested to use the initial planning CT and the daily 4D-
10 CBCT to generate a 4D-virtual CT (vCT) with the help of deformable image registration
11 (DIR) [30–33]. The retrieved image will exhibit the anatomy and motion imaged by 4D-
12 CBCT and contain the HU of the of the initial planning CT, such that accurate dose
13 calculation can be performed [34–38]. This technique has been applied in the lungs by
14 retrospectively sorting the CBCT images from a linac-mounted scanner into phases from
15 extracted ventilation signals and performing phase-by-phase DIR [39]. However, the direct
16 deformation of CT to CBCT phases for dosimetric evaluation means that each phase may
17 suffer from CT to CBCT deformation uncertainties. In this work, we have investigated a
18 novel mid position based vCT approach using the MA-ROOSTER workflow [40, 41] and
19 compared the dose calculation quality against planning 4D-CT for accumulated and phase-by-
20 phase dosimetric evaluation. Measurements and evaluation were performed on a functional
21 lung phantom using a proton-gantry-mounted CBCT system. In the presented workflow, only
22 a single CT to CBCT DIR in mid position is used, followed by 3D-CBCT-to-4D-CBCT DIR
23 to yield corrected CBCT images for each motion state, which should reduce uncertainties. To
24 our knowledge, this is the first study to evaluate this novel 4D-vCT workflow using proton
25 therapy specific imaging equipment.

26 **2. Materials and Methods**

27 **2.1. Ex-vivo functional lung phantom**

28 4D-CT and CBCT lung imaging was performed using a functional ex-vivo porcine lung
29 phantom (Artichest®, PROdesign GmbH, Heilikonsteinach, Germany) capable of executing
30 user-defined breathing curves [42] (figure 1). The phantom is comprised of a water filled
31 plastic shell which has a similar shape as a human thorax and contains inflatable porcine
32 lungs. A thin layer of ultrasound gel was applied to the inside of the plastic shell, as well as
33 onto the porcine lungs, to reduce friction between the plastic and lung surfaces. The lungs

1 were then inflated by lowering the pressure inside the container with a constantly powered
2 vacuum pump and the bronchi connected to outside pressure. A second pump was connected
3 to a fabricated diaphragm layer, that cyclically changed its volume to simulate breathing
4 motion. The breathing curve was defined manually to resemble a typical patient's breathing
5 motion and was cyclically repeated with a frequency of 0.25 Hertz (15 breaths per minute).

6

7 Figure 1: Ex-vivo functional porcine lung phantom used for CBCT and CT measurements.

8 **2.2. Image Acquisition**

9 **2.2.1. 4D-CT**

10 A 4D-CT scan was acquired (Somatom Definition AS, Siemens Healthineers, Erlangen,
11 Germany) covering the whole lung phantom during motion. The image set was sorted into 10
12 equidistant phase bins based on the diaphragm system pressure signal measured with an Anzai
13 load cell (Anzai, Tokyo, Japan). The pressure sensor was connected via a T-pipe attached to
14 the pressure input tube using a coupling adapter with an elastic membrane. The reconstruction
15 grid was $0.977 \times 0.977 \times 2 \text{ mm}^3$ with 512×512 pixels per slice and 325 slices. CT images
16 were reconstructed using an iterative reconstruction algorithm.

17 **2.2.2. CBCT**

18 The phantom was moved right after the CT acquisition to the treatment couch of a Proteus
19 PLUS proton gantry (IBA, Louvain-la-Neuve, Belgium) for CBCT imaging. To ensure a
20 reproducible ventilation cycle, the lung phantom was kept breathing with an uninterruptible
21 power supply. The couch was equipped with a 6D robotic positioning system that was used to
22 align the phantom to the treatment room's isocentre by using the on-board CBCT system.
23 Images were acquired with an offset detector yielding a field of view of 50 cm diameter. The
24 CBCT acquisition entailed the following parameters: rotation time 123s, source to image
25 distance (SID) = 3053.5 mm, source to axis distance (SAD) = 2536 mm, tube voltage = 120
26 kVp, exposure time = 12.5 ms, tube current = 320 mA, number of projections = 910, gantry's
27 angular range = 359.23° .

28 **2.3. Image Reconstruction and Generation**

29 Reconstruction of 4D-CBCTs and 4D-vCT generation was performed with OpenReggui [43].
30 The 4D-CT and the CBCT projections were used as inputs to generate a 4D-CBCT and a mid
31 position CBCT with the MA-ROOSTER workflow, as described below. These images were

1 then used in the following step to generate the final 4D-vCT. For the purpose of presenting a
 2 clear overview, the workflow of the 4D-vCT reconstruction has been illustrated in figure 2.
 3 All DIRs were performed with an 8-level diffeomorphic Morphon algorithm [44]. The
 4 number of iterations between level 1-8 was set to 2/5/10/10/10/10/10/10 (finest to coarsest),
 5 similar to previous studies that performed CT-to-CBCT DIR [38].

6

7 Figure 2: Workflow to generate a 4D-vCT image from a 4D-CT image and CBCT projections. MA-ROOSTER
 8 uses the CBCT projections to generate a 4D-CBCT. The initial planning 4D-CT is used to generate a mid
 9 position CT as well as to extract the DVFs input to the MA-ROOSTER.

