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Optimization of adaptive radiation therapy in cervical cancer: Solutions for photon and proton therapy

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Chapter 2

Dosimetric advantages of a clinical daily adaptive plan selection strategy compared with a non-adaptive strategy in cervical cancer radiation therapy

A version of this chapter has been submitted to Acta Oncologica as:

Dosimetric advantages of a clinical daily adaptive plan selection strategy compared with a non-adaptive strategy in cervical cancer radiation therapy

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Abstract

Purpose

Radiation therapy (RT) using a daily plan selection adaptive strategy can be applied to account for interfraction organ motion while limiting organ at risk dose. The aim of this study was to quantify the dosimetric consequences of daily plan selection compared to the non-adaptive approach in cervical cancer RT.

Material & Methods

Ten consecutive patients who received pelvic irradiation, planning CTs (full and empty bladder), weekly post-fraction CTs and pre-fraction CBCTs were included. Non-adaptive plans were generated based on the PTV defined using the full bladder planning CT. For the adaptive strategy, multiple PTVs were created based on both planning CTs by ITV of the primary CTVs (i.e. GTV, cervix, corpus-uterus and upper part of the vagina) and corresponding library plans were generated. Daily CBCTs were rigidly aligned to the full bladder planning CT and plans were selected. Post-fraction CTs were non-rigidly registered to CBCTs and used to recalculate the non-adaptive and selected library plans. Differences in target coverage ($D_{98\%} > 95\%$) and in daily $V_{0.5Gy}$, $V_{1.5Gy}$, V_{2Gy} , $D_{50\%}$ and $D_{2\%}$ for rectum, bladder and bowel were assessed.

Results

The non-adaptive strategy showed inadequate primary CTV coverage in 17% of the fractions. Daily plan selection compensated for anatomical changes and improved primary CTV coverage significantly ($p < 0.01$) to 98%. Compared to the non-adaptive approach, daily plan selection decreased the dose to rectum and bowel indicated by significant ($p < 0.01$) improvements for daily $V_{0.5Gy}$, $V_{1.5Gy}$, V_{2Gy} , $D_{50\%}$ and $D_{2\%}$. However, daily plan selection significantly increased the bladder $V_{1.5Gy}$, V_{2Gy} , $D_{50\%}$ and $D_{2\%}$.

Conclusion

Cervical cancer RT using the non-adaptive strategy showed inadequate target coverage. Daily plan selection corrected for day-to-day anatomical variations and resulted in adequate target coverage in all fractions. The dose to bowel and rectum was decreased significantly when applying adaptive RT.

2.1 | Introduction

The primary treatment for locally advanced cervical cancer consists of external beam radiation therapy (EBRT) with concomitant chemotherapy and subsequently a brachytherapy boost [72]. For patients with a contra-indication for chemotherapy, radiation therapy with concurrent hyperthermia is the recommended treatment strategy [18]. Advanced EBRT techniques such as intensity-modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT) allow highly conformal dose distributions. These advanced techniques are most effective when combined with adequate image guidance. However, large interfraction anatomical changes limit the efficacy of these treatment techniques [73]. Despite drinking instructions, day-to-day bladder volume variations contribute to an increased risk of target under-dosing and consequently increase the dose to surrounding healthy tissue [73].

Adaptive radiation therapy (ART) has the potential to anticipate on anatomical changes during fractionated EBRT by adapting the radiation delivery during the treatment course based on pre-fraction imaging. Several adaptive strategies, both offline and online approaches, have been investigated [53,56]. The most widely reported approach for pelvic EBRT is the plan-library based plan-of-the-day strategy [58-60]. Prior to treatment, a patient-specific plan library is defined by generating multiple treatment plans corresponding to different target volumes. Each treatment day the library plan best fitting the anatomy as observed on pre-fraction cone-beam CT (CBCT) is selected in order to anticipate on interfraction anatomical changes.

Despite the use of large population-based margins added to the clinical target volume (CTV) to form the planning target volume (PTV), the interfraction anatomical changes in cervical cancer EBRT might still induce target under-dosing. Furthermore, these large safety margins increase the dose to surrounding healthy tissues, which results in the enhancement of radiation-induced toxicities. Recently, several adaptive strategies in cervical cancer were investigated to anticipate on anatomical changes during the course of radiation therapy [54,65]. Next to the description of a clinically implemented adaptive strategy [59], most studies reported on tools to support adaptive strategies [65,74-76]. However, the actual dosimetric improvements of an adaptive strategy compared with the non-adaptive approach in terms of target coverage and organ at risk (OAR) sparing are still unknown.

To investigate the dosimetric consequences of an adaptive strategy and determine the area of improvement, differences in dose delivery between an adaptive and non-adaptive strategy need to be assessed. Therefore, the purpose of this study was to quantify the potential dosimetric advantages of a daily adaptive plan selection treatment strategy compared with a non-adaptive treatment approach in cervical cancer radiation therapy.

2.2 | Material & Methods

Patients and imaging

Ten consecutive cervical cancer patients who received pelvic irradiation and additional CT imaging were included. All patients, treated between January 2014 and August 2015, gave written informed consent after local medical ethical approval for additional CT imaging initially acquired for a study to investigate adaptive proton therapy [77]. Besides two planning CTs (i.e. full and empty bladder), all patients received pre-fraction CBCT imaging (Synergy platform, Elekta AB, Stockholm, Sweden) and weekly CT imaging in treatment position directly after irradiation. Due to the limited field of view of CBCT imaging, volumes of interest in patients who received para-aortic lymph nodes irradiation were not completely visualized on pre-fraction CBCTs and therefore unsuitable for analysis. For tumor localization on CBCT, fiducial markers (2–4 per patient, Visicoil, 0.35 mm diameter, IBA Dosimetry GmbH, Schwarzenbruck, Germany) were implanted in the cervix during the pre-treatment examination under anesthesia.

Six patients were treated in the recommended prone position using a belly board device and for four patients the supine position was applied since the prone position was not possible. Aiming at irradiations with a full bladder, patients were instructed to empty their bladder, to drink 0.5 liter of water, and to refrain from voiding 1.5 h prior to each treatment fraction. As a result of the clinical introduction of ART at our department in April 2015, two out of the ten included patients were actually treated according to the adaptive strategy (Table 2.1). Instead of the adaptive strategy, for these patients the non-adaptive approach was simulated.

Target and OAR definition

According to clinical guidelines [29], the gross tumor volume (GTV), corpus-uterus, cervix, upper part of the vagina and lymph nodes were delineated on all CTs by an experienced radiation oncologist. Also, rectum, bowel cavity, as a surrogate for small bowel and bladder were delineated according to RTOG guidelines. The bladder wall was created using a 3 mm inwards expansion of the delineated bladder [52].

The library of target structures for the adaptive strategy was created based on the planning CTs acquired with an empty and a full bladder. After bony registration of both planning CTs, corresponding primary CTVs (pCTVs) which encompassed the GTV, cervix, corpus-uterus and upper part of the vagina were registered using a structure-based deformable image registration algorithm [78]. The patient-specific full-range primary internal target volume (ITV) was divided in pITV subranges by scaling the deformation vectors (Figure 2.1). According to our clinically applied adaptive strategy, the full-range pITV was divided into one (pITV₀₋₁₀₀), two (pITV₀₋₅₀, pITV₅₀₋₁₀₀) or three (pITV₀₋₃₃, pITV₃₃₋₆₇, pITV₆₇₋₁₀₀) subranges when the top of corpus-uterus displacement was below 10 mm, between 10–20 mm or above 20 mm, respectively. Corresponding to each pITV

subrange an ITV was constructed by including the lymph nodes and PTVs were generated by enlarging ITVs with an 8 mm isotropic margin. The part of the pITV including the cervix and vagina was enlarged with a margin of 8 mm, 8 mm and 13 mm in left-right, superior-inferior and anterior-posterior direction, respectively.

