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

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# Chapter 7

Should excluding uninvaded uterine tissue  
be combined with proton therapy for  
cervical cancer?

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*Should excluding uninvaded uterine tissue be combined with proton therapy for  
cervical cancer?*

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## Abstract

### Purpose

In cervical cancer radiation therapy, including the entire uterus in the target volume results in large target volumes and consequently leads to high organ at risk (OAR) dose. Our aim is to quantify the dosimetric advantages of excluding the uninvaded uterine body from the target volume combined with either photon or proton therapy.

### Material & Methods

Eleven patients with locally advanced cervical cancer with a substantial (>4cm) tumor free part of the uterus towards the fundus on pre-treatment magnetic resonance imaging (MRI) were selected retrospectively. Conventional target volumes including the entire uterus and MRI-based target volumes including only the invaded part of the uterus were compared. Photon and proton plans were generated for both target volumes, resulting in four treatment plans per patient. Differences in  $V_{15Gy}$ ,  $V_{30Gy}$ ,  $V_{45Gy}$  and  $D_{mean}$  for bladder, sigmoid, rectum and small bowel were assessed. Additionally, differences in normal tissue complication probability (NTCP) were estimated for small bowel.

### Results

Compared to conventional volumes, MRI-based target volumes resulted in an average reduction of the primary internal target volume and planning target volume by 37% and by 8%, respectively. The use of MRI-based target volumes resulted in significant reductions in  $V_{15Gy}$ ,  $V_{30Gy}$ ,  $V_{45Gy}$  and  $D_{mean}$  for bladder and small bowel when applying photon therapy and were further reduced when applying proton therapy. MRI-based target volumes reduced the average NTCP for small bowel from 25% to 18% and the addition of proton therapy resulted in an average of 9%. Substantial NTCP differences (>10%) are expected in 4 patients (36%) using MRI-based target volumes and in 6 patients (55%) when adding proton therapy.

### Conclusion

MRI-based target volume definition in cervical cancer radiation therapy decreased OAR dose and acute small bowel toxicity probabilities. In the presence of smaller targets, the addition of proton therapy reduces the toxicity even more.

## 7.1 | Introduction

Chemoradiation, i.e. radiation therapy and weekly cisplatin, is the mainstay for locally advanced uterine cervical cancer. Radiation therapy typically consists of external beam radiation therapy (EBRT), followed by a brachytherapy boost. Adequate coverage of the high risk clinical target volume (CTV) in the brachytherapy boost results in a high probability of local control [161]. However, the main dose limiting factors in EBRT are acute complications such as radiation enteritis, proctitis, cystitis as well as late complications such as small bowel obstruction, perforation, fistulae and sexual dysfunction [162,163].

Large volumes of normal tissue are being irradiated during EBRT despite modern techniques such as intensity modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT) combined with an adaptive treatment strategy [54]. A contributing factor to late complications is the EBRT target volume, which includes the whole uterine body plus generous safety margins to compensate for interfraction position uncertainties. The obtained planning target volume (PTV) implicitly results in a substantial overlap of the high dose area with vulnerable small bowel [164-166]. In the present study, we aim to reduce these large volumes of irradiated healthy tissue and investigated two strategies.

There is no doubt that the conventional strategy of target volume definition by including the whole uterus in the CTV is indicated for patients in whom the uterine body is extensively invaded by tumor. But, particularly since the size and extension of tumors can increasingly better be visualized by magnetic resonance imaging (MRI) [167,168], it is not evident why the (whole) uterine body should be included if there is no or only limited invasion of the tumor in the uterine corpus.

Secondly, the application of proton therapy may reduce the organ at risk (OAR) dose. The characteristic Bragg peak of protons enables steep dose fall-offs around the target volume and results in limited dose to OARs [71]. However, due to these physical properties dose delivery in proton therapy is sensitive to range and position uncertainties and anatomical changes can largely influence dose delivery in proton therapy. Therefore, proton plan robustness is required together with appropriate image guidance during dose delivery.

If we assume that both strategies are applicable, the combination of proton therapy and target volume definition using MRI may result in even less collateral dose to small bowel, bladder and rectum compared to the conventional EBRT strategy. If we further correlate the potentially dosimetric advantages with existing normal tissue complication probability (NTCP) models, we will be able to estimate the reduction in small bowel toxicity after cervical cancer EBRT [141]. Therefore, the aim of this study was to quantify dosimetric advantages of proton therapy using MRI-based target volume definition in terms of DVH parameters compared to the best standard of care based on the conventional target definition strategy in photon-based EBRT. Next, we correlated these dosimetric advantages to potential reductions in small bowel toxicity probability.

## 7.2 | Material & Methods

### Patients

All patients with uterine cervical cancer receive MRI for tumor staging. As part of the clinical protocol, anatomical T2-weighted MRI is acquired using either a 1.5 Tesla MRI system (Siemens Avanto, Erlangen, Germany) or a 3.0 Tesla MRI system (Philips Ingenia, Best, the Netherlands). Patients with locally advanced cervical cancer who received curative chemoradiation underwent fludeoxyglucose (FDG) positron emitting tