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## **Including anatomical variations in robust optimization for head and neck proton therapy can reduce the need of adaptation**

Macarena Cubillos-Mesías<sup>1</sup>, Esther G. C. Troost<sup>1,2,3,4,5</sup>, Fabian Lohaus<sup>1,3,4</sup>, Linda Agolli<sup>3</sup>, Maximilian Rehm<sup>3</sup>, Christian Richter<sup>1,2,3,4,\*</sup>, Kristin Stützer<sup>1,2,\*</sup>

<sup>1</sup> OncoRay – National Center for Radiation Research in Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Helmholtz-Zentrum Dresden - Rossendorf, Dresden, Germany

<sup>2</sup> Helmholtz-Zentrum Dresden - Rossendorf, Institute of Radiooncology – OncoRay, Dresden, Germany

<sup>3</sup> Department of Radiotherapy and Radiation Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany

<sup>4</sup> German Cancer Consortium (DKTK), Partner Site Dresden, and German Cancer Research Center (DKFZ), Heidelberg, Germany

<sup>5</sup> National Center for Tumor Diseases (NCT), Partner Site Dresden, Germany: German Cancer Research Center (DKFZ), Heidelberg, Germany; Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany, and; Helmholtz Association / Helmholtz-Zentrum Dresden - Rossendorf (HZDR), Dresden, Germany

\* Both authors share senior authorship

**Corresponding author:** Macarena Cubillos-Mesías, OncoRay – National Center for Radiation Research in Oncology, Fetscherstraße 74, PF 41, 01307 Dresden, Germany, Tel. +49 351 458 7664, E-mail: [Macarena.Cubillos@OncoRay.de](mailto:Macarena.Cubillos@OncoRay.de)

**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

1 **Including anatomical variations in robust optimization for head and neck proton**  
2 **therapy can reduce the need of adaptation**

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5 <sup>1</sup> OncoRay – National Center for Radiation Research in Oncology, Faculty of Medicine and University Hospital  
6 Carl Gustav Carus, Technische Universität Dresden, Helmholtz-Zentrum Dresden - Rossendorf, Dresden,  
7 Germany

8 <sup>2</sup> Helmholtz-Zentrum Dresden - Rossendorf, Institute of Radiooncology – OncoRay, Dresden, Germany

9 <sup>3</sup> Department of Radiotherapy and Radiation Oncology, Faculty of Medicine and University Hospital Carl  
10 Gustav Carus, Technische Universität Dresden, Dresden, Germany

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12 Heidelberg, Germany

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14 (DKFZ), Heidelberg, Germany; Faculty of Medicine and University Hospital Carl Gustav Carus, Technische  
15 Universität Dresden, Dresden, Germany, and; Helmholtz Association / Helmholtz-Zentrum Dresden -  
16 Rossendorf (HZDR), Dresden, Germany

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18

19 **Corresponding author:** Macarena Cubillos-Mesías, OncoRay – National Center for  
20 Radiation Research in Oncology, Fetscherstraße 74, PF 41, 01307 Dresden, Germany, Tel.  
21 +49 351 458 7664, E-mail: Macarena.Cubillos@OncoRay.de

22

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26 anatomical variations; dose accumulation; plan adaptation

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31

32 **Abstract**

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

38

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

45

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

51

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

55

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57

## 58 **Introduction**

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

66  
67 To overcome this problem, different optimization methods have been investigated to generate  
68 robust plans, which consider uncertainties in patient setup and particle range during the  
69 optimization process, resulting in a plan which is robust against them [9–12]. Previous studies  
70 with robust optimization in HNSCC have focused on the plan robustness improvement in  
71 comparison with a non-robust plan, when the nominal plan is recalculated considering  
72 different ‘perturbed’ scenarios with modified setup (i.e. translational shifts) and range values  
73 [13–17]. However, anatomical changes that may occur during the treatment course, e.g.  
74 modified positioning and tumour shrinkage, potentially causing a degradation of the plan  
75 quality, are not considered in the optimization. The influence of anatomical variations in the  
76 plan robustness has already been investigated for IMPT plans of lung cancer patients [18–20].

77  
78 Usually the optimization of a radiotherapy plan is based on one computed tomography (CT)  
79 image dataset. Including information of anatomical variability, e.g. additional CT with small  
80 random variations as shoulder positioning, neck or mandible rotations in the plan optimization  
81 process, may increase the robustness of the treatment plan against anatomical variations, and  
82 therefore may decrease the need of plan adaptation. The aim of this work was to compare two  
83 different plan strategies using robust optimization for HNSCC: classical robust optimization

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

88

## 89 **Materials and Methods**

### 90 *Patient data*

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

96

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

106

### 107 *Treatment planning*

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

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

119

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

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



135 A relative biological effectiveness (RBE) of 1.1 for proton beams was used. Three beams  
136 were used with the same configuration for both plans, with beam angles of 180°, 60° and  
137 300°, respectively. An IBA universal nozzle beam, with a pencil beam spot size sigma  
138 ranging from 4 mm (220 MeV) to 8 mm (100 MeV) was used. A calculation dose grid of  
139 3×3×3 mm<sup>3</sup>, a range shifter of 7.5 cm water equivalent thickness and a minimum air gap of 3  
140 cm were considered.