In the non-adaptive approach, target definition was based on only the full bladder planning CT using associated delineations. The pCTV, encompassing the GTV, cervix, corpus-uterus and upper part of the vagina was expanded with an isotropic margin of 10 mm. The expanded pCTV was combined with the lymph nodes and enlarged with an 8 mm isotropic margin to form the PTV.

Table 2.1 | Patient characteristics.

Patient	FIGO stage	Clinical treatment strategy	Treatment position	No. of ITVs
1 *	IB2	non-ART	prone	1
2 **	IIB	non-ART	prone	3
3 *	IB2	non-ART	prone	3
4 **	IIA	non-ART	prone	3
5 **	IIB	non-ART	supine	3
6 *	IIA	non-ART	prone	2
7 **	IIB	non-ART	prone	3
8 **	IIB	non-ART	supine	3
9 *	IB1	ART	supine	2
10 *	IB1	ART	supine	3

Abbreviations: FIGO = International Federation of Gynecology and Obstetrics; CT = computed tomography; ITV = internal target volume; non-ART = non-adaptive radiation therapy; ART = adaptive radiation therapy.

* Both planning CTs acquired with LightSpeed RT16, General Electric Company, Waukesha WI, USA.

** Full bladder planning CT acquired with Gemini TF, Philips Medical Systems, Eindhoven, the Netherlands and empty bladder planning CT acquired with LightSpeed RT16, General Electric Company, Waukesha WI, USA.

Treatment planning

In the adaptive strategy, plans based on the defined PTVs were created to form the plan library and for the non-adaptive approach a single treatment plan was generated based on the corresponding PTV. Dual-arc VMAT (356° per arc, fixed 20° collimator angle) treatment plans with 10 MV beam energy and a prescribed PTV dose of 46 Gy (23 x 2 Gy) were created (Oncentra, Elekta AB, Stockholm, Sweden). All plans were optimized on a uniform 3 mm dose grid with the beam isocenter set to the PTV center of mass using the full bladder planning CT. Plan optimizations were performed using the clinically used set of planning objectives in order to minimize OAR dose while maintaining ICRU-based PTV coverage ($D_{98\%} > 95\%$, $D_{2\%} < 107\%$).

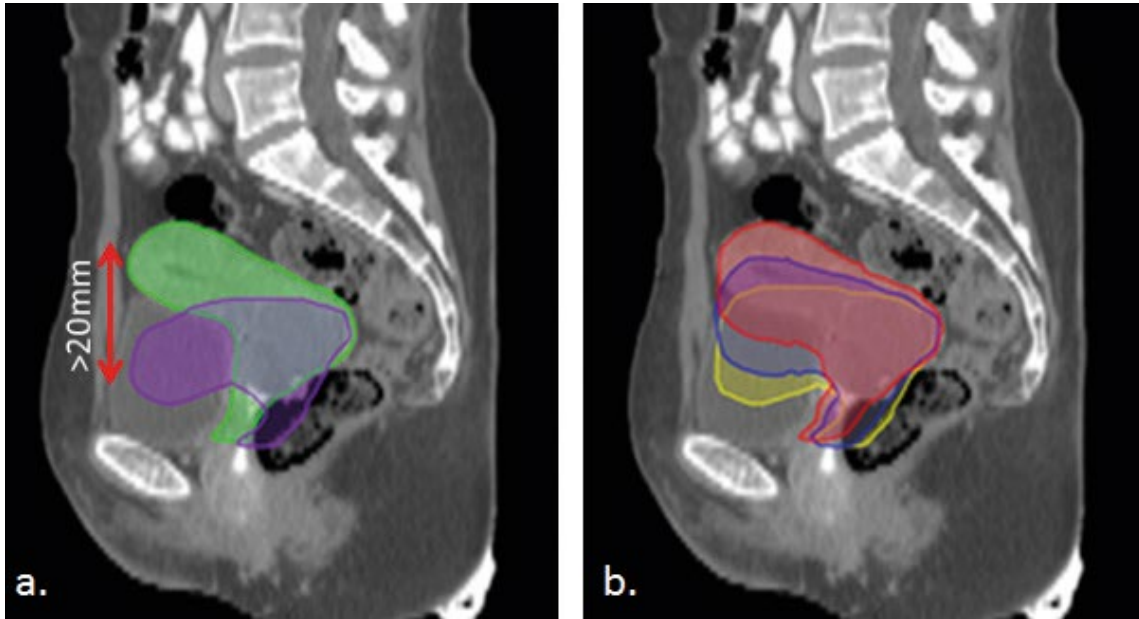


Figure 2.1 | **a:** Sagittal view of the full bladder planning CT for patient 10 with in green the primary CTV corresponding to the full bladder planning CT and in purple the primary CTV corresponding to the empty bladder planning CT. The corpus-uterus top displacement is larger than 20 mm. **b:** Sagittal view of the full bladder planning CT for patient 10 with the primary ITV subranges (red, blue, yellow), obtained by dividing the full-range primary ITV based on linear scaling of the deformation vectors.

Image analysis

Since CBCT grey values do not represent Hounsfield units (HU), CBCT images are not directly suitable for dose calculation. To enable daily dose distribution calculation, selected CTs were deformably registered to CBCT images (VelocityAI, version 3.1.0, Varian Medical Systems, Inc., Palo Alto, CA, USA) [79]. For each pre-fraction CBCT image, the CT best representing the daily pelvic anatomy (i.e. one of the planning CTs or weekly CTs) was selected to maximize deformable registration accuracy. After rigid alignment based on bony anatomy, selected CTs were deformed to represent CBCT images. Accordingly, delineations were deformed to match the deformed CT. Reported evaluations on deformable CT-to-CBCT registration performances in the pelvic area using the VelocityAI software showed accurate results and allowed for HU modification and structure deformation after deformable image registration [80,81]. Next to the reported evaluations, derived registration results in this study were also validated visually to verify plausible deformations.

For plan selection in the adaptive strategy, deformed CTs representing daily anatomy were aligned with the full bladder planning CT based on bony anatomy. Next, patient-specific PTVs were projected on the daily images and the PTV encompassing the target with the implanted fiducial markers inside the PTV was selected.

Dosimetric analysis

The library plan corresponding to the selected ITV and the non-adaptive plan were recalculated to obtain daily dose distributions according to both treatment strategies. Dose-volume histograms (DVHs) of daily dose distributions were calculated for the pCTV, lymph nodes, CTV, bladder, bladder wall, bowel cavity and rectum. For the target structures, the fraction dose to 98%, 50% and 2% of the volume ($D_{98\%}$, $D_{50\%}$, $D_{2\%}$) were calculated and differences between ICRU-based coverage ($D_{98\%} > 95\%$) were tested pairwise for significance (McNemar chi-square test). Besides the median ($D_{50\%}$) and near-maximum ($D_{2\%}$) fraction dose, the $V_{0.5\text{Gy}}$, $V_{1.5\text{Gy}}$ and $V_{2\text{Gy}}$ for OARs were extracted from daily DVHs and tested pairwise for significance using a non-parametric statistical test (Wilcoxon signed-rank test).

2.3 | Results

Since five fractions were excluded because CBCT quality was not suitable for analysis, in total 225 fractions were evaluated. Seven out of the ten patients showed pre-treatment displacements of the corpus-uterus top larger than 20 mm and resulted in plan libraries consisting of three plans. For two patients, the plan library consisted of two plans and a one-plan library was generated for one patient.

The selected library plans per patient for the adaptive strategy are presented (Figure 2.2). For most of the patients, in the majority of fractions the selected library plan corresponded to the target position related to a full bladder (PTV_{67-100} , PTV_{50-100}). However, despite drinking instructions, the preferred irradiation with a full bladder was not achieved for all fractions and library plans were selected corresponding to target positions related to low or intermediate bladder volumes. For patients with a three-plan library, the selection frequency of the library plan with the target position related to a full bladder (PTV_{67-100}) was on average 50% and 57% for the prone and supine treatment position, respectively (Figure 2.2).

