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Running title: Robust optimization considering anatomy

Keywords: Robust optimization; head and neck cancer; proton therapy; treatment planning; anatomical variations; dose accumulation; plan adaptation

Highlights

- Classical robust optimization does not consider potential anatomical variations
- Anatomical robust optimization considers additional image datasets in optimization
- Including anatomical information in the optimization improves plan robustness
- The need for plan adaptation can be reduced with anatomical robust optimization

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Abstract

Background and purpose: Classical robust optimization considers uncertainties in patient setup and particle range. However, anatomical changes occurring during the treatment are neglected. Our aim was to compare classical robust optimization (cRO) with anatomical robust optimization (aRO), to quantify the influence of anatomical variations during the treatment course, and to assess the need of adaptation.

Materials and methods: Planning CT and weekly control CTs (cCTs) from 20 head and neck patients were analysed. Three intensity-modulated proton therapy (IMPT) plans were compared: conventional PTV-based plan; cRO, using solely the planning CT, and aRO, including additionally the first 2 cCTs in the optimization. Weekly and total cumulative doses, considering anatomical variations during the treatment, were calculated and compared with the nominal plans.

Results: Nominal plans fulfilled clinical specifications for target coverage ($D_{98\%} \geq 95\%$ of prescribed dose). The PTV-based and cRO approaches were not sufficient to account for anatomical changes during the treatment in 10 and 5 patients, respectively, resulting in the need of plan adaptation. With the aRO approach, in all except one patient the target coverage was conserved, and no adaptations were necessary.

Conclusion: In 25% of the investigated cases, classical robust optimization is not sufficient to account for anatomical changes during the treatment. Adding additional information of random anatomical variations in the optimization improves plan robustness.

Introduction

Intensity-modulated proton therapy (IMPT) has shown to be promising for the treatment of head and neck squamous cell carcinoma (HNSCC) patients, due to its high-dose conformity and reduced dose to the normal tissue in comparison with photon-based intensity-modulated radiation therapy (IMRT) [1–4]. However, due to its physical characteristics, protons are more sensitive to deviations from the nominal situation, for instance variations in the patient setup, uncertainties in the proton range and treatment-induced changes in the patient anatomy during the treatment course, which can result in degradation of the delivered dose [5–8].

To overcome this problem, different optimization methods have been investigated to generate robust plans, which consider uncertainties in patient setup and particle range during the optimization process, resulting in a plan which is robust against them [9–12]. Previous studies with robust optimization in HNSCC have focused on the plan robustness improvement in comparison with a non-robust plan, when the nominal plan is recalculated considering different 'perturbed' scenarios with modified setup (i.e. translational shifts) and range values [13–17]. However, anatomical changes that may occur during the treatment course, e.g. modified positioning and tumour shrinkage, potentially causing a degradation of the plan quality, are not considered in the optimization. The influence of anatomical variations in the plan robustness has already been investigated for IMPT plans of lung cancer patients [18–20].

Usually the optimization of a radiotherapy plan is based on one computed tomography (CT) image dataset. Including information of anatomical variability, e.g. additional CT with small random variations as shoulder positioning, neck or mandible rotations in the plan optimization process, may increase the robustness of the treatment plan against anatomical variations, and therefore may decrease the need of plan adaptation. The aim of this work was to compare two different plan strategies using robust optimization for HNSCC: classical robust optimization

(cRO) considering the different error scenarios in setup and range, and anatomical robust optimization (aRO) considering additionally random anatomical variations; to quantify the influence of anatomical changes during the treatment course and to assess the need of plan adaptation.

Materials and Methods

Patient data

Twenty subsequent patients with locoregionally advanced HNSCC and irradiation to the primary tumour and bilateral neck, treated with IMRT at our institution between January and July 2016, were selected. Each patient dataset consisted of a planning CT (2 mm slice thickness) and weekly control CTs (cCT) acquired during the course of the treatment with the same imaging protocol (median: 6, range: 4-7).

Clinical target volumes (CTV) and organs at risk (OAR: spinal cord, brainstem, parotid glands, larynx, oral mucosa, pharyngeal constrictor muscles and oesophageal inlet muscle) were contoured on the planning CT by an experienced radiation oncologist. Two CTVs were delineated: a high-risk CTV including the primary tumour, surgical cavity and potential metastatic lymph nodes, and a low-risk CTV including elective bilateral lymph nodes. The contours were transferred through deformable registration from the planning CT to cCT [21], reviewed and corrected by the same radiation oncologist. The volumes on both target volumes can be found in the Supplementary File I. Planning target volumes (PTV) were generated by isotropic expansion of the CTV by 5 mm.

Treatment planning

The prescribed mean doses to the targets were 57 Gy to the low-risk CTV and 70 Gy to the high-risk CTV, delivered with simultaneous integrated boost (SIB) in 33 fractions. An

additional transitional intermediate volume between low-risk and high-risk region of 10 mm margin was created assuring a steep SIB dose gradient [16,17,22]. The plans were optimized to deliver the prescribed dose to the CTVs following the institutional protocol ($D_{98\%} \geq 95\%$ and $D_{2\%} \leq 107\%$ of the prescribed dose, where $D_{98\%}$ and $D_{2\%}$ are the minimum doses to 98% and 2% of the target volume, respectively). Doses to the OARs were defined as: spinal cord: maximum dose (D_{max}) < 45 Gy; brainstem: D_{max} < 54 Gy; parotid glands: mean dose (D_{mean}) ≤ 26 Gy; larynx: D_{mean} < 40 Gy; constrictor muscles: D_{mean} < 42 Gy; oral mucosa and oesophageal inlet: doses as low as reasonably achievable. The OAR volumes outside the CTV were considered during the optimization process.