141

#### 142 *Influence of anatomical changes in treatment course*

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

152

#### 153 *Statistical analysis*

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

157

## 158 **Results**

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

161 the OARs remained below the constraints (Table 1). However, in the PTVb plan the total  
162 cumulative doses were reduced to as little as 80.81% and 84.49% for the low- and high-risk  
163 CT, respectively, and in the cRO plan to 88.39% and 89.16%, compared to 92.37% and  
164 94.21% in the aRO plan, respectively. The underdosage of the low-risk CTV  $D_{98\%}$  in the total  
165 cumulative doses was significant for the PTVb and cRO plans in comparison to the aRO plan  
166 ( $p = 0.002$  and  $p < 0.001$ , respectively), with values up to -14.19% for PTVb, -6.61% for cRO  
167 and -2.63% for the aRO approach respectively, as shown in Figure 2. The underdosage of the  
168 total cumulative doses in the high-risk CTV  $D_{98\%}$  was also significant different for both PTVb  
169 and cRO plans, compared with the aRO plan ( $p < 0.001$  and  $p = 0.001$ , respectively). The  $D_{2\%}$   
170 to the high-risk CTV showed a maximum value up to 111.7% for the PTVb plan, but always  
171 remained below 107% for both robust plans. An increased mean dose of up to 4.7 Gy was  
172 observed for the cumulative larynx dose in both robust approaches, whereas the remaining  
173 OARs presented no major deviations between nominal and total cumulative doses.

174

175 Target coverage degradation for the PTVb approach, with mean differences between planned  
176 and total cumulative dose of 5.84% for the low-risk CTV and 4.97% for the high-risk CTV,  
177 illustrate that a margin expansion of the CTV alone cannot sufficiently account for anatomical  
178 changes during the treatment course. Although in 10 out of 20 patients the CTV coverage was  
179 acceptable, in the other 10 patients a plan adaptation was needed. Furthermore, also the cRO  
180 plan was not sufficient to account for anatomical changes during the treatment course. Figure  
181 3 shows the weekly and total cumulative doses for all patients: degradation in the target  
182 coverage was observed for the PTVb and cRO plan. Analysing the individual patient doses, 5  
183 out of 20 patients (25%) showed target coverage degradation in the cRO plan. Therefore,  
184 these patients would undergo plan adaptation according to the intervention criterion ( $D_{98\%} <$   
185 95% of the prescribed dose).

186

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

196

## 197 **Discussion**

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

204

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

210

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

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

227

228 Integral dose to the normal tissue were slightly higher for the PTVb and aRO plans in  
229 comparison with the cRO plan, with mean values averaged over the entire patient cohort of  
230 110.89 Gy·L, 110.64 Gy·L and 103.45 Gy·L, respectively. Moreover, the dose to the OARs  
231 remained similar between the planning approaches. Thus, we can affirm that the price for a  
232 higher robustness against anatomical changes by using aRO is negligible compared to the  
233 PTVb plan, which yields similar integral dose, but substantially less robustness compared to  
234 cRO with only a slightly lower integral dose (-7%) than the aRO plan.

235

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

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

247

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

258

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

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

281

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

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294

295 **Declaration of interest**

296 Conflicts of interest: none.

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397

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

ROI Metric	Plan	Median (range)	
		Nominal dose	Total cumulative dose
Low-risk CTV D <sub>98%</sub> (%)	PTVb	99.3 (97.47 - 99.93)	94.63 (80.81 - 99.09)
	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 D <sub>98%</sub> (%)	PTVb	98.7 (98.24 - 99.51)	95.03 (84.49 - 98.46)
	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 <sub>2%</sub> (%)	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 D <sub>1cc</sub> (Gy)	PTVb	26.44 (11.23 - 35.22)	27.79 (11.29 - 35.46)
	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 D <sub>1cc</sub> (Gy)	PTVb	11.9 (0.37 - 26.03)	12.9 (0.38 - 26.83)
	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 D <sub>mean</sub> (Gy)	PTVb	23.33 (19.84 - 58.24)	24.85 (20.56 - 59.20)
	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 D <sub>mean</sub> (Gy)	PTVb	20.18 (18.68 - 22.26)	19.94 (17.27 - 24.58)
	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 D <sub>mean</sub> (Gy)	PTVb	37.91 (24.88 - 70.14)	39.63 (25.46 - 68.79)
	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 D <sub>mean</sub> (Gy)	PTVb	39.54 (17.07 - 66.53)	39.64 (19.59 - 66.20)
	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 D <sub>mean</sub> (Gy)	PTVb	51.71 (40.33 - 65.48)	51.67 (38.51 - 66.43)
	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 <sub>mean</sub> (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)

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Abbreviations: PTVb, PTV-based plan; cRO, classical robust optimization; aRO, anatomical robust optimization; ROI, region of interest; CTV, clinical target volume; D<sub>98%</sub>, dose to the 98% of the volume; D<sub>2%</sub>, dose to the 2% of the volume; D1<sub>cc</sub>, near maximum dose to the 1 cc of the volume; D<sub>mean</sub>, mean dose.

## Figure captions

Figure 1. Workflow for dose tracking calculation.