A typical example of fraction DVHs is shown for the target structures (Figure 2.3). In total, 24 (11%) and 38 (17%) fractions in the non-adaptive approach showed inadequate coverage ($D_{98\%} < 95\%$) for the CTV and pCTV, respectively. Daily plan selection anticipated on day-to-day anatomical variations and resulted in adequate target coverage in 225 (100%) and 220 (98%) fractions for the CTV and pCTV, respectively. An adaptive strategy instead of a non-adaptive approach significantly ($p < 0.01$) improved daily coverage ($D_{98\%} > 95\%$) for the pCTV and CTV (Figure 2.4).

As an example, for one patient also fraction DVHs for OARs are shown (Figure 2.3). Figures 2.A.1–2.A.10 show fraction DVHs of target volumes and OARs for each patient. Compared to the non-adaptive approach, daily plan selection reduced the dose to rectum and bowel cavity indicated by significant improvements ($p < 0.01$) of all DVH parameters of interest (Figure 2.5). However, the $D_{50\%}$, $V_{1.5\text{Gy}}$ and $V_{2\text{Gy}}$ for bladder were increased significantly ($p < 0.05$) when applying the adaptive strategy instead of the non-adaptive approach. Table 2.2 presents the mean parameter values for

the OARs and the absolute and relative differences between non-adaptive and adaptive radiation therapy.

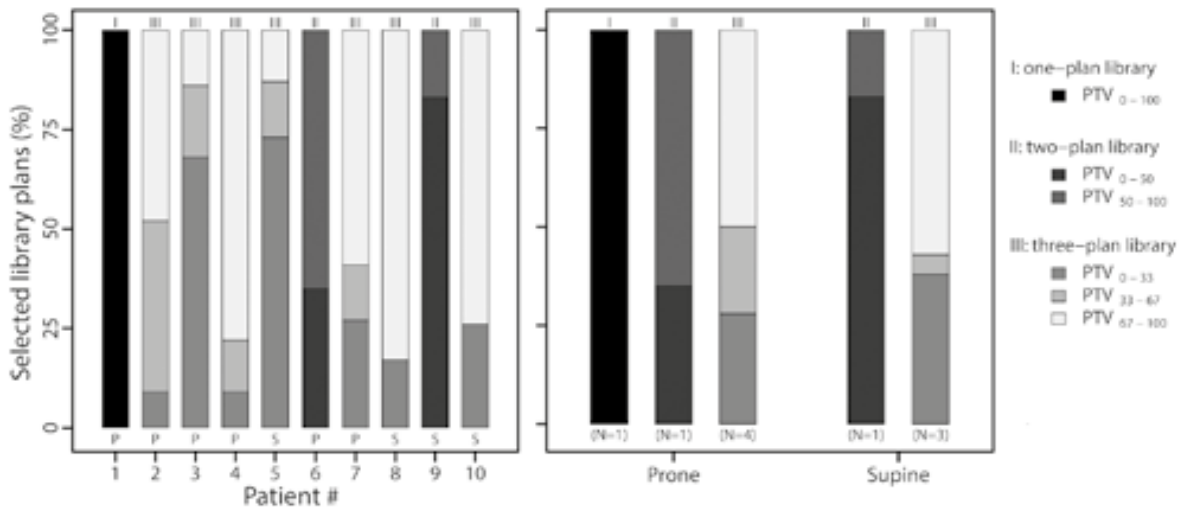


Figure 2.2 | Frequency of selected library plans during the course of treatment per patient (left) and average percentages per treatment position (right). The number on top of each bar represents the number of available library plans and the character in the left bar plot (*P*; *S*) represents the treatment position (*prone*; *supine*).

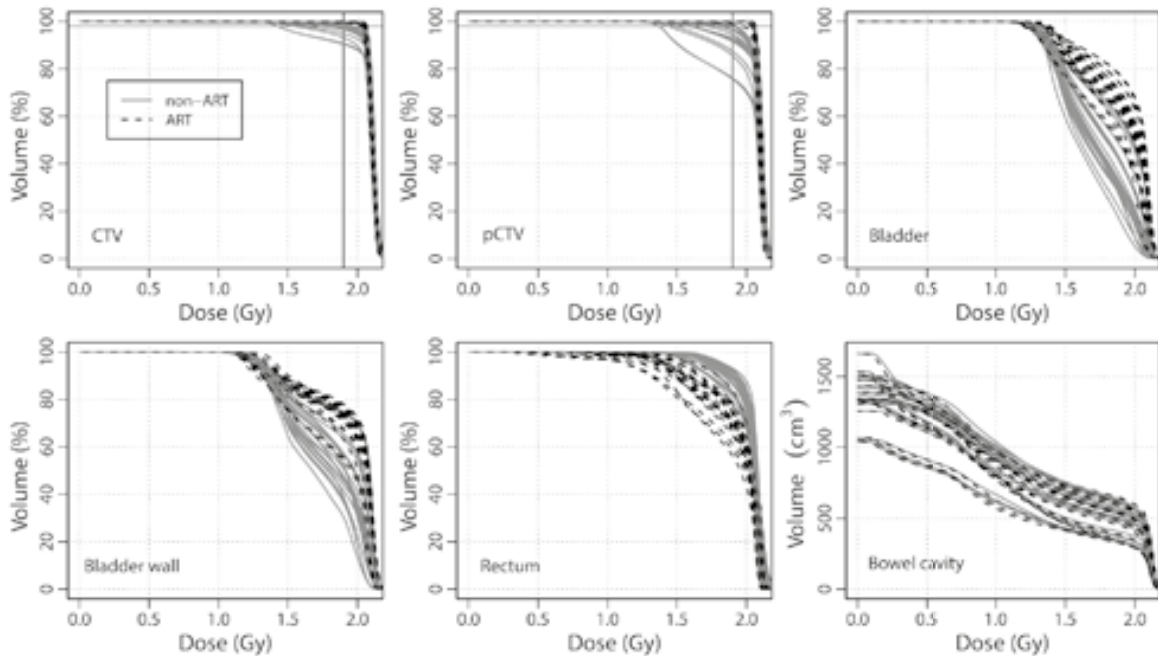


Figure 2.3 | For patient 3, DVHs of recalculated fraction dose distributions are shown for target volumes (CTV, pCTV) and OARs (bladder, bladder wall, rectum, bowel cavity) based on the non-adaptive (solid lines) and adaptive (dashed lines) treatment strategy. The intersection of the 2 solid black lines in the DVHs for target structures indicates $V_{95\%}=98\%$.

Table 2.2 | Comparison of the mean DVH parameter values for the recalculated fractions of all patients.

	non-ART	ART	Absolute difference (non-ART – ART)	Relative difference (%)	p-Value
Bladder					
V _{0.5Gy} (%)	99.9	99.9	0.0	0.0	0.4
V _{1.5Gy} (%)	82.6	85.4	-2.8	-3.3	<0.01
V _{2Gy} (%)	38.5	42.8	-4.3	-11.1	0.02
D _{50%} (Gy)	1.9	1.9	0.0	-2.2	0.02
D _{2%} (Gy)	2.0	2.0	0.0	-0.1	0.7
Rectum					
V _{0.5Gy} (%)	99.9	99.9	0.1	0.1	<0.001
V _{1.5Gy} (%)	93.5	91.4	2.1	2.3	<0.001
V _{2Gy} (%)	36.1	28.8	7.3	20.2	<0.001
D _{50%} (Gy)	1.9	1.9	0.0	1.0	<0.001
D _{2%} (Gy)	2.0	2.0	0.0	0.4	<0.001
Bowel cavity					
V _{0.5Gy} (cm ³)	1490	1470.4	19.6	1.3	<0.001
V _{1.5Gy} (cm ³)	688.6	668.9	19.6	2.9	<0.001
V _{2Gy} (cm ³)	406.7	372.2	34.5	8.5	<0.001
D _{50%} (Gy)	1.2	1.2	0.0	2.7	<0.001
D _{2%} (Gy)	2.0	2.0	0.0	0.2	<0.001

Abbreviations: non-ART = non-adaptive radiation therapy; ART = adaptive radiation therapy.