10 **2.3.1. MA-ROOSTER**

11 MA-ROOSTER can be best understood as a general case of the initial 4D-ROOSTER
 12 algorithm [19] which in turn builds upon a 4D-conjugate gradient algorithm by adding
 13 temporal and spatial regularization terms. 4D-conjugate gradient (CG) aims to minimize the
 14 single-term cost function $\sum_{\alpha} \|R_{\alpha} S_{\alpha} f - p_{\alpha}\|_2^2$ where

- 15 1. $\|\cdot\|_2$ is the l_2 – norm.
- 16 2. α is the projection index.
- 17 3. f is a 4D-sequence of volumes to be reconstructed.
- 18 4. R_{α} is the forward projection operator at index α , mapping a 3D volume onto a 2D-
 19 projection image.
- 20 5. S_{α} is a linear interpolator that maps a 3D + time-sequence onto a 3D volume with the
 21 ventilation phase of projection α .
- 22 6. p_{α} is the measured projection with index α .

23

24 The ROOSTER algorithm adds regularization by considering the following constraints in
 25 every iteration:

- 26 • Minimize the single-term cost function $\sum_{\alpha} \|R_{\alpha} S_{\alpha} f - p_{\alpha}\|_2^2$ with 4D-CG.
- 27 • Enforce positivity, by setting all negative voxels of f to zero.
- 28 • Remove motion where it is not expected to occur with a motion mask.
- 29 • Enforce the spatial and temporal gradients' sparsity in each volume using 3D- and 1D-
 30 total variation (TV) denoising along their respective dimensions [45].

31 It uses the output in every step as input for the next. However, as 1D-TV denoising is
 32 performed in the temporal direction by the ROOSTER method, moving objects in the lung

1 have been observed to gradually fade from one position to another instead of displaying their
2 actual sharp edges and a distinct position in every time frame. MA-ROOSTER tries to
3 mitigate this specific problem by curving the regularization direction to follow moving
4 structures. The MA-ROOSTER uses CBCT projections to generate a 3D-CBCT volume
5 which, in turn, is used to extract a motion mask via segmentation to only include regions
6 where motion is expected. The ventilation phase is usually extracted from the CBCT
7 projections with the Amsterdam shroud method [46, 47], but was ineffective with the lung
8 phantom. It was instead extracted by tracking the areal change of a manually selected region
9 in the CBCT projections that contained both lung and diaphragm. For extracting the motion
10 that is used for curved regularization, deformation vector fields (DVF) [48] were generated
11 from the 4D planning CT. The full MA-ROOSTER workflow is visualized inside the dotted
12 box of figure 2. The implementation of the workflow can be summarized in the following
13 steps:

- 14 1) The motion-averaged 3D-CBCT volume was reconstructed from the projections with
15 the conjugate gradient descent method.
- 16 2) The motion mask was created from the blurry 3D-CBCT volume by segmenting the
17 phantom (excluding surrounding air and the treatment couch).
- 18 3) The averaged 4D-CT was rigidly aligned to the 3D-CBCT with a mutual information
19 metric and its rigid transformation was extracted.
- 20 4) A mid position CT and the corresponding 10 DVFs from each phase to mid position
21 were generated following the steps described below. The DVFs were aligned to CBCT
22 space with the rigid transformation.
- 23 5) The inverse of the DVFs from ventilation phases to mid position CT were used to
24 generate the final 4D-CBCT in accordance with the MA-ROOSTER optimization
25 steps described above.

26 The mid position CT and DVFs from ventilation phases to mid position were generated with
27 the following steps:

- 28 1) DVFs from 9 phases to one reference phase were generated with DIR (see above for
29 settings).
- 30 2) A mid position DVF was calculated by averaging the DVFs. All phases' DVFs are
31 then subtracted from that to have them pointing towards the mid position.
- 32 3) The mid position image is then generated by deforming all images to mid position and
33 calculating their median image.

1 The MA-ROOSTER workflow was performed using $359 \times 289 \times 270$ voxels on a $1 \times 1 \times$
2 1mm^3 grid. Regularization parameter γ_{space} and γ_{time} were set to 2×10^{-5} and 1×10^{-3} ,
3 respectively in accordance with the initial study's recommendation [26].

4 Since mismatching ventilation positions between the 4D planning CT and 4D-CBCT phases
5 can cause anatomical differences [49], 9 incremental shifts of 1% (corresponding to 40ms) of
6 the CBCT ventilation phase were performed on the extracted phase curve. 4D-CBCTs were
7 reconstructed for every incremental shift and the breathing curves extracted by tracking the
8 areal change in a manually selected region in the slices containing both lung and diaphragm.
9 Correspondingly, the 4D-CT breathing curve was also extracted and compared against the
10 extracted breathing curves with the smallest squared difference. This yielded an optimal
11 incremental phase shift of 3% for matching 4D-CT and 4D-CBCT ventilation phases.

12 **2.3.2. 4D-vCT**

13 The 4D-vCT generation uses the mid position CT and 4D-CBCT that were generated in the
14 MA-ROOSTER workflow as inputs. Its workflow consists of the following steps:

- 15 1) A mid position CBCT phase was generated with the same multistep workflow
16 described above to produce the mid position CT.
- 17 2) The mid position CT was non-rigidly registered onto the mid position CBCT (using
18 the settings described above), generating a virtual mid position CT.
- 19 3) The mid position vCT was propagated to 4D with the extracted DVFs from the 4D-
20 CBCT, yielding the 4D-vCT.