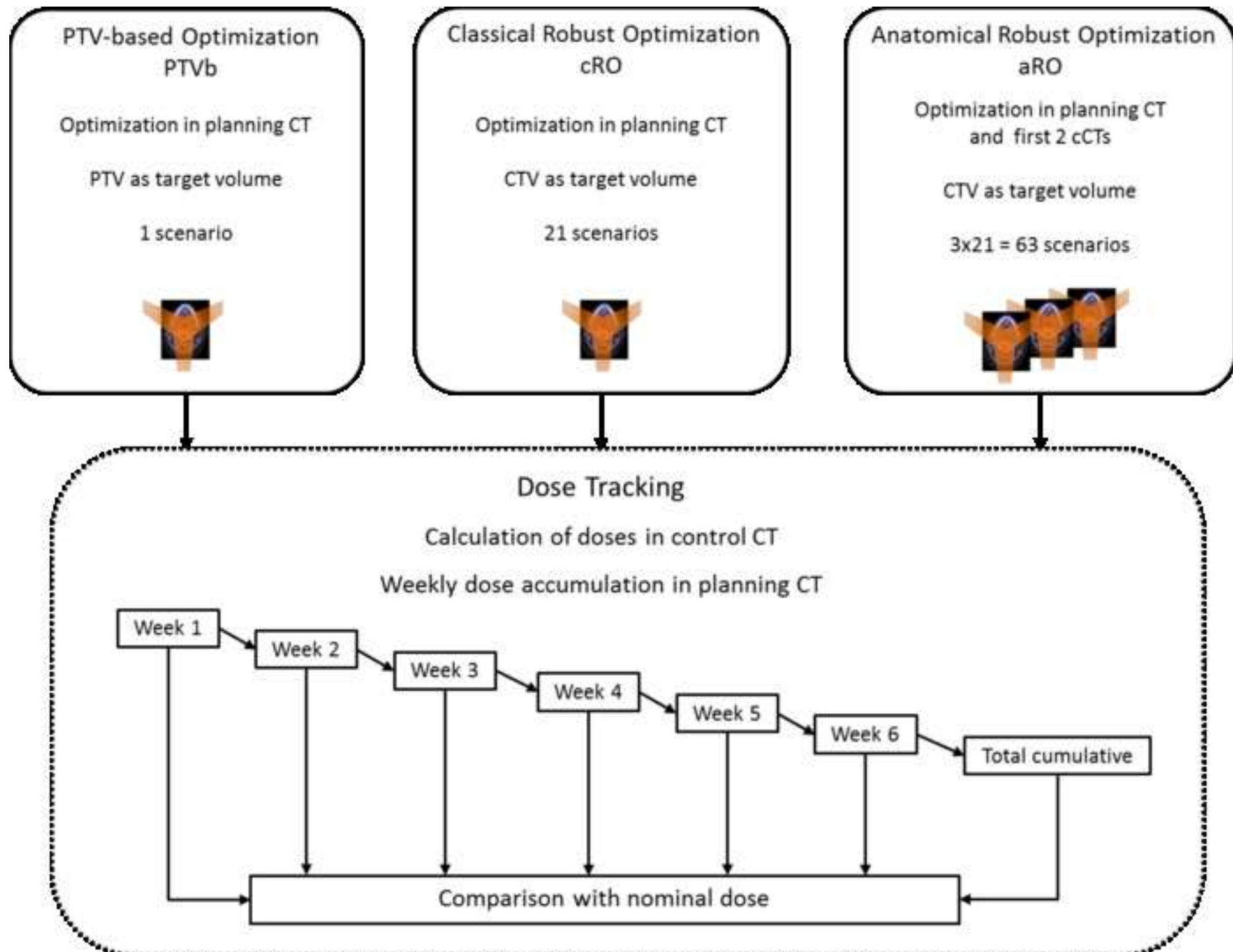
Figure 2. Difference between  $D_{98\%}$  and objective value (95%) for the total cumulative dose calculated for each patient: a negative value means target coverage below the clinical objective. The patients were rearranged for a better visualization.

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).