Three plans were generated in RayStation v5.99 (RaySearch Laboratories AB, Stockholm, Sweden) for each patient:

- PTV-based plan (PTVb), using the planning CT and the PTV as target volume without robust optimization.
- Classical robust optimization (cRO), using the planning CT and the CTV as target volume. The robustness parameters were 3 mm for setup uncertainty and 3.5% for range uncertainty, considering in total 21 different scenarios in the minimax approach [11]. Robust optimization was selected for minimum, maximum and uniform dose to the CTVs, as well as for both parotid glands, spinal cord and brainstem.
- Anatomical robust optimization (aRO), using the planning CT and the first two weekly cCTs in the plan optimization, representing small random anatomical variations in comparison with the planning CT. The same target volumes and robustness parameters as for cRO were used. Since there are two additional CT datasets included in the optimization, the algorithm considers in total 3 × 21 = 63 different scenarios.

A relative biological effectiveness (RBE) of 1.1 for proton beams was used. Three beams were used with the same configuration for both plans, with beam angles of 180°, 60° and 300°, respectively. An IBA universal nozzle beam, with a pencil beam spot size sigma ranging from 4 mm (220 MeV) to 8 mm (100 MeV) was used. A calculation dose grid of 3×3×3 mm^3, a range shifter of 7.5 cm water equivalent thickness and a minimum air gap of 3 cm were considered.

Influence of anatomical changes in treatment course

To evaluate the influence of induced anatomical changes during the course of treatment, weekly dose tracking was performed (Figure 1). The procedure consisted in recalculation of the plan in each cCT, followed by the assessment of weekly cumulative doses, i.e. the dose received by the patient considering all cCTs up to that time point, by non-rigidly deforming the calculated dose to the planning CT for dose accumulation. The intervention criterion for plan adaptation was a reduction in the target coverage (i.e. $D_{98\%} < 95\%$ of the prescribed dose) in comparison with the nominal plan. Furthermore, a total cumulative dose, which takes into account the induced anatomical changes in the cCTs during the whole treatment course, was calculated and compared with the nominal plan.

Statistical analysis

Wilcoxon signed-rank test was performed in SPSS v.25 (IBM Corporation, New York, USA) to evaluate differences between plan approaches over the whole patient cohort. A *p*-value < 0.05 was considered to be statistically significant.

Results

For all patients, the nominal plans for the three cases (PTVb, cRO and aRO) presented adequate target coverage, fulfilling the clinical specification of $D_{98\%} \geq 95\%$, and the doses to

the OARs remained below the constraints (Table 1). However, in the PTVb plan the total cumulative doses were reduced to as little as 80.81% and 84.49% for the low- and high-risk CT, respectively, and in the cRO plan to 88.39% and 89.16%, compared to 92.37% and 94.21% in the aRO plan, respectively. The underdosage of the low-risk CTV $D_{98\%}$ in the total cumulative doses was significant for the PTVb and cRO plans in comparison to the aRO plan ($p = 0.002$ and $p < 0.001$, respectively), with values up to -14.19% for PTVb, -6.61% for cRO and -2.63% for the aRO approach respectively, as shown in Figure 2. The underdosage of the total cumulative doses in the high-risk CTV $D_{98\%}$ was also significant different for both PTVb and cRO plans, compared with the aRO plan ($p < 0.001$ and $p = 0.001$, respectively). The $D_{2\%}$ to the high-risk CTV showed a maximum value up to 111.7% for the PTVb plan, but always remained below 107% for both robust plans. An increased mean dose of up to 4.7 Gy was observed for the cumulative larynx dose in both robust approaches, whereas the remaining OARs presented no major deviations between nominal and total cumulative doses.

Target coverage degradation for the PTVb approach, with mean differences between planned and total cumulative dose of 5.84% for the low-risk CTV and 4.97% for the high-risk CTV, illustrate that a margin expansion of the CTV alone cannot sufficiently account for anatomical changes during the treatment course. Although in 10 out of 20 patients the CTV coverage was acceptable, in the other 10 patients a plan adaptation was needed. Furthermore, also the cRO plan was not sufficient to account for anatomical changes during the treatment course. Figure 3 shows the weekly and total cumulative doses for all patients: degradation in the target coverage was observed for the PTVb and cRO plan. Analysing the individual patient doses, 5 out of 20 patients (25%) showed target coverage degradation in the cRO plan. Therefore, these patients would undergo plan adaptation according to the intervention criterion ($D_{98\%} <$ 95% of the prescribed dose).

In four of these five patients the aRO approach conserved the target coverage, both weekly doses and total cumulative doses, fulfilling the objective. For the remaining patient, the $D_{98\%}$ of the low-risk CTV was reduced to 94.30% in the week 6 cumulative dose, and therefore also demanding plan adaptation. For these 5 patients, the accumulation of the dose during the course of treatment is shown for both planning approaches in Figure 4. In Figure 5, the dose distributions for the total cumulative doses in the three plans are depicted and in Supplementary File II more information of anatomical variations in the CT scans used for anatomical robust optimization as well as in the last control CT are presented for these 5 patients.