21 **2.4. Treatment plan and dose optimization**

22 Proton treatment plans were generated on a 3D average CT intensity image, obtained from
23 voxel-wise averaging the 10 ventilation phases of the 4D-CT. A part of the oesophagus still
24 attached to the lungs served as a surrogate gross tumour volume (GTV). An ITV was
25 approximated by delineating this GTV with a narrow display (high contrast) window on the
26 motion averaged CT image. The ITV was then copied onto each CT and vCT ventilation
27 phase. The plan did not aim at reproducing treatment planning precisely, given the artificial
28 nature of the simulated GTV. Rather, the goal was to generate reasonable dose distributions
29 that could be used for recalculation and evaluation, and which covered the GTV at all
30 ventilation phases. No density override was performed. Two pencil-beam scanning proton
31 radiation fields at gantry angles 0° and 65° (on the International Electrotechnical Commission
32 Scale) were planned to deliver 60 Gy in 30 fractions. Dose calculation was performed with a

1 pencil beam algorithm. Robust single field uniform dose optimization was performed for 21
2 scenarios with an isotropic position uncertainty of 5 mm and a range uncertainty of 3% using
3 a research version of a commercial treatment planning system Raystation 6.99 (Raysearch
4 Laboratories, Sweden) [50]. The optimized treatment plan was then recalculated on each
5 phase of the 4D-CT and 4D-vCT.

6 **2.5. Calculated accumulated dose**

7 The generated diffeomorphic DVFs from phases to mid positions were used to subsequently
8 deform and accumulate CT and vCT doses on their respective reference phase, similar to
9 other recent dose accumulation studies [51, 52]. The DVFs from the 4D-CBCT were used on
10 the vCT doses, while the 4D-CT DVFs were used for the CT doses. The workflow for dose
11 calculation and accumulation is further illustrated in figure 3.

12

13 Figure 3: Workflow to calculate the accumulated dose for both 4D-CT and 4D-vCT. The optimized treatment
14 plan was generated on the averaged intensity image of the 4D-CT. The treatment plan (upper left corner) was
15 optimized on a voxel-wise image averaged along the 10 ventilation phases.

16 Doses on CT and vCT were compared between phases as well as between the two
17 accumulated results. DVH values (D_{mean} , $D_{2\%}$, $D_{95\%}$ and $D_{98\%}$) were calculated on the ITV as
18 well as in the lungs not containing the ITV (D_{mean}). Cumulative DVH curves were obtained
19 for the ITV as well as for the lungs excluding the ITV. 3D global gamma pass-rates were also
20 calculated using a (3%, 3mm) criterion and (total) dose thresholds of 5 Gy, 20 Gy and 30 Gy
21 (corresponding to 8.3%, 33.3% and 50% of the prescribed dose).

22 **3. Results**

23 **3.1. Comparison between registered CT and vCT**

24 Figure 4 displays sagittal slices of five exemplary ventilation phases of the 4D-CT, the
25 reconstructed 4D-CBCT and the 4D-vCT images. The motion amplitude was estimated with
26 the positional peak-to-peak change in the cranio-caudal direction of the diaphragm as well as
27 the GTV, which showed to be 13 mm and 14 mm, respectively. Comparing the 4D-CT and
28 4D-vCT, a slight blurring was apparent on the latter due to interpolation. The bottom row
29 displays the subtracted image of the 4D-CT and 4D-vCT, illustrating anatomical differences
30 caused by the 4D-vCT generation algorithm. The difference images highlight a phase-
31 dependent misalignment at the edges of the diaphragm position, particularly visible in phases

1 2 and 6 (red arrows). However, this area was far from the simulated treatment area in our
 2 study and subject to substantial sliding tissue motion due to the construction of the phantom.

3

4 Figure 4: (1st to 3rd row) Display of sagittal slices from 4D-CT as well as reconstructed 4D-CBCT and 4D-vCT
 5 images (ventilation phases 2, 4, 6, 8 and 10). Dotted lines highlight the diaphragm position at maximum exhale.
 6 The ITV is depicted in yellow. (4th row) Sagittal slices of difference images (4D vCT minus 4D-CT) in HU. Red
 7 arrows highlight particular registration discrepancies occurring particularly around transitional points between
 8 tissue and the phantom. The black arrow highlights a vertical registration discrepancy at the same height as
 9 streaking artefacts produced in the CBCT reconstructions.

10 3.2. Accumulated dose CT and vCT

11 The difference in dose distribution between the 4D-CT and 4D-vCT is depicted in figure 5 for
 12 ventilation phases 2, 4, 6, 8 and 10. The figure highlights that doses within the 50% threshold
 13 region differ by less than 0.3 Gy (compared to the 2Gy fraction dose). Larger dose differences
 14 were observed in the distal, low dose areas, of each field, where range differences expand
 15 given the low lung density. Gamma index pass-rates for the accumulated dose distributions
 16 between 4D-CT and 4D-vCT were 96.7%, 99.6% and 99.9% respectively for the 5 Gy, 20 Gy
 17 and 30 Gy thresholds, respectively. Table 1 further displays the gamma pass-rates for all
 18 single-phase dose recalculations, ranging from 85.5%-95.2%, 88.4%-98.0% and 97.6%-
 19 99.9% for the three considered thresholds. The DVHs (figure 6) confirm the good agreement
 20 between CT and vCT based dose for both the ITV and lungs excluding the ITV, with worst
 21 performance for phases 8 and 10. Table 2 shows the quantitative DVH comparison results
 22 between 4D-CT and 4D-vCT for all ventilation phases and the accumulated doses.
 23 Discrepancies for the ITV were found to be within 5.7% for the single phases and within
 24 0.2% for the accumulated dose. Discrepancies for the phase-by-phase evaluation in the lungs
 25 without the ITV were found to be within 5.8% and within 2.3% for the accumulated dose.