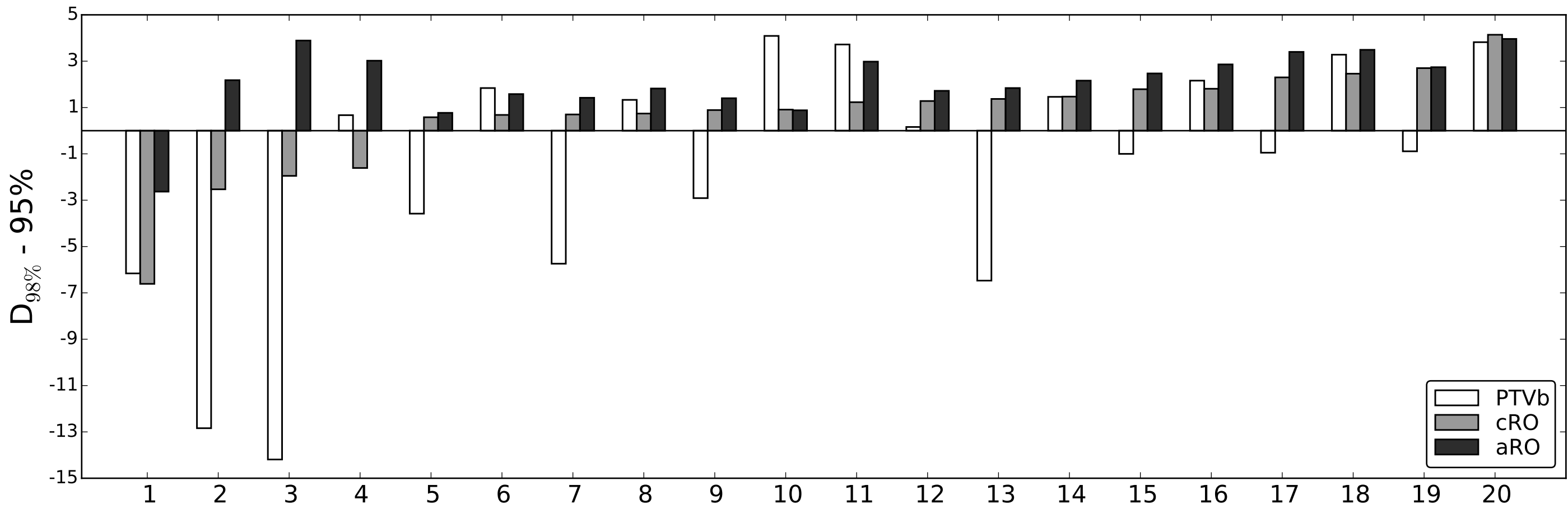
Figure 4. Planned, weekly and total cumulative dose for five patients. All patients present dose degradation with PTVb and cRO approach, whereas the last four patients showed improvement in the target coverage in the aRO plan. In patient 1, the target coverage was reduced in all three plans, still showing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