Discussion

In the presented study, for the first time plan robustness of anatomical robust optimization was evaluated in a clinically realistic setting based on in-treatment control CT data. Its robustness against anatomical changes during treatment was superior to classical robust optimization. In this work, for every fourth of the evaluated patients, classical robust optimization was not sufficient to account for anatomical variations during the treatment course.

Patients with HNSCC frequently show anatomical changes during the treatment course, e.g. patient weight loss and volume shrinkage in target volume and OARs, which might require plan adaptation [7,8,22–25]. Plan adaptation strategies are usually time consuming, needing resources from clinicians, medical physicists and radiation technicians, therefore a calculation algorithm that reduces the need of adaptation benefits directly the clinical workflow.

Although in our current work the first two cCT (usually from the first two weeks of treatment) were used for aRO, it is in principle possible to apply aRO also before treatment by

performing more than one treatment planning CT, which is for example done for moving target regions (e.g. lung and liver). This is supported by the fact that in the first weeks of treatment, treatment-induced anatomical (systematic) changes such as progressive tumour shrinkage and weight loss, are not significant [7,25]. The changes we observed in the first two cCT were of random nature, e.g. shoulder positioning or small rotations. Thus, our investigation showed that including such random variations in the optimization may increase the robustness of the plan against further treatment-induced anatomical changes. Further studies should be conducted to verify our hypothesis that this holds true also for the use of multiple CT scans acquired before treatment. Moreover, it should be noted that for aRO the initial planning effort would be increased (additional CT acquisition and processing) moderately for all patients, whereas only for a subset of patients (20% in this study) there is a benefit by avoiding a time-intense replanning as for the majority of patients no adaptation is needed. Follow-up studies could also address cost-benefit evaluations that are depending on the institutional workflow and patient population, which were out of the scope in this study.

Integral dose to the normal tissue were slightly higher for the PTVb and aRO plans in comparison with the cRO plan, with mean values averaged over the entire patient cohort of 110.89 Gy·L, 110.64 Gy·L and 103.45 Gy·L, respectively. Moreover, the dose to the OARs remained similar between the planning approaches. Thus, we can affirm that the price for a higher robustness against anatomical changes by using aRO is negligible compared to the PTVb plan, which yields similar integral dose, but substantially less robustness compared to cRO with only a slightly lower integral dose (-7%) than the aRO plan.

In this work, we focused on the influence of anatomical changes during the treatment course in both plans; we did not consider additional setup and range perturbed scenarios. By doing so, we were able to assign the differences of the approaches solely to the influence of real

anatomical changes during treatment. We can conclude from this evaluation that the dose perturbation effect of anatomical changes during treatment are at least in the same order of magnitude as the setup and range uncertainties we considered during planning. Otherwise, the cRO approach, i.e. the range and setup error robustness, would have been able to compensate those anatomical effects while showing sufficient target coverage. In a next step, we plan to evaluate the robustness against combinations of error sources (setup, range, anatomical changes) in an extensive and therefore dedicated study using probabilistic scenario selection for setup- and range uncertainties combined with dose accumulation on control CTs.

In very recent pioneer studies, the use of additional anatomy data has shown to increase the robustness of the plans against anatomical changes, for example Wang *et al.* [20] for lung tumours and van de Water *et al.* [26] for tumours in the sinonasal region. However, Wang *et al.* did not have additional CT datasets available, therefore it remained unclear whether the multiple CT plans were robust against successive anatomical variations. Van de Water *et al.* generated synthetic CTs with variable nasal cavity filling which were included in the plan optimization, showing adequate target coverage in a repeated CT acquired during the treatment course, but they did not consider additional random variations outside the manipulated area. In both cases, the plans with additional anatomy data did not consider setup and range uncertainties during the optimization process.

Our study has several limitations. First, the CT datasets used were acquired for patients receiving photon therapy. In our clinical proton therapy practice, a different mask and dual-energy CT are used [27]. Second, we implicitly assumed that a patient undergoing proton therapy would, when receiving the same prescribed fraction dose and schedule, have similar anatomical changes as in photon therapy. Prospective studies with patients treated with IMPT and the assessment of anatomical variations with this treatment modality are necessary.

Moreover, the span of anatomical changes covered in the investigated patient cohort of 20 patients might be limited and it should be considered that more severe anatomical changes might occur in other patients. The third limitation is related to the image registration procedure, which can lead to uncertainties in the calculation of cumulative doses. The rigid and deformable registrations between the planning and cCT might be not satisfactory, if for instance significant rotations in shoulders and neck are present, potentially leading to a dose recalculation that might be not accurate [28]. For the rigid registrations in this work, we focused on the upper neck region and manually corrected it whenever necessary. Therefore, it is important to have an exact patient positioning method between fractions, checking patient rotations and shoulder position to ensure an accurate image registration [8]. Limitations of deformable image registration, e.g. for dose accumulation purposes, are well known and a general limitation of planning studies performing dose accumulation [5,28,29]. Fourth, only CTV coverage was chosen as a trigger for adaption as OAR doses were not affected in this patient cohort, consistent with other literature. Despite that, in general, also OAR constraint violations can be used as additional trigger, without loss of generality of our results.