26 Table 1: Gamma pass-rates (PR) calculated for a global 3%/3mm passing criteria and different dose thresholds.

	PR 5 Gy threshold [%]	PR 20 Gy threshold [%]	PR 30 Gy threshold [%]
Phase 1	97.4	98.0	97.6
Phase 2	89.3	94.8	98.3
Phase 3	85.5	91.3	99.7
Phase 4	87.7	88.4	99.9
Phase 5	87.6	90.4	99.8
Phase 6	91.5	93.3	99.7
Phase 7	95.2	96.8	99.9
Phase 8	92.4	95.9	94.4

Phase 9	95.7	97.5	99.7
Phase10	95.2	96.7	94.1
Accumulated	96.7	99.6	99.9

1

2 Table 2: (2nd to 4th column) Differences ((CT-vCT)/CT) in $D_{2\%}$, $D_{95\%}$, $D_{98\%}$ and D_{mean} between dose
3 calculations on 4D-CT and 4D-vCT for the ITV. (5th column) D_{mean} differences between dose calculations on
4 4D-CT and 4D-vCT for the lungs (without the ITV). Values are displayed for all ventilation phases as well as for
5 the accumulated dose from all 10 phases.

	$\Delta D_{2\%}(ITV)[\%]$	$\Delta D_{95\%}(ITV)[\%]$	$\Delta D_{98\%}(ITV)[\%]$	$\Delta D_{mean}(ITV)[\%]$	$\Delta D_{mean}(lungs)[\%]$
Phase 1	0.4	0.1	0.3	0.2	-0.4
Phase 2	0.1	0.3	0.7	0.1	5.1
Phase 3	-0.1	-0.2	-0.3	-0.2	5.5
Phase 4	-0.1	-0.7	-0.9	-0.3	5.8
Phase 5	-0.1	0.6	1.1	-0.1	5.1
Phase 6	-0.2	1.5	2.3	0.1	4.3
Phase 7	-0.1	0.7	1.2	0.1	3.2
Phase 8	0.1	-2.8	-4.9	-0.25	-5.4
Phase 9	0.1	0.1	0.0	0.1	1.1
Phase 10	0.5	-3.5	-5.7	-0.5	1.5
Accumulated	-0.0	-0.2	-0.1	-0.1	2.3

6

7

8

9 Figure 5: Dose distributions (top and middle row) and dose differences (bottom row) on phases 2, 4, 6, 8 and 10
10 between 4D-CT and 4D-vCT images. The ITV is displayed on the 4D-CT in yellow.

11

12 Figure 6: Comparison of DVH curves for the ITV and lungs (without the ITV) from 4D-vCT (solid) and 4D-CT
13 (dotted) doses (all phases and accumulated).

14 4. Discussion

15 In this work we have generated 4D-vCTs using diffeomorphic mid position CT to mid
16 position CBCT DIR and the MA-ROOSTER workflow for calculating the accumulated proton
17 dose in a porcine lung phantom. For the comparison of the accumulated doses on 4D-CT and
18 4D-vCT, gamma pass-rates of 96.7%, 99.6% and 99.9% were determined for 5 Gy, 20 Gy and
19 30 Gy dose thresholds (prescribed total dose was 60 Gy). Considering also the observed
20 discrepancies of only -0.1% for D_{mean} , 0.0% for $D_{2\%}$, -0.2% for $D_{95\%}$ and -0.1% for $D_{98\%}$ of
21 the ITV, the feasibility to deform the planning 4D-CT into a 4D-vCT with updated motion, to

1 be used for daily 4D proton dose estimation, can be concluded. The motion amplitudes (peak-
2 to-peak) for the lung phantom's diaphragm and the GTV in this study were 13 mm and 14
3 mm showing a good correspondence with clinically observed values [53]. For the phase-
4 resolved evaluation, the largest DVH differences on the ITV were observed in phases 8 and
5 10, which also had the lowest pass-rates for the 30 Gy threshold gamma analysis. The lower
6 the used dose threshold was in the gamma evaluation, the lower pass-rates were yielded. This
7 is probably due to the low density of the lung in the lower dose region, where small errors in
8 the 4D-vCT can translate into large range shifts. Comparing reconstructed vCT images
9 against the reference CT for the respective phases, registration artefacts are found, as shown
10 in figure 4 (red arrows), at the anterior side of the lungs. This is particularly visible when
11 observing the transitional points between tissue and the phantom diaphragm where the DVF
12 in phase 2 has caused a slight bend in diaphragm and outer shell shape. Furthermore,
13 streaking artefacts from the CBCT reconstruction have been observed in several phases but
14 were particularly visible in phase 10 (black arrow in figure 4). Regularization parameters can
15 be manually adapted to remedy this effect, however, it is conceptually challenging to model
16 substantial tissue motion while maintaining diffeomorphic properties of the DVFs [26]. Still,
17 it should be noticed that the artefacts were far from the treatment field in our study. However,
18 this could cause issues for dosimetric calculations of irradiated tumours positioned in the
19 lower parts of the lung. It should, nevertheless, also be considered that the anatomy of the
20 phantom is not entirely realistic in the lower part of the lung due to the excessive sliding
21 motion, which would likely not appear to such extent in a real patient. Blurring was visible in
22 all reconstructed images, but the good agreement of dose distributions suggests that it likely
23 only has a negligible effect. Furthermore, compared to previous similar attempts to perform
24 dose evaluation on 4D-vCT phases from photon radiotherapy CBCT systems with phase-by-
25 phase CT to CBCT DIR all gamma pass-rates and dose differences were comparable or
26 improved [39].