## CTV High-Risk

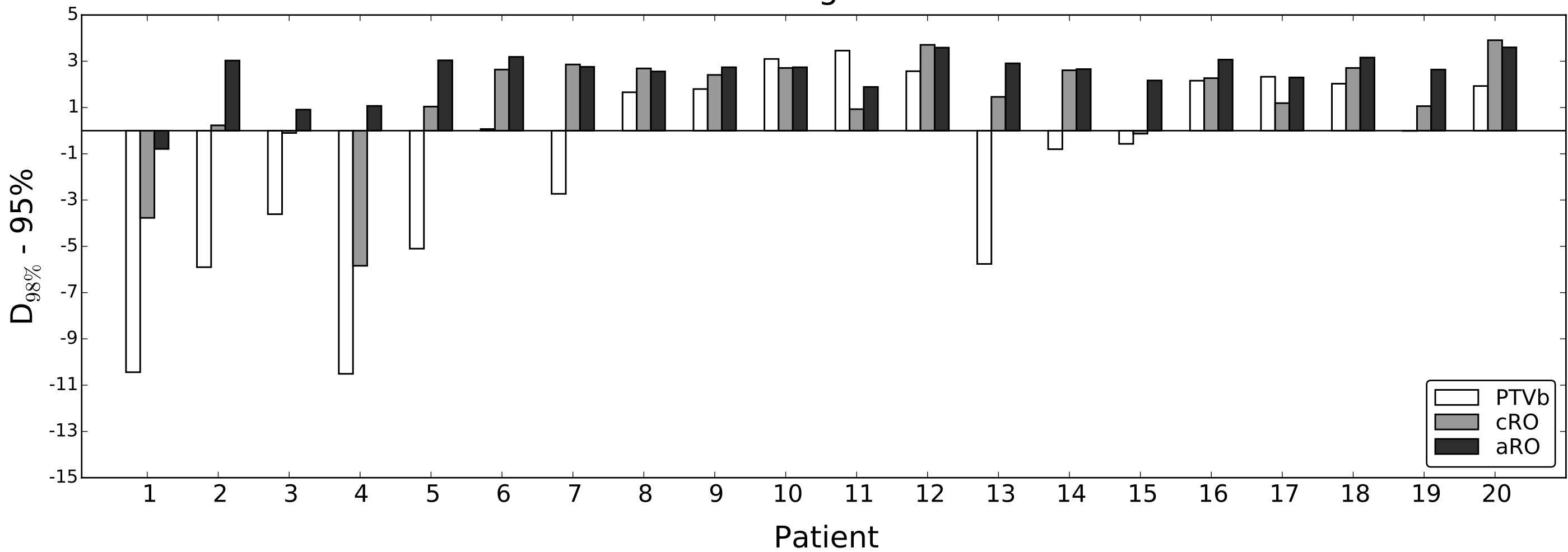
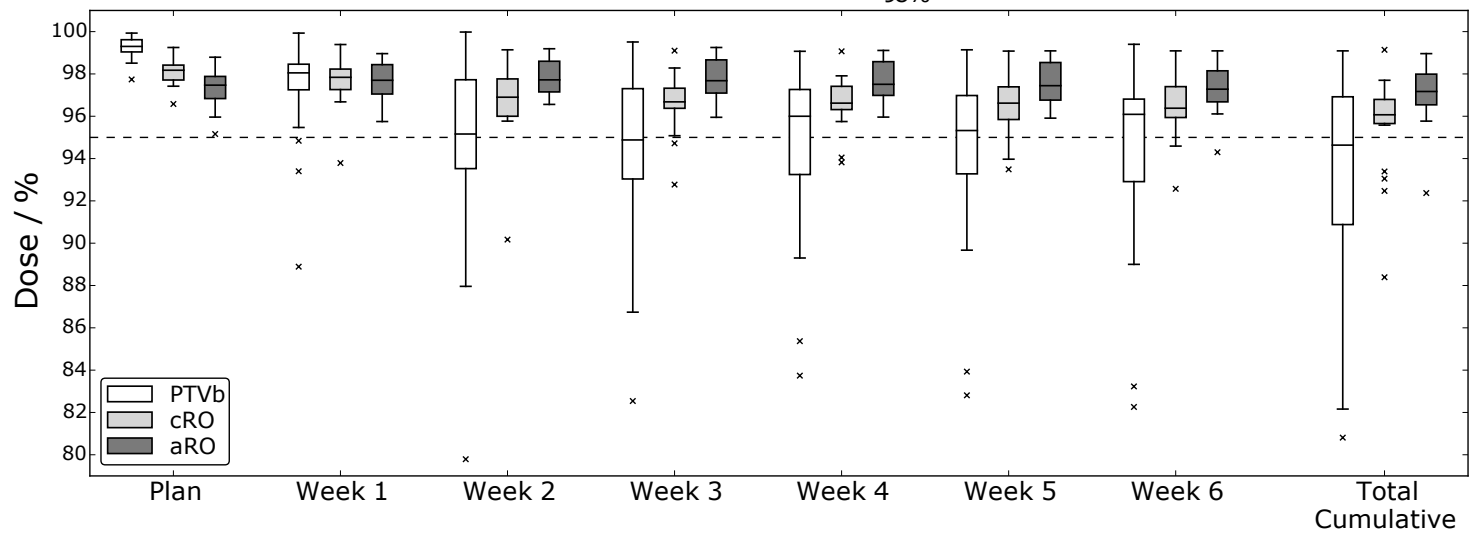