In conclusion, neither PTV-based planning nor classical robust optimization are sufficient to account for anatomical changes. Including additional CTs containing random anatomical variations in robust optimization can improve the robustness of the plan against anatomical changes occurring in the later course of treatment. The anatomical robust optimization approach, already implemented in a clinical treatment planning system, is in principle clinically feasible, using two or three instead of one planning CT. The dose perturbing effect of these changes is at least in the same magnitude as the combination of setup and range uncertainties. In addition, these facts underline the importance of image guidance in proton therapy, which enables an early detection of target coverage loss.

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Declaration of interest

Conflicts of interest: none.

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Table1

Table 1. Dose statistics for the three plan approaches; median (range).

ROI Metric	Plan	Median (range)	
		Nominal dose	Total cumulative dose
Low-risk CTV	PTVb	99.3 (97.47 - 99.93)	94.63 (80.81 - 99.09)
$D_{98\%}$ (%)	cRO	98.18 (96.58 - 99.25)	96.07 (88.39 - 99.14)
	aRO	97.47 (95.16 - 98.79)	97.17 (92.37 - 98.96)
High-risk CTV	PTVb	98.7 (98.24 - 99.51)	95.03 (84.49 - 98.46)
$D_{98\%}$ (%)	cRO	97.91 (96.83 - 98.76)	96.86 (89.16 - 98.91)
	aRO	97.44 (95.36 - 98.54)	97.74 (94.21 - 98.60)
$D_{2\%}$ (%)	PTVb	102.52 (100.74 - 104.76)	103.74 (99.64 - 111.7)
	cRO	103.89 (101.97 - 105.53)	103.46 (101.47 - 106.67)
	aRO	103.94 (100.61 - 105.94)	103.48 (100.57 - 106.01)
Spinal cord	PTVb	26.44 (11.23 - 35.22)	27.79 (11.29 - 35.46)
D_{1cc} (Gy)	cRO	24.86 (11.75 - 31.42)	26.17 (11.42 - 31.93)
	aRO	23.82 (11.99 - 33.22)	24.51 (11.17 - 32.75)
Brainstem	PTVb	11.9 (0.37 - 26.03)	12.9 (0.38 - 26.83)
D_{1cc} (Gy)	cRO	12.75 (0.41 - 22.85)	12.26 (0.41 - 23.95)
	aRO	11.48 (0.72 - 23.42)	11.85 (0.75 - 23.74)
Ipsilateral parotid	PTVb	23.33 (19.84 - 58.24)	24.85 (20.56 - 59.20)
D_{mean} (Gy)	cRO	21.16 (19.19 - 55.21)	23.05 (19.21 - 56.76)
	aRO	21.04 (16.69 - 54.40)	21.74 (17.79 - 55.58)
Contralateral parotid	PTVb	20.18 (18.68 - 22.26)	19.94 (17.27 - 24.58)
D_{mean} (Gy)	cRO	19.99 (17.08 - 21.37)	19.93 (16.33 - 25.54)
	aRO	20.02 (10.76 - 21.33)	19.77 (10.61 - 23.28)
Larynx	PTVb	37.91 (24.88 - 70.14)	39.63 (25.46 - 68.79)
D_{mean} (Gy)	cRO	36.58 (23.71 - 69.92)	40.1 (26.93 - 69.81)
	aRO	35.35 (24.25 - 69.82)	40.13 (27.08 - 69.91)
Oral mucosa	PTVb	39.54 (17.07 - 66.53)	39.64 (19.59 - 66.20)
D_{mean} (Gy)	cRO	38.74 (17.15 - 65.40)	39.62 (19.58 - 65.40)
	aRO	40.01 (17.45 - 65.31)	39.96 (19.34 - 65.43)
Constrictor muscles	PTVb	51.71 (40.33 - 65.48)	51.67 (38.51 - 66.43)
D_{mean} (Gy)	cRO	50.6 (39.38 - 64.39)	50.08 (39.47 - 63.64)
	aRO	50.9 (40.34 - 64.39)	50.8 (40.23 - 63.83)

Esophageal inlet	PTVb	38.43 (15.06 - 69.34)	39.53 (12.37 - 68.03)
D_{mean} (Gy)	cRO	38.2 (16.18 - 69.69)	39.38 (13.61 - 66.34)
	aRO	38.47 (21.78 - 69.33)	39.98 (16.78 - 70.24)

Abbreviations: PTVb, PTV-based plan; cRO, classical robust optimization; aRO, anatomical robust optimization; ROI, region of interest; CTV, clinical target volume; $D_{98\%}$, dose to the 98% of the volume; $D_{2\%}$, dose to the 2% of the volume; $D1_{cc}$, near maximum dose to the 1 cc of the volume; D_{mean}, mean dose.

Figure captions

Figure 1. Workflow for dose tracking calculation.

Figure 2. Difference between $D_{98\%}$ and objective value (95%) for the total cumulative dose calculated for each patient: a negative value means target coverage below the clinical objective. The patients were rearranged for a better visualization.

Figure 3. Box plots for the whole patient cohort comparing the three plans. Planned dose, weekly cumulative doses and total cumulative doses are depicted. The dashed line represents the clinical objective (95% and 107%, respectively).