27 Establishing a precise daily 4D motion model with the patient in treatment position is
28 essential for tracking tumour motion since it may enable adaptive dose planning. This in turn
29 could be used to optimize coverage of dose to the target while sparing essential organs-at-risk
30 during radiation therapy treatment. The presented 4D-vCT workflow adapts the necessary
31 balance between stable and motion-aware reconstruction by using the novel MA-ROOSTER
32 method and enables accurate estimation of the accumulated and phase-specific dose compared
33 to the 4D planning CT. This may subsequently improve estimation of the accumulated dose
34 between treatments and adaptation of the total treatment plan accordingly. The conjugate

1 gradient descent method for the initial 3D-CBCT reconstruction ensures that regularization
2 can be utilized to decrease movement artefacts compared to the analytical Feldkamp, Davis
3 and Kress reconstruction [54, 55]. Additionally, the MA-ROOSTER has shown to yield a
4 good agreement with daily motion as well as attenuation properties when DVFs from CT and
5 CBCT differ strongly [26], highlighting the 4D-vCT workflow's generality also for differing
6 ventilation trajectories. Also, since the focus of this study was mainly on dosimetric
7 evaluation of the 4D-vCT workflow, investigation of the impact of inconsistent ventilation
8 trajectories in 4D-CT and 4D-CBCT was considered out of scope.

9 There are some limitations to this study besides the use of the same motion between the 4D-
10 CT and the 4D-CBCT scans. Since measurements were performed on a porcine lung phantom
11 this should be seen as a proof of principle study. Future studies with patient measurements
12 and larger sample sizes are required to establish further clinical relevance. For example, to
13 compare the presented dose comparison workflow between an initial planning 4D-CT and a
14 CBCT with differing tumour size would be of particular interest. On the other hand,
15 investigating clinical patient data typically lacks ground truth information, since breathing
16 motion is not reproducible between 4D-CT and 4D-CBCT acquisitions. The used pencil beam
17 algorithm for dose calculation in lieu of a Monte Carlo algorithm may have yielded less
18 precise dose estimates, particularly in the low dose heterogeneous regions of the lung [56].
19 However, since a single algorithm was consistently used for optimization and recalculation,
20 we deem that the performed dosimetric analysis allows for reliable estimation of the accuracy
21 achievable with the presented 4DvCT approach.

22 Furthermore, as the workflow requires approximately 50 minutes performing the
23 reconstructions with multiple registration steps, it needs further improvements before it can be
24 implemented into online clinical application. The workflow currently performs image
25 reconstruction both on the GPU and CPU and faster reconstruction could potentially be
26 reached if all parts would run on the GPU.

27 **5. Conclusion**

28 In this work, a porcine lung phantom was used to show that the suggested 4D-vCT
29 reconstruction workflow for CBCT intensity correction is feasible using proton therapy
30 specific imaging equipment. A dosimetric evaluation using a 4D-CT exhibiting the same
31 motion as the 4D-CBCT shows promise for the method to be used for daily 4D-proton dose
32 estimation. Comparison between 4D-vCT and 4D-CT showed discrepancies for ITV D_{mean} .

1 $D_{2\%}$, $D_{95\%}$ and $D_{98\%}$ within 0.2%. Global 3%/3 gamma pass-rates for the accumulated doses
2 were above 96.7% for dose thresholds of 5 Gy, 20 Gy and 30 Gy. A more detailed evaluation,
3 also encompassing 4D-CT and 4D-CBCT data with different motion trajectories was deemed
4 beyond the scope of this proof-of-principle study but might be addressed in follow-up studies.