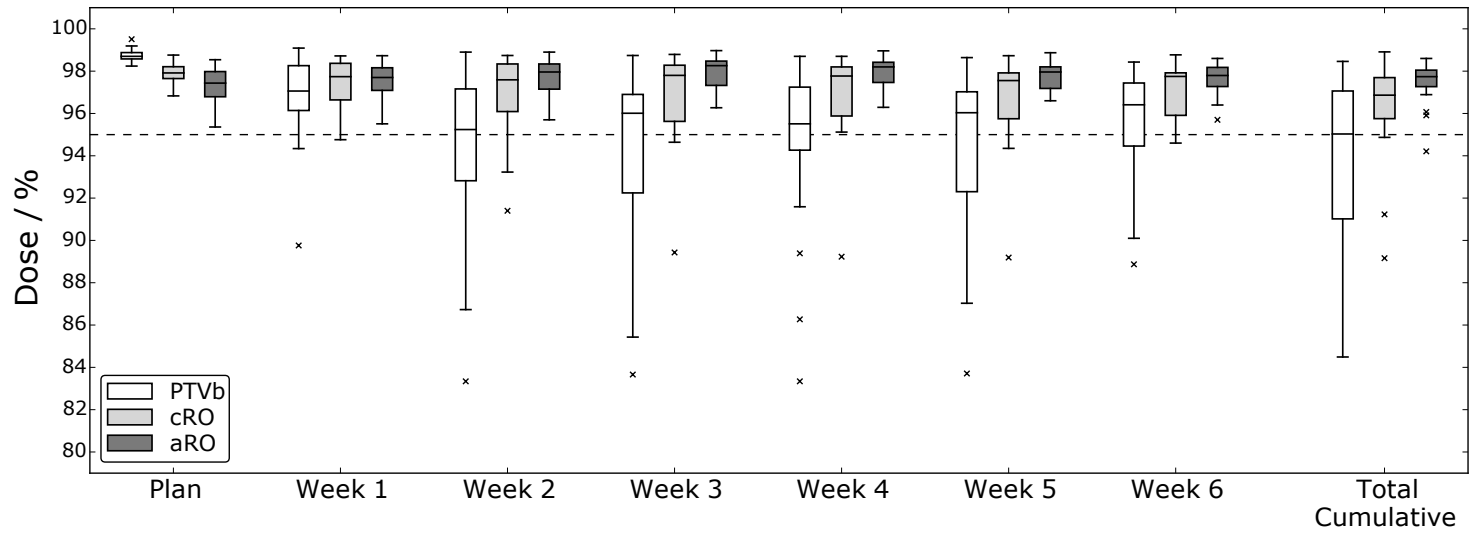
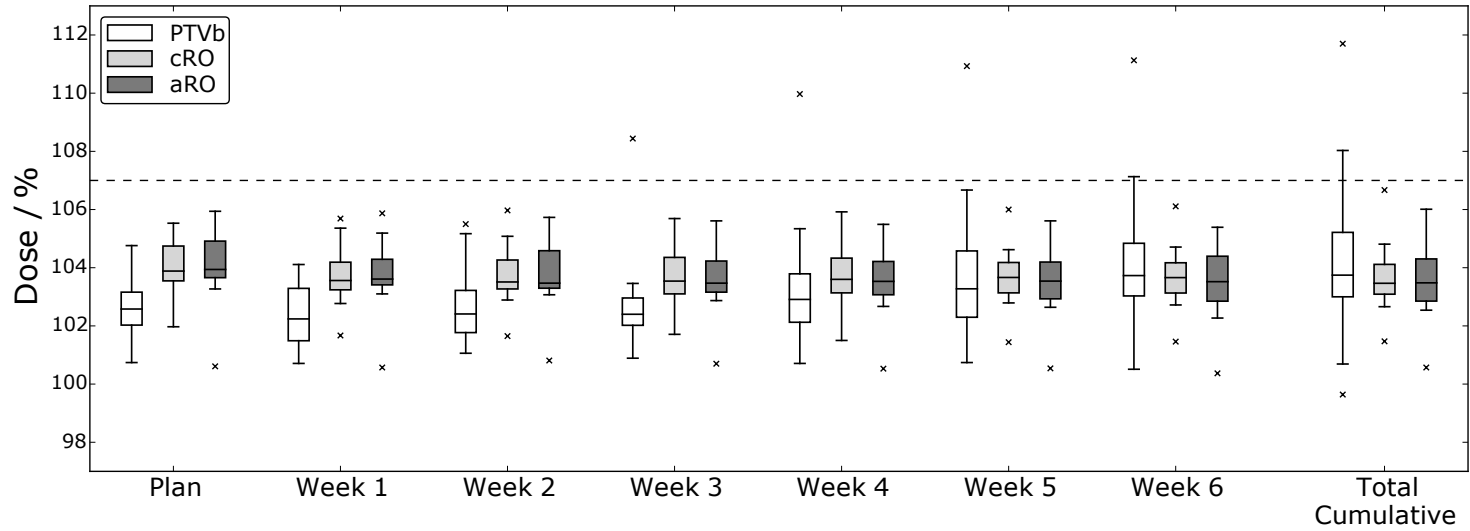