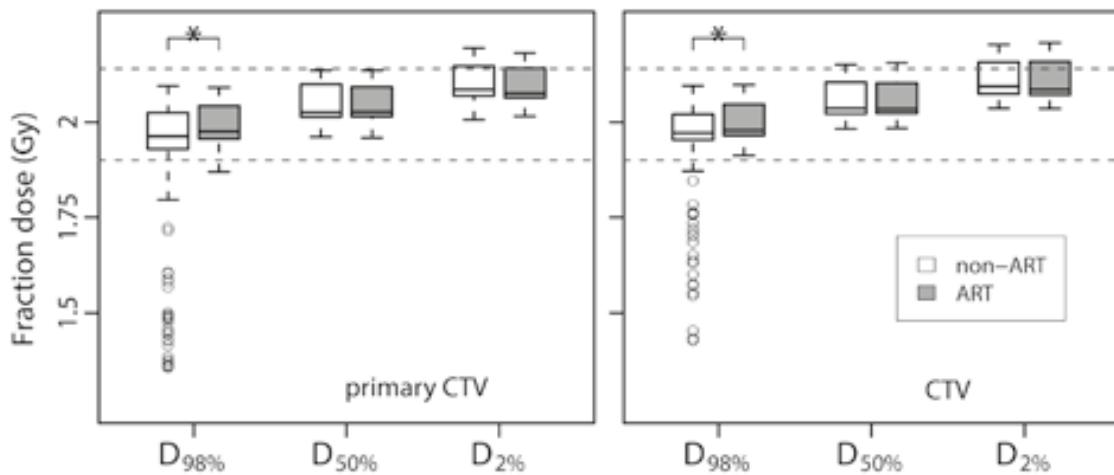


Figure 2.4 | For the recalculated fraction dose distributions based on the primary CTV (left) and the CTV (right), boxplots of daily dose parameters over all analyzed fractions of all included patients are shown for both the non-adaptive (non-ART) and the adaptive (ART) strategy. Boxes represent upper and lower quartiles (IQR), the band inside the box the median value and the whiskers the highest (lowest) value within 1.5 IQR of the upper (lower) quartile. Dashed gray horizontal lines indicate 95% and 107% of the prescribed fraction dose. Horizontal lines including an asterisk indicate statistical significant difference ($p < 0.01$).

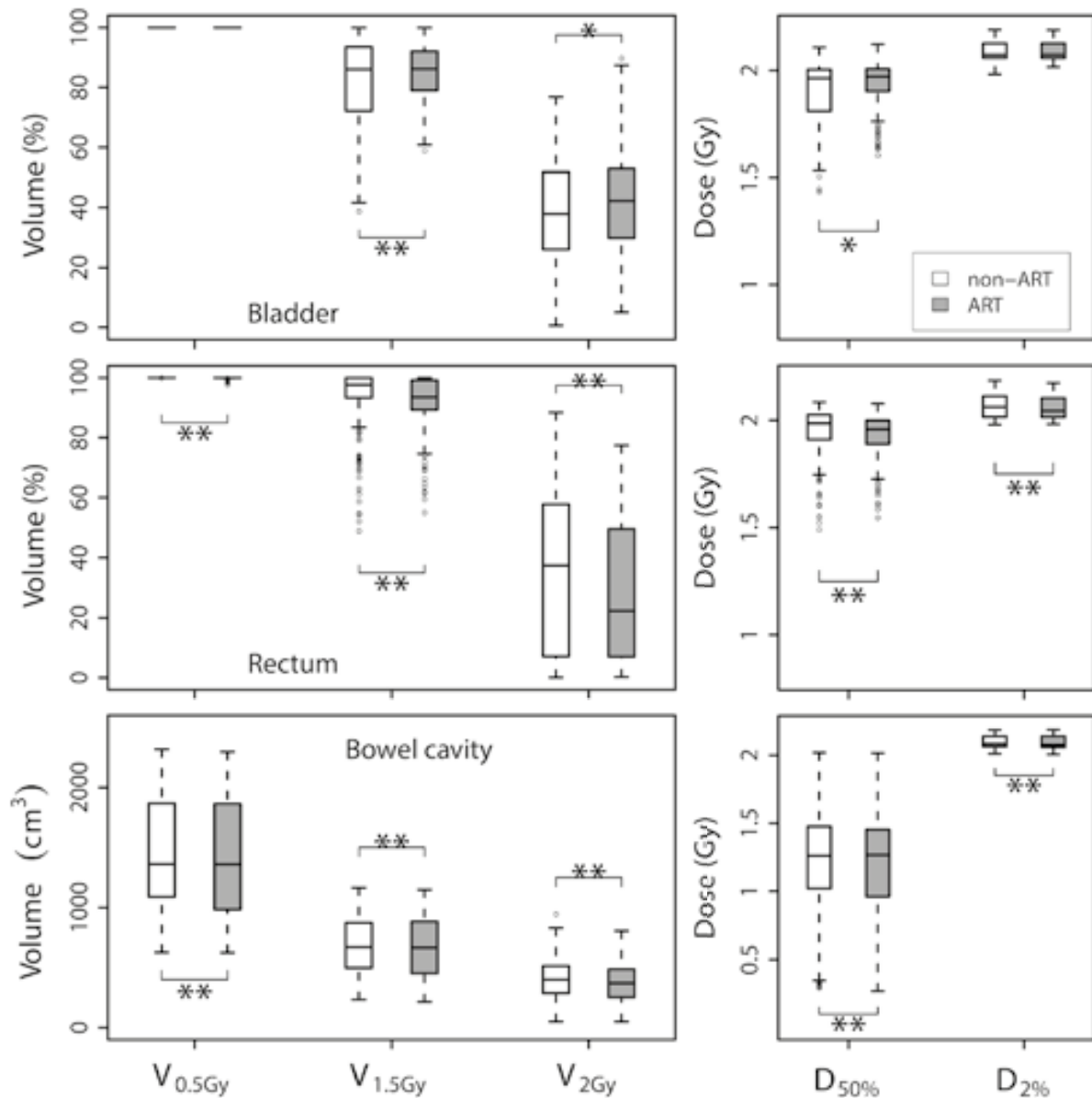


Figure 2.5 | For the non-adaptive (non-ART) and adaptive (ART) strategy, boxplots of fraction DVH parameters over all analyzed fractions of all patients are shown for bladder (upper), rectum (middle) and bowel cavity (lower). For the meaning of box, whiskers and dots: see Figure 2.4. Horizontal lines including asterisks indicate statistical significant difference (* $p < 0.05$; ** $p < 0.01$).

2.4 | Discussion

In this first realistic dosimetric analysis of an adaptive strategy in cervical cancer radiation therapy, we investigated the potential advantages of a daily plan selection strategy compared to a non-adaptive approach in cervical cancer radiation therapy. Using a plan-library based plan-of-the-day adaptive strategy to anticipate on day-to-day anatomical variations, daily dose distributions of both adaptive and non-adaptive treatments were calculated based on pre-fraction CBCT

imaging and compared for target coverage and OAR sparing. Compared to non-adaptive radiation therapy, a daily plan selection adaptive strategy allowed us to anticipate on anatomical changes and consequently improved daily target coverage significantly. Additionally, daily plan selection reduced the dose to rectum and bowel significantly, however the clinical relevance of the limited dose differences has to be investigated.

Previously conducted research on ART in cervical cancer focused either on the optimization of various adaptive strategies to correct for interfraction anatomical changes [54,65,82], tools to guide or automate adaptive strategies [75,76] or the clinical implementation of cervical cancer ART [59]. However, none of them validated the actual benefit of an adaptive strategy in terms of delivered dose while taking into account the day-to-day anatomical variations. Our recalculated daily dose distributions based on pre-fraction imaging for both a non-adaptive and adaptive strategy resulted in representative comparisons in terms of differences in target coverage and OAR sparing.