Figure 4. Planned, weekly and total cumulative dose for five patients. All patients present dose degradation with PTVb and cRO approach, whereas the last four patients showed improvement in the target coverage in the aRO plan. In patient 1, the target coverage was reduced in all three plans, still showing higher dose degradation in the PTVb and cRO plans.

Figure 5. Dose distribution of total cumulative doses for five patients shown on an axial planning CT slice. Yellow arrows represent a reduction in target coverage in comparison with the nominal plan, whereas magenta arrows represent overdosage. Low- and high-risk CTV are delineated in yellow and cyan, respectively.

Figure1

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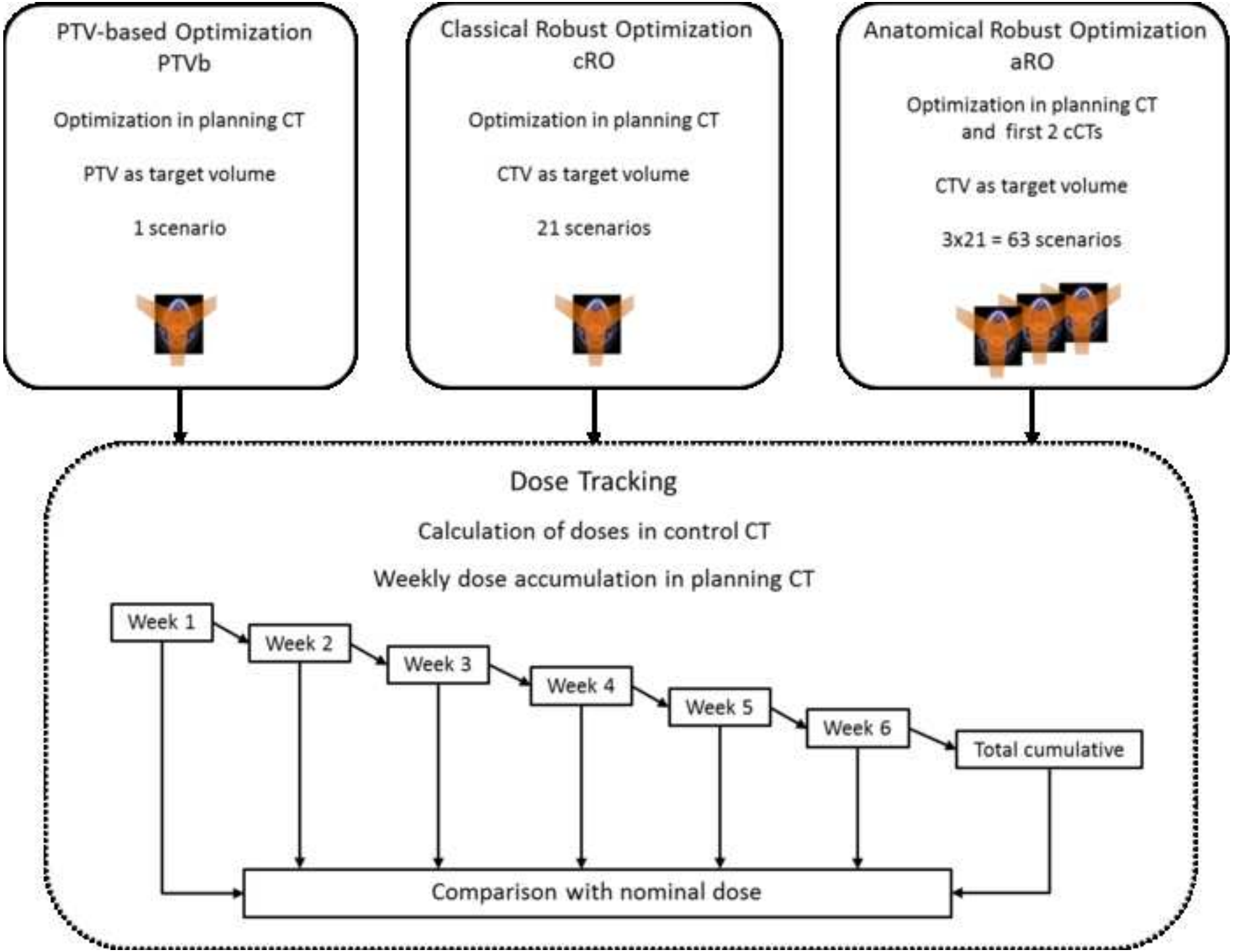