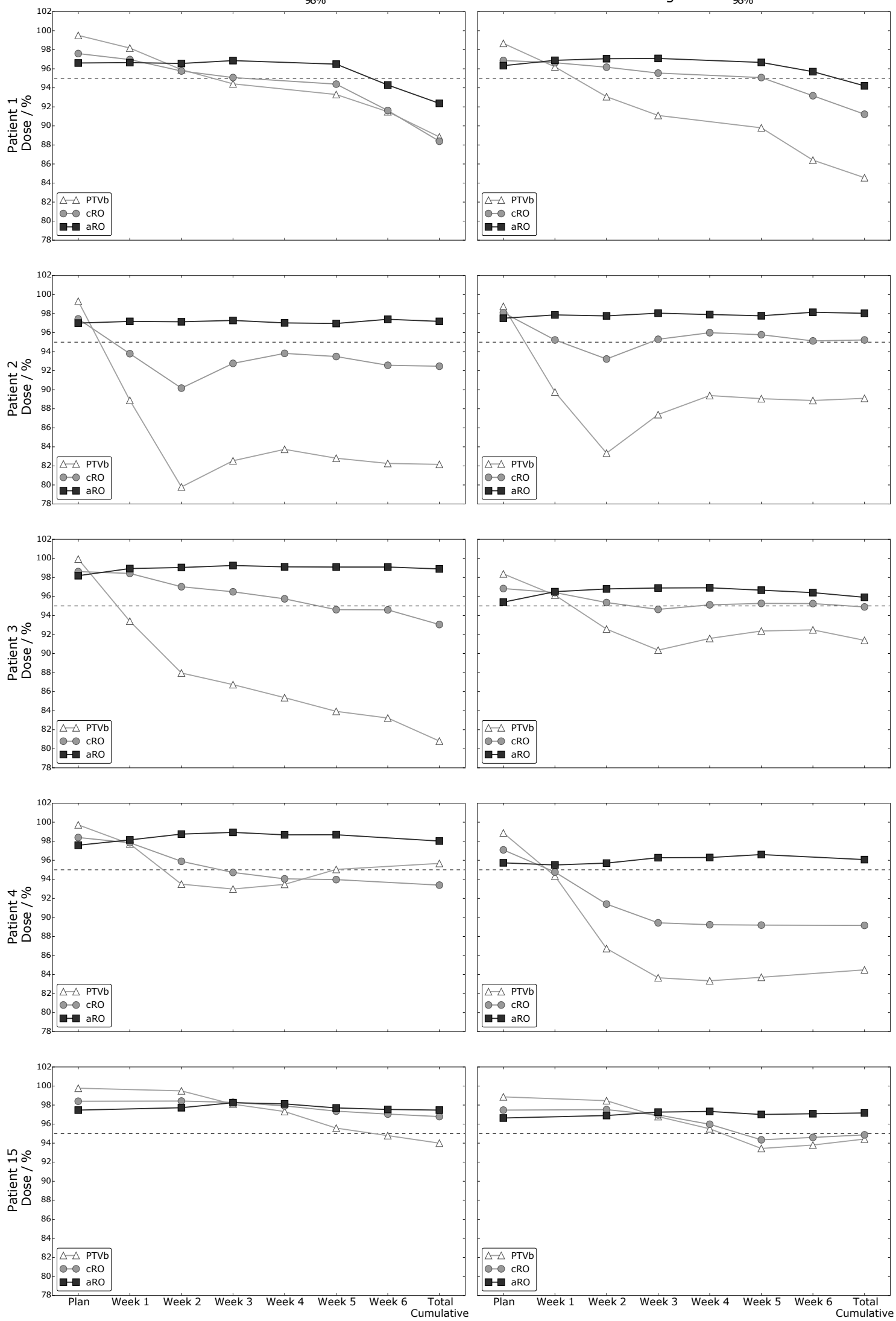
Figure 3

CTV Low-risk  $D_{98\%}$ CTV High-risk  $D_{98\%}$ CTV High-risk  $D_{2\%}$ 

**Figure 4**

CTV Low-risk  $D_{98\%}$

CTV High-risk  $D_{98\%}$



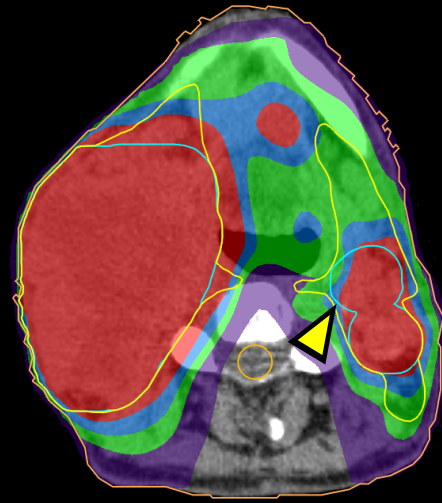
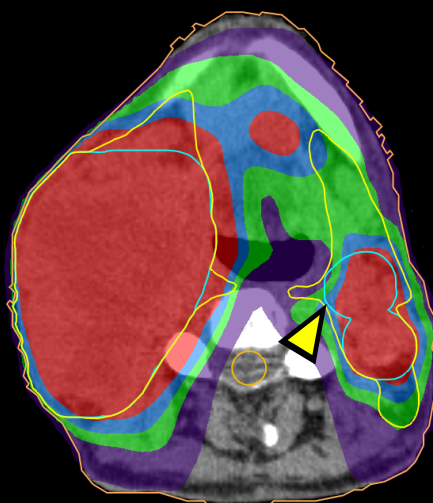
Cumulated dose  
PTVb

Cumulated dose  
cRO

Cumulated dose  
aRO

% of 70 Gy

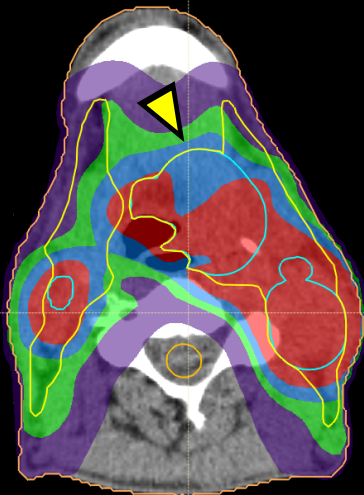
Pat. 1



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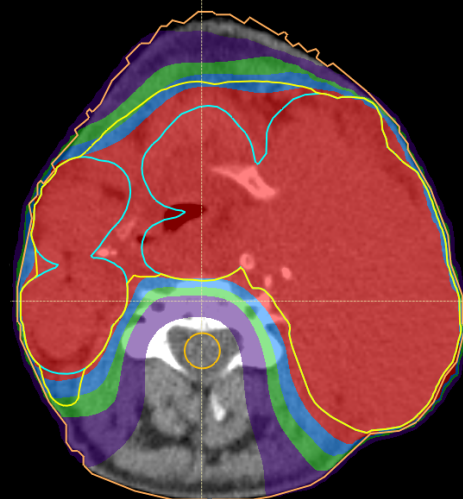
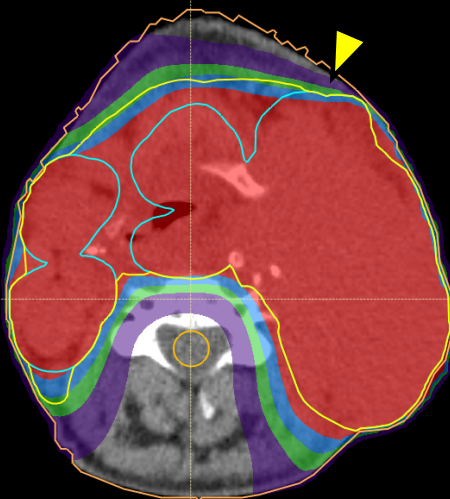
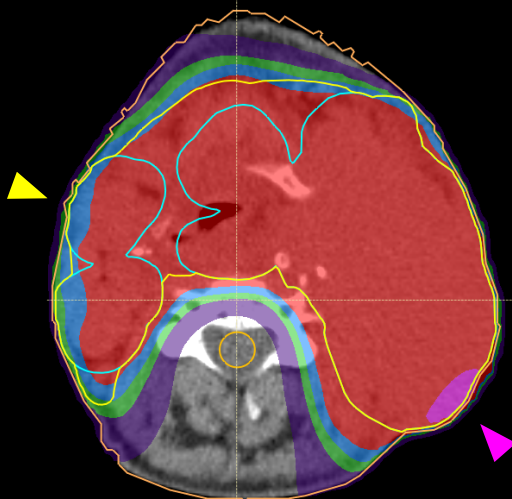
Pat. 2