5 **6. Acknowledgement**

6 This work was supported by the German Research Foundation (DFG) project 399148265 “4D
7 cone beam computed tomography as a novel tool for accurate time-resolved dose calculation
8 in particle therapy”, the DFG’s Cluster of Excellence Munich–Centre for Advanced Photonics
9 (MAP) and the DFG Research Training Group GRK2274 Advanced Medical Physics for
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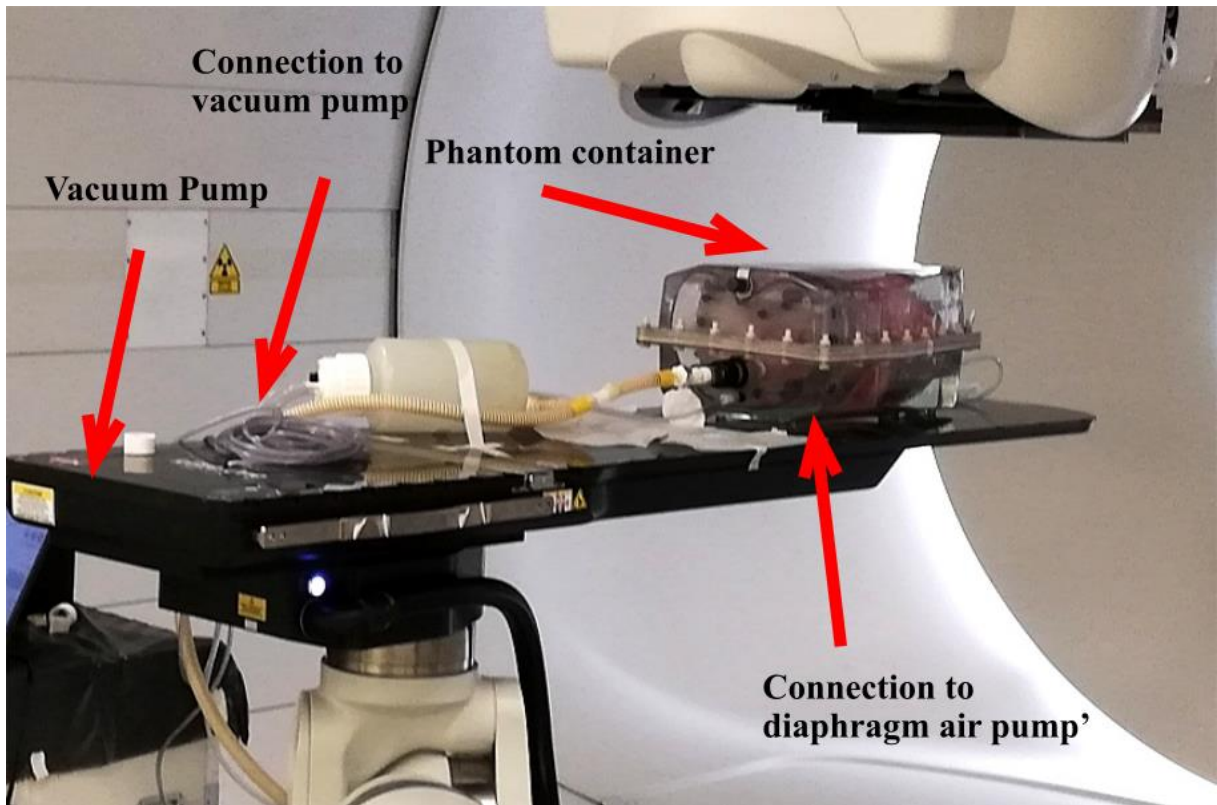
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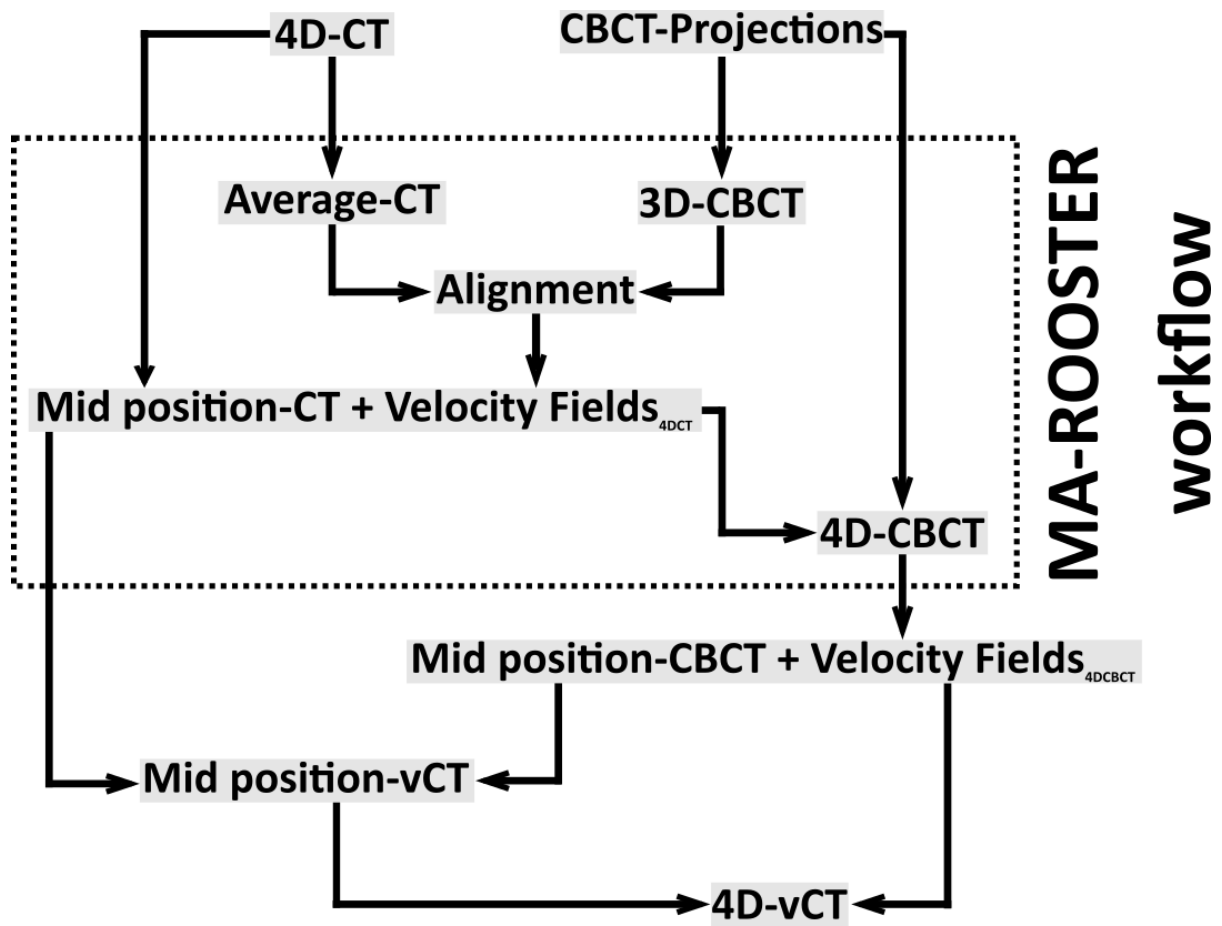
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2 Figure 1