Our dosimetric analysis was performed based on a relatively small patient population. Because the majority of patients were treated using the non-adaptive approach, we simulated for these patients adaptive treatments according to the current clinical practice. For the two patients treated using the adaptive strategy, treatments were simulated according to the non-adaptive approach to fairly quantify the dosimetric consequences of the adaptive strategy. Although we quantified dosimetric differences, a prospective evaluation of clinically applied adaptive treatments is required to determine its actual dosimetric benefit. Furthermore, a larger number of patients will provide more information on target coverage improvement and maximum achievable OAR sparing.

Although the median and near-maximum target dose remained similar, we found a significant improvement on target coverage ($D_{98\%} > 95\%$) when applying the adaptive strategy while the dose to rectum and bowel decreased significantly. However, the anticipation on anatomical changes by daily plan selection resulted in an increased dose to the adjacent bladder, indicated by the V_{2Gy} , $V_{1.5Gy}$ and $D_{50\%}$ bladder parameters. Since adaptive target volumes were created based on bladder volume variations, bladder sparing in ART was expected to be less [83]. To avoid the increase of bladder dose when applying the adaptive strategy, reductions of CTV-to-PTV margins could be considered. Furthermore, target volume definitions could be optimized based on magnetic resonance imaging (MRI) by excluding the healthy corpus-uterus part from the target volume [6,84].

Instead of accumulated dose distributions, we compared recalculated fraction dose distributions. To reliably accumulate dose distributions within delineated organs, deformable image registration including accurate voxel-to-voxel correspondence is required. Due to the limited soft-tissue contrast in CBCT imaging, we decided to evaluate fraction dose distributions separately, but statistical tests were applied pairwise.

In this study, HU modification and structure warping was performed based on deformable image registration between CT and CBCT imaging using the implemented algorithm in VelocityAI. Deformable registrations between CT and CBCT imaging for pelvic anatomy using this algorithm

were previously evaluated in terms of registration errors and associated dose distribution uncertainties [80,81]. Compared to the average registration error (1.9 mm) across the whole pelvic area, the average registration error for bladder (4.6 mm) was relatively large due to initial large bladder volume differences [80]. Since we minimized the registration errors by selecting the CT best representing the daily pelvic anatomy, our deformable registrations used for HU modification and structure warping are considered accurate. In addition, all deformable registration results were validated by visual inspection for plausible deformations. Furthermore, Onozato *et al.* [81] evaluated the accuracy of dose calculation for pelvic anatomy after deformable registration between CT and CBCT imaging and reported dose uncertainties of on average 1.2%. The effect of residual deformation errors on our results was expected to be negligible, also because dose distributions for both the non-adaptive and adaptive strategy were calculated using identical deformed CT images including similar residual errors.

Intrafraction organ motion during cervical cancer irradiation can be considerable and might affect dose delivery [74]. In this study, CBCTs acquired prior to irradiation were used for both plan selection and dose recalculation. Possible consequences of intrafraction anatomical changes are therefore not represented by our calculated dose distributions. However, the reported intrafraction organ motion by Heijkoop *et al.* [74] is based on pre- and post-fraction CBCT imaging with a relatively large interval time of 20.8 minutes. According to our clinical experience, all operations between pre-fraction CBCT and the end of dose delivery, including patient position correction, library plan selection and VMAT dose delivery, is estimated to take up to 7 minutes. Consequently, the intrafraction organ motion present in our patients is assumed to be much smaller compared to the reported intrafraction displacements. Also, the use of ITVs in our adaptive strategy already compensates for possible intrafraction target motion induced by intrafraction bladder filling. Hence, dosimetric uncertainties induced by intrafraction anatomical changes in cervical cancer radiation therapy is assumed to be limited.

The presented adaptive strategy is designed to anticipate on day-to-day anatomical variations based on pre-treatment predicted deformations. However, anatomical changes not represented by the library plans (e.g. due to changing bowel or rectum volume) can limit the efficiency of this adaptive strategy. Heijkoop *et al.* [59] selected a motion-robust backup plan with very generous margins in 17.5% of all fractions to cover these unpredicted variations, however this will consequently limit OAR sparing.

In the future, our adaptive procedure will be optimized to reduce clinical workload and minimize OAR dose. Also, the use of online plan adaptations based on daily MRI will be implemented [85]. First of all, MRI guidance can be introduced to avoid plan selection difficulties due to limited CBCT image quality or to implement additional boost techniques based on tumor response. Moreover, the clinical introduction of MRI-guided radiation therapy allows online plan adaptations and could be the next step in online adaptive cervical cancer RT [85].

2.5 | Conclusion

An adaptive strategy using daily plan selection allows correcting for day-to-day anatomical variations in cervical cancer radiation therapy. Compared to a non-adaptive approach, significant improvements in target coverage were found when applying the adaptive strategy. Additionally, a significant reduction in dose to bowel cavity and rectum was observed with a yet unclear clinical relevance.

Appendix 2.A

Patient 1 – plan library for adaptive radiation therapy consisted of 1 plan

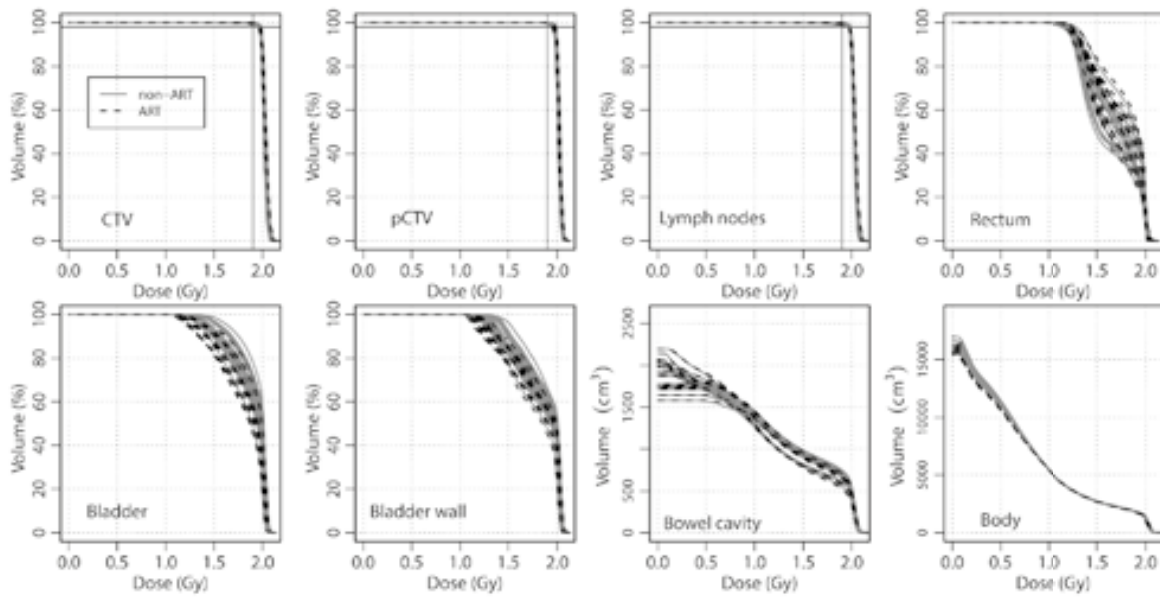


Figure 2.A.1 | Dose-volume histograms of the recalculated fraction dose distributions are shown based on the non-adaptive and the adaptive strategy for both the target volumes and OARs. The intersection of the two solid lines indicates $D_{98\%}=95\%$ of the prescribed fraction dose.