Figure2

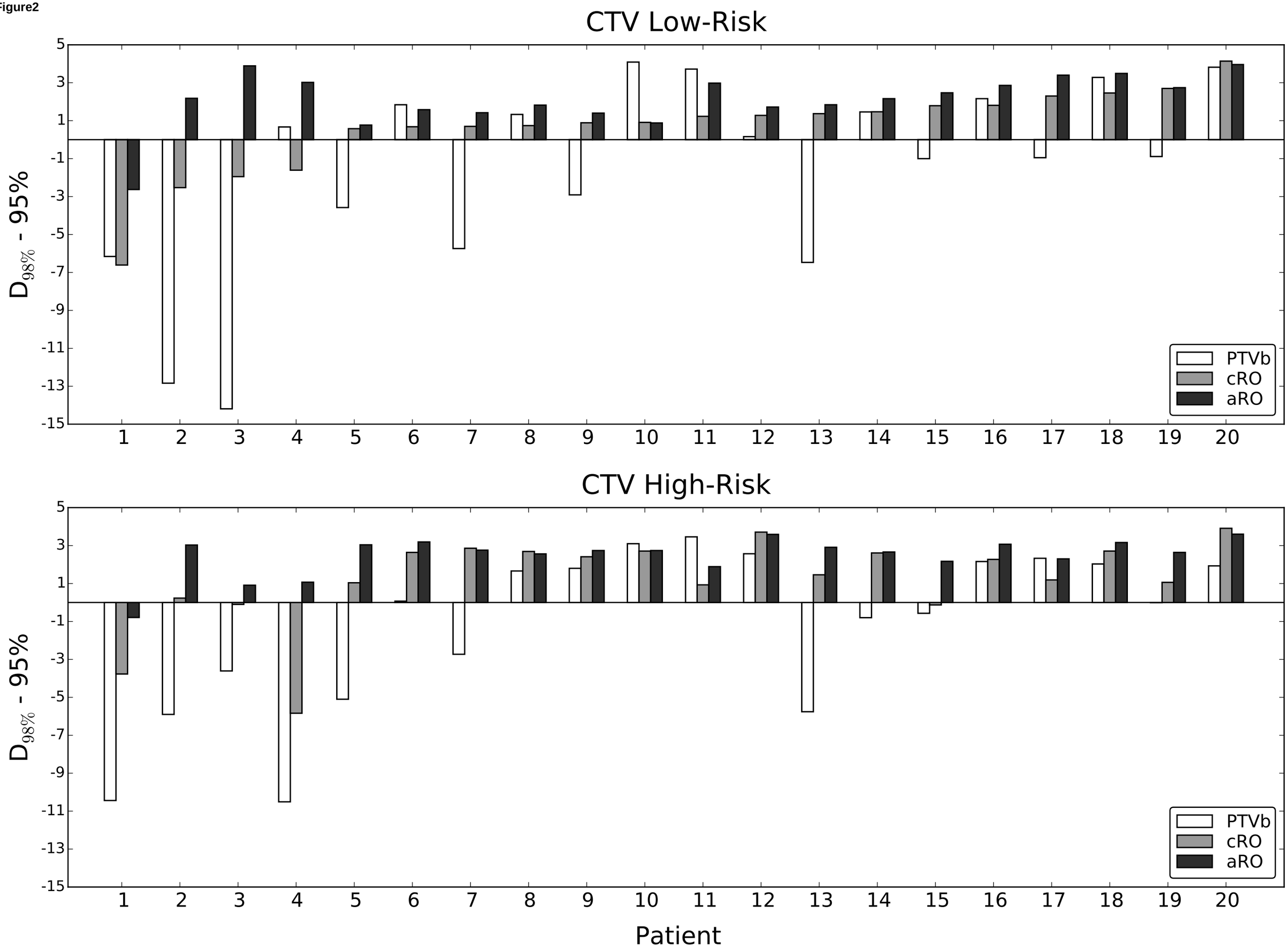

CTV Low-Risk
CTV High-Risk
$D_{98\%}$ - 95%
Patient
PTVb
cRO
aRO
5
3
1
-1
-3
-5
-7
-9
-11
-13
-15
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20