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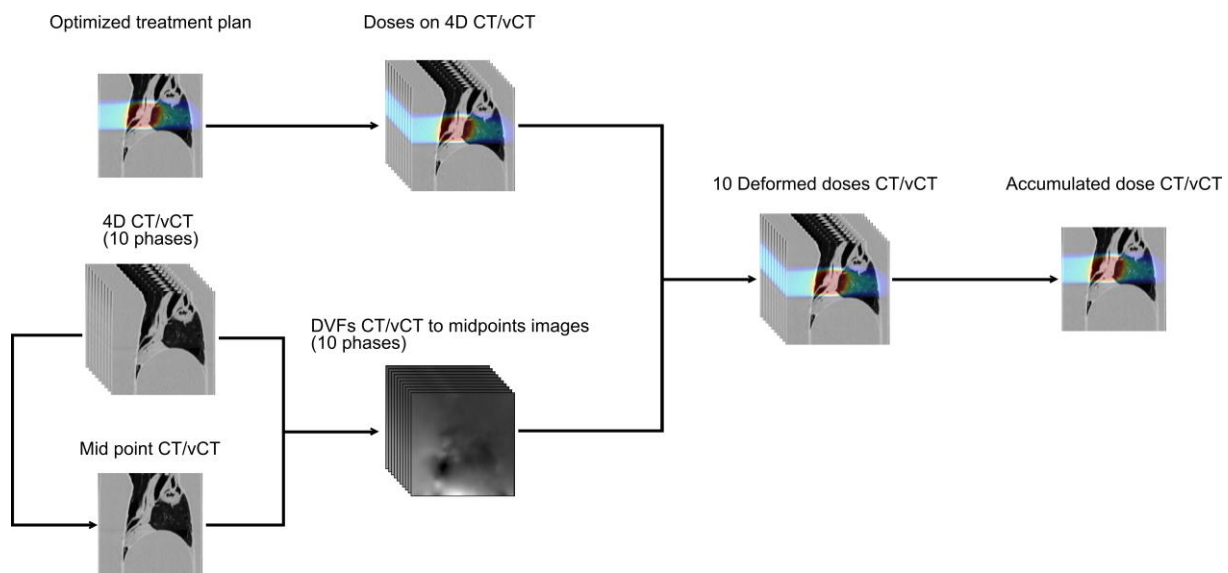
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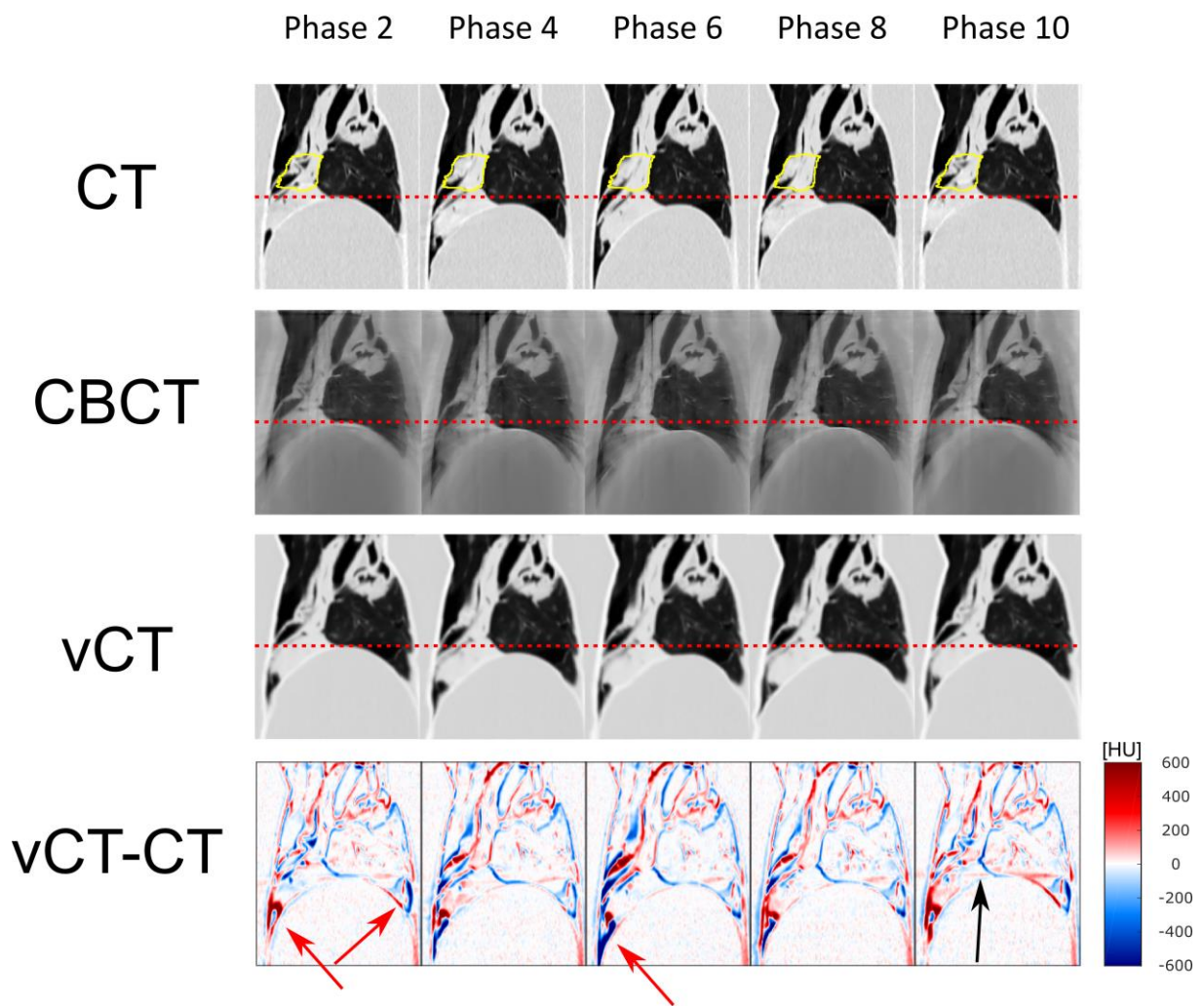