Patient 2 – plan library for adaptive radiation therapy consisted of 3 plans

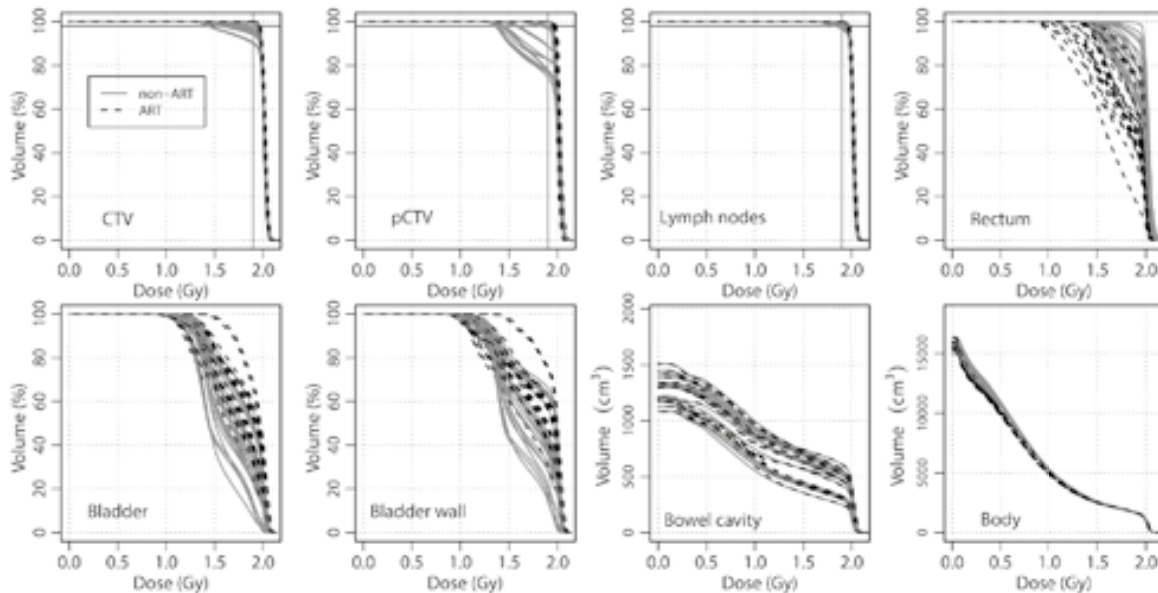


Figure 2.A.2 | Dose-volume histograms of the recalculated fraction dose distributions are shown based on the non-adaptive and the adaptive strategy for both the target volumes and OARs. The intersection of the two solid lines indicates $D_{98\%}=95\%$ of the prescribed fraction dose.

Patient 3 – plan library for adaptive radiation therapy consisted of 3 plans

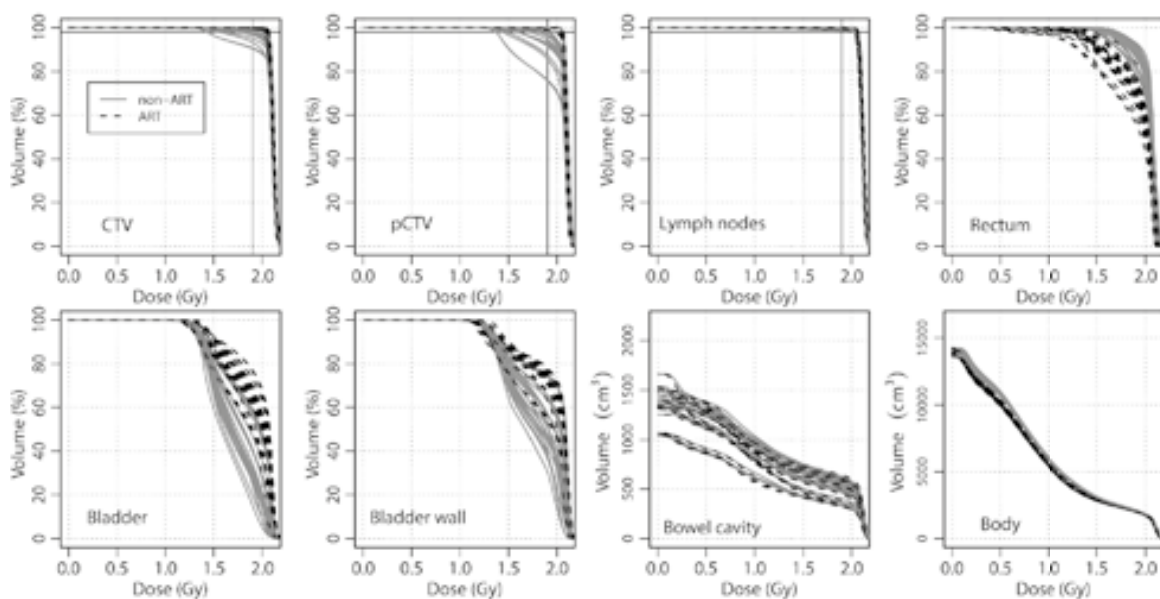


Figure 2.A.3 | Dose-volume histograms of the recalculated fraction dose distributions are shown based on the non-adaptive and the adaptive strategy for both the target volumes and OARs. The intersection of the two solid lines indicates $D_{98\%}=95\%$ of the prescribed fraction dose.

Patient 4 – plan library for adaptive radiation therapy consisted of 3 plans

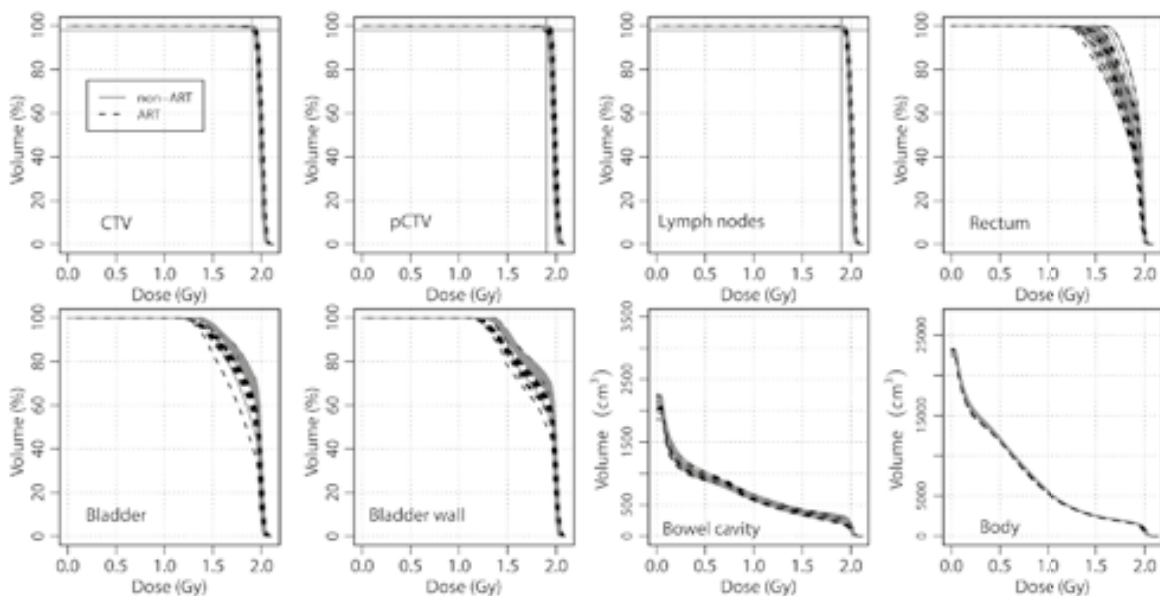


Figure 2.A.4 | Dose-volume histograms of the recalculated fraction dose distributions are shown based on the non-adaptive and the adaptive strategy for both the target volumes and OARs. The intersection of the two solid lines indicates $D_{98\%}=95\%$ of the prescribed fraction dose.