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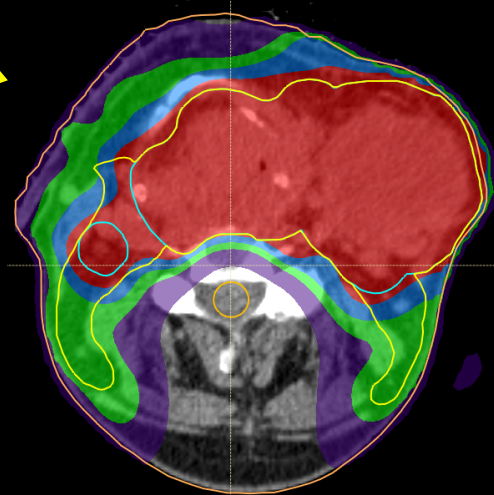
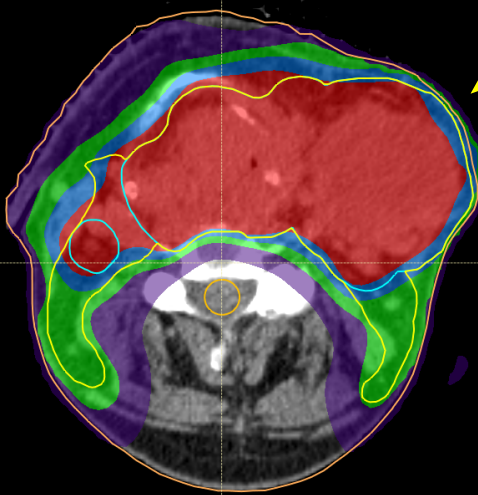
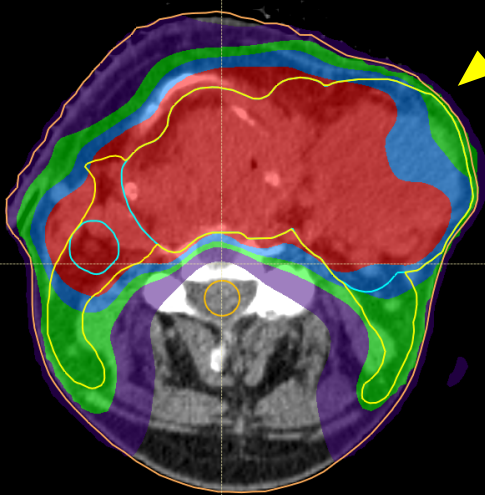
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Pat. 3

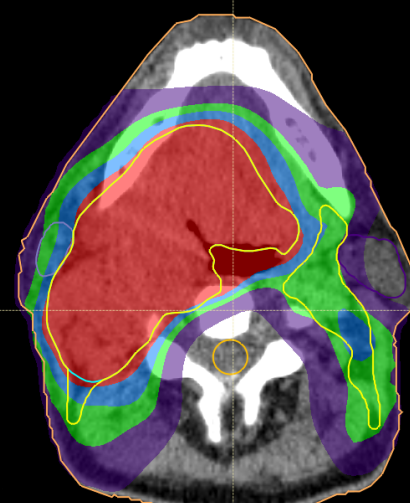
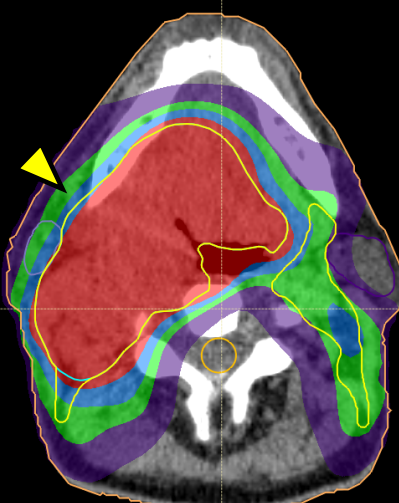
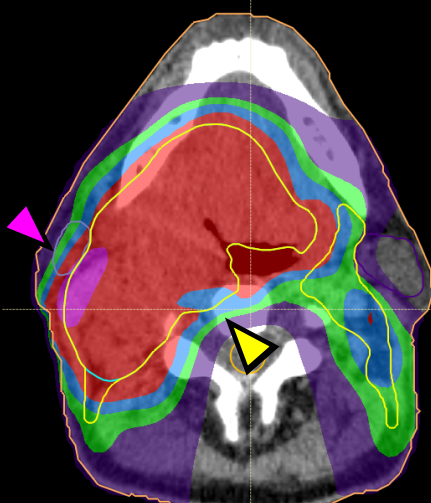


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Pat. 4



Pat. 15



**Supplementary File 1**

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**Supplementary File II**

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### **Conflict of Interest Statement**

The authors report no conflict of interest.