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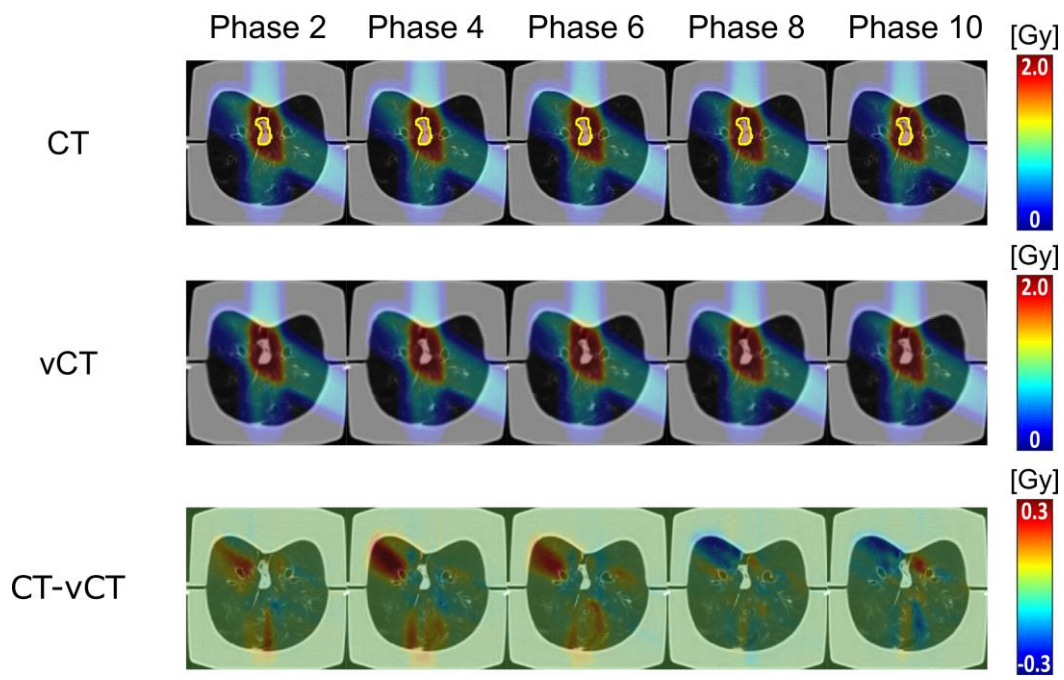
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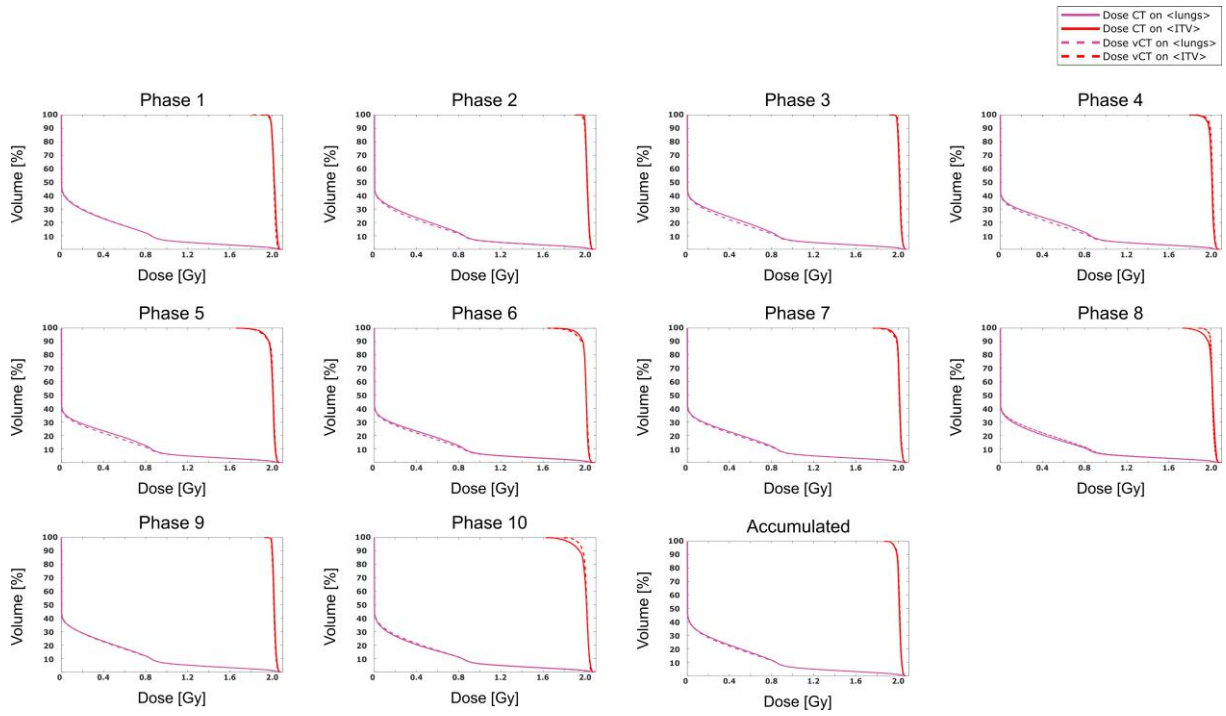
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2 Figure 6