Patient 5 – plan library for adaptive radiation therapy consisted of 3 plans

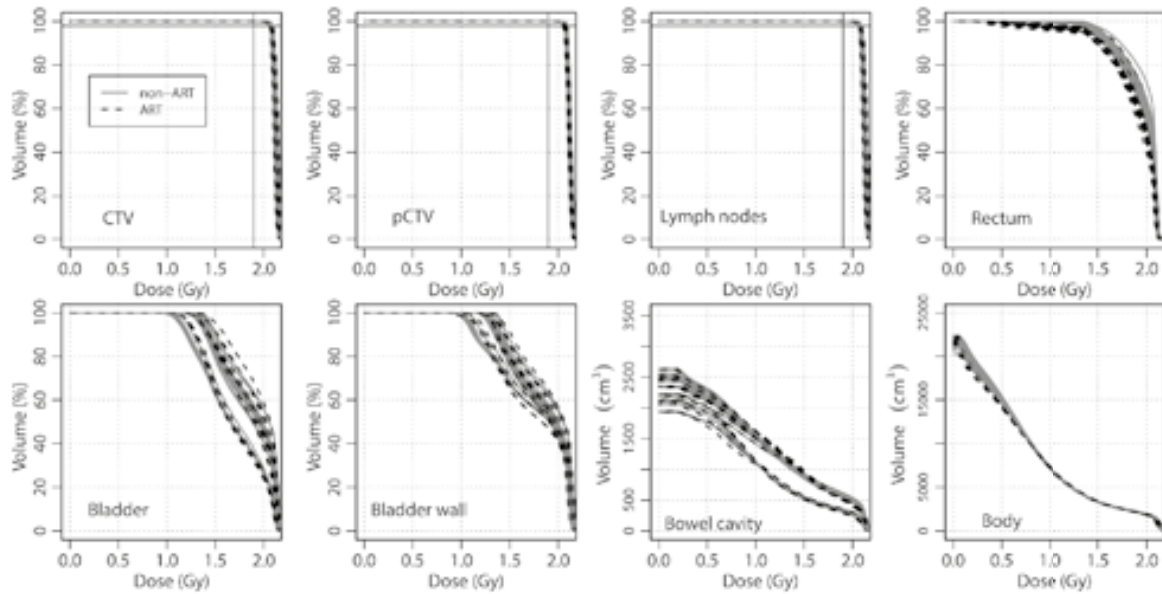


Figure 2.A.5 | Dose-volume histograms of the recalculated fraction dose distributions are shown based on the non-adaptive and the adaptive strategy for both the target volumes and OARs. The intersection of the two solid lines indicates $D_{98\%}=95\%$ of the prescribed fraction dose.

Patient 6 – plan library for adaptive radiation therapy consisted of 2 plans

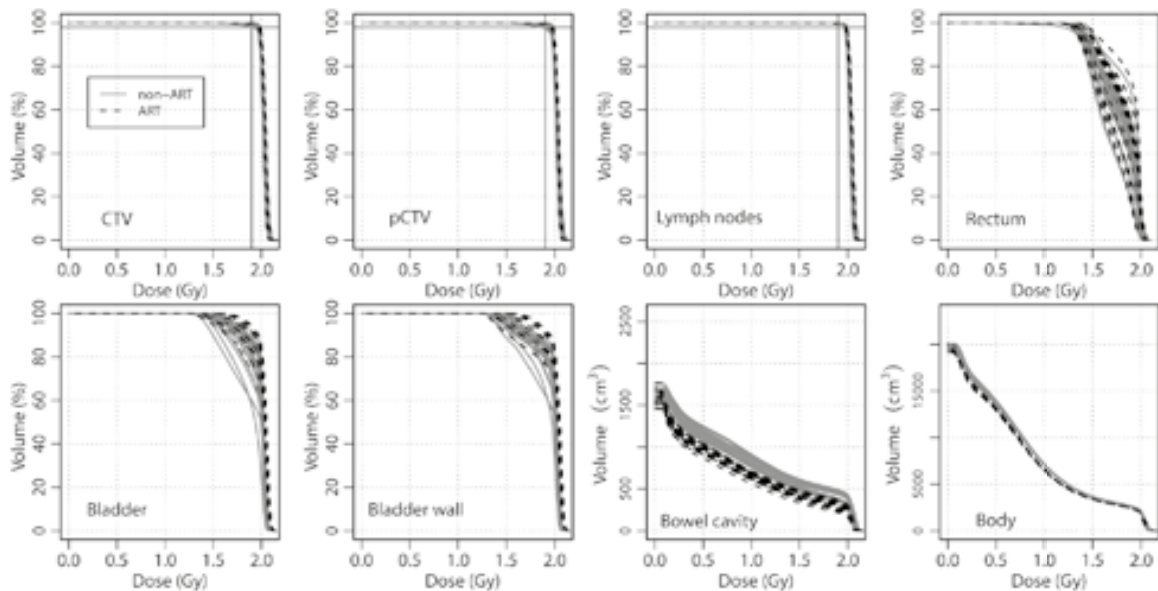


Figure 2.A.6 | Dose-volume histograms of the recalculated fraction dose distributions are shown based on the non-adaptive and the adaptive strategy for both the target volumes and OARs. The intersection of the two solid lines indicates $D_{98\%}=95\%$ of the prescribed fraction dose.

Patient 7 – plan library for adaptive radiation therapy consisted of 3 plans

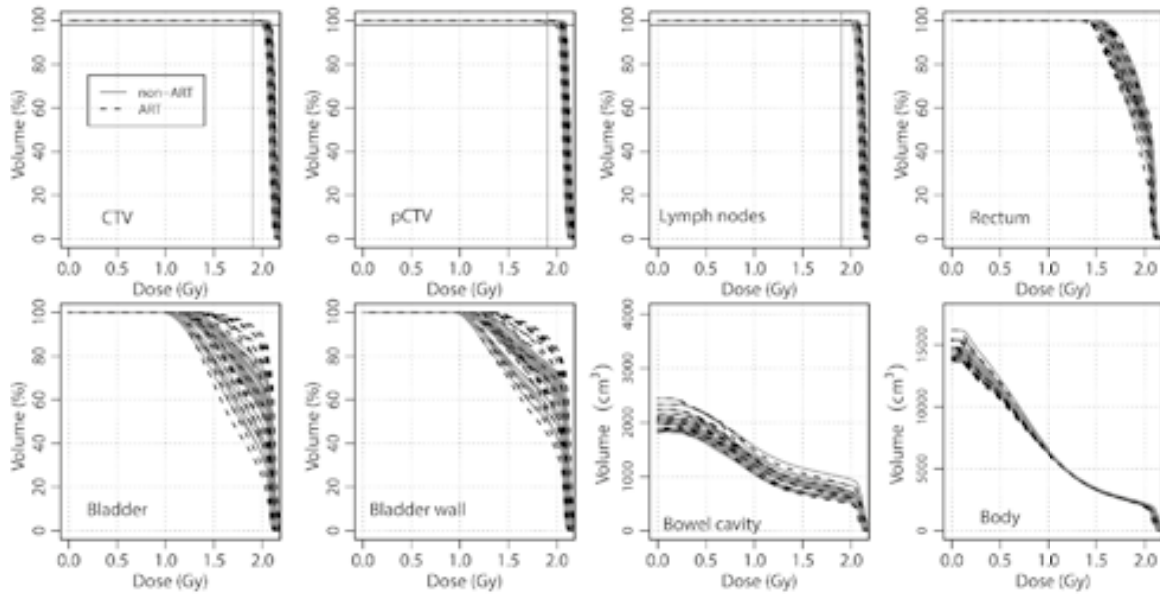


Figure 2.A.7 | Dose-volume histograms of the recalculated fraction dose distributions are shown based on the non-adaptive and the adaptive strategy for both the target volumes and OARs. The intersection of the two solid lines indicates $D_{98\%}=95\%$ of the prescribed fraction dose.