Figure3

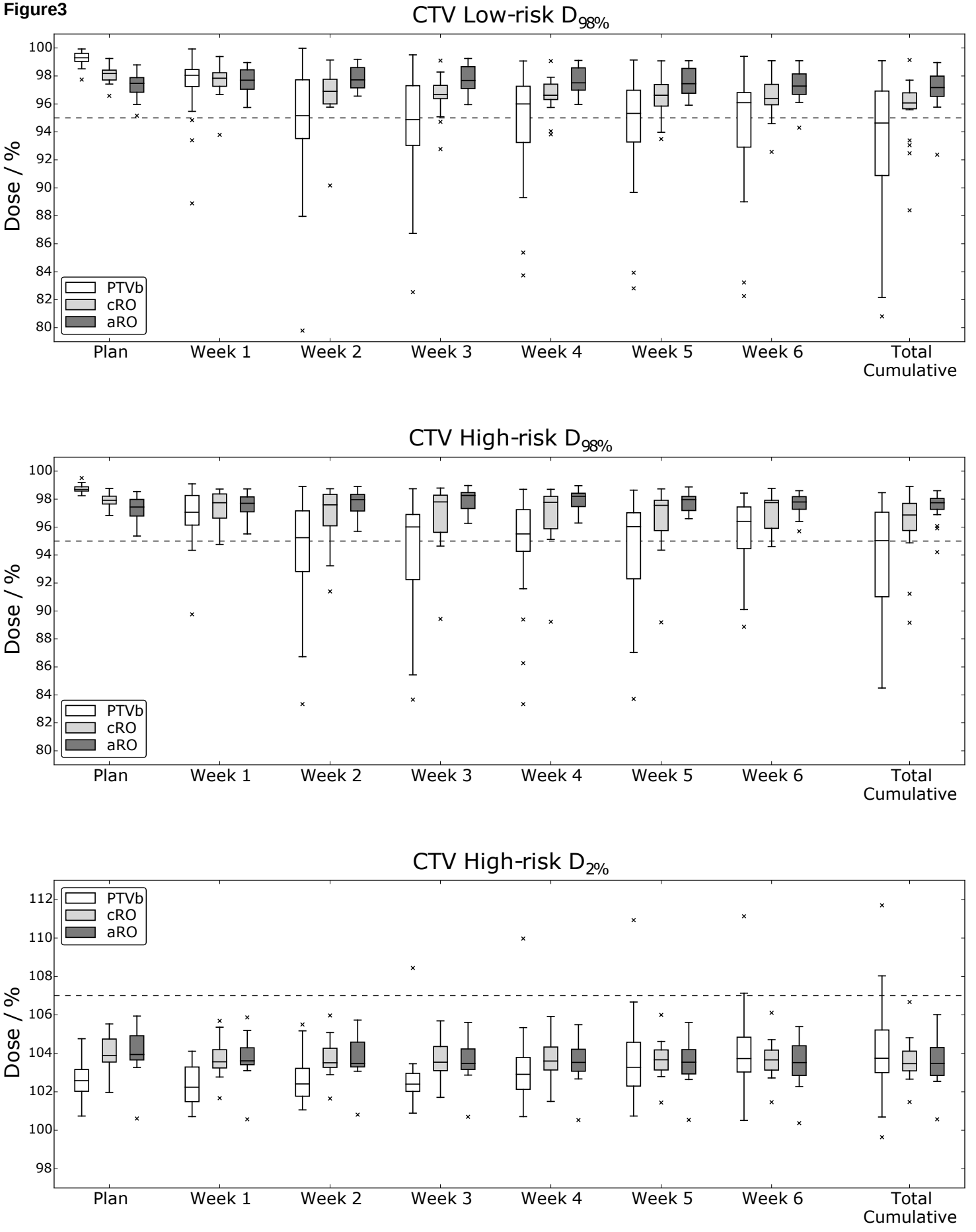
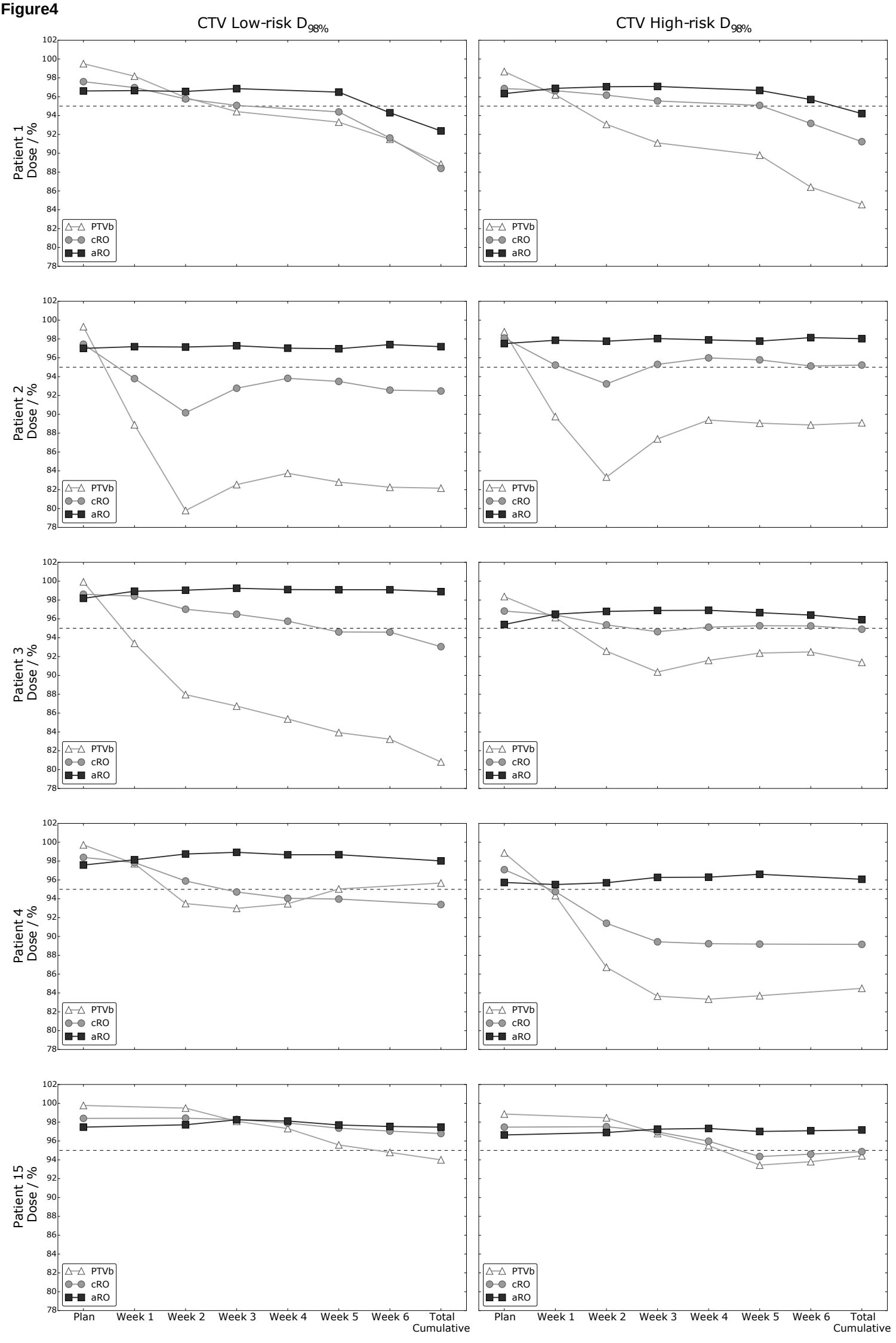
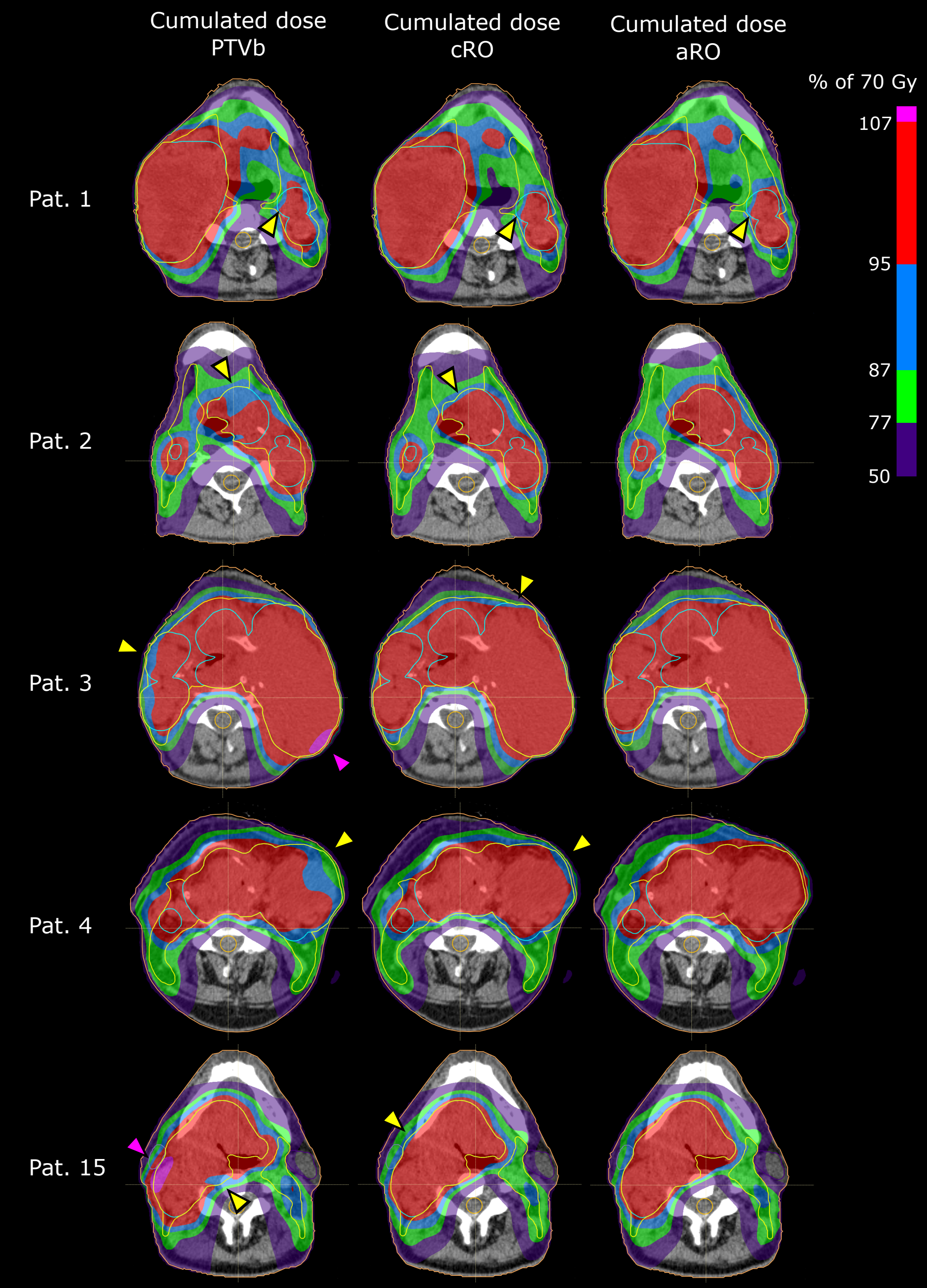

CTV Low-risk D98%
Dose / %
PTVb
cRO
aRO
Plan
Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Total Cumulative
CTV High-risk D98%
Dose / %
PTVb
cRO
aRO
Plan
Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Total Cumulative
CTV High-risk D2%
Dose / %
PTVb
cRO
aRO
Plan
Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Total Cumulative

Figure4


CTV Low-risk D98%
CTV High-risk D98%
Patient 1
Patient 2
Patient 3
Patient 4
Patient 15
Dose / %
PTVb
cRO
aRO
Plan
Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Total Cumulative


Cumulated dose PTVb
Cumulated dose cRO
Cumulated dose aRO
% of 70 Gy
107
95
87
77
50
Pat. 1
Pat. 2
Pat. 3
Pat. 4
Pat. 15

Supplementary File I

Click here to download Supplementary Files: SupplementaryFileI.doc

Supplementary File II

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Conflict of Interest Statement

The authors report no conflict of interest.