Patient 8 – plan library for adaptive radiation therapy consisted of 3 plans

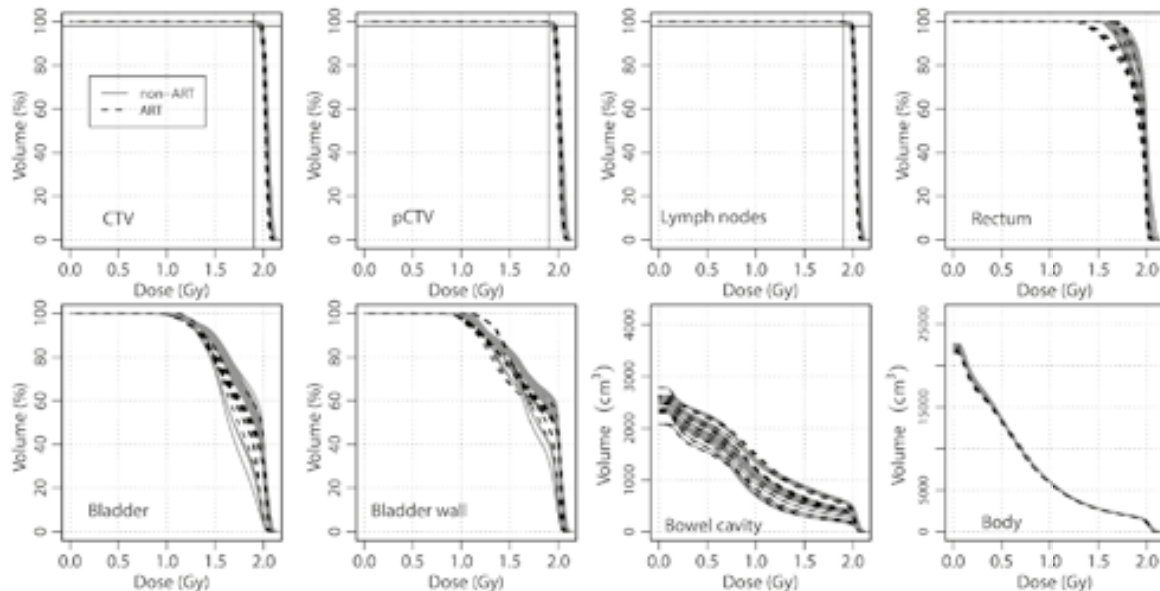


Figure 2.A.8 | Dose-volume histograms of the recalculated fraction dose distributions are shown based on the non-adaptive and the adaptive strategy for both the target volumes and OARs. The intersection of the two solid lines indicates $D_{98\%}=95\%$ of the prescribed fraction dose.

Patient 9 – plan library for adaptive radiation therapy consisted of 2 plans

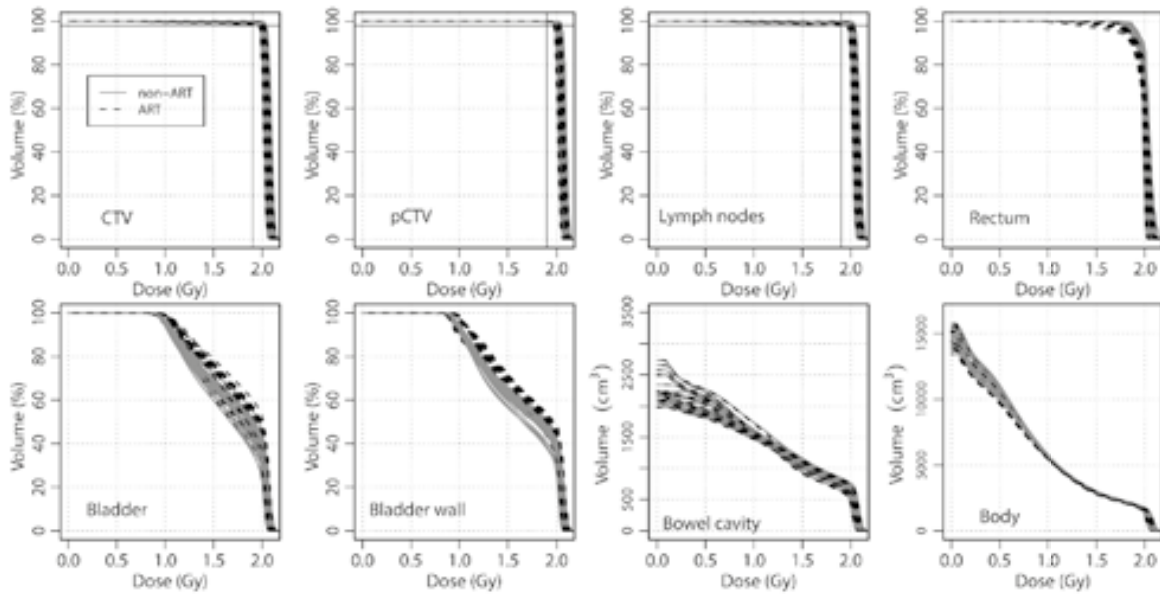


Figure 2.A.9 | Dose-volume histograms of the recalculated fraction dose distributions are shown based on the non-adaptive and the adaptive strategy for both the target volumes and OARs. The intersection of the two solid lines indicates $D_{98\%} = 95\%$ of the prescribed fraction dose.

Patient 10 – plan library for adaptive radiation therapy consisted of 3 plans

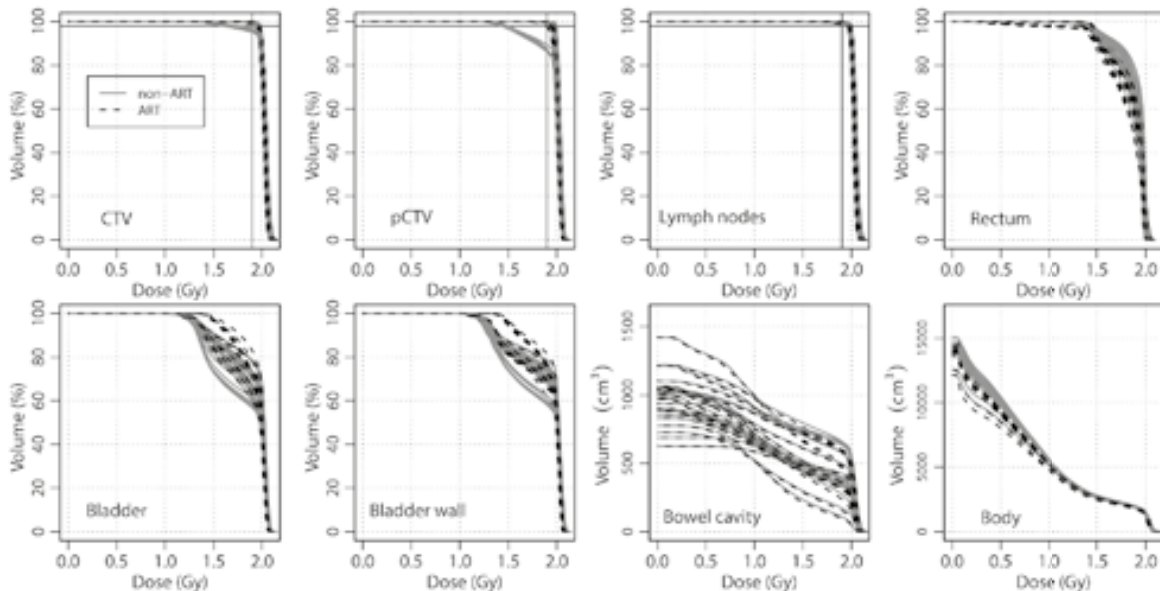


Figure 2.A.10 | Dose-volume histograms of the recalculated fraction dose distributions are shown based on the non-adaptive and the adaptive strategy for both the target volumes and OARs. The intersection of the two solid lines indicates $D_{98\%} = 95\%$ of the prescribed fraction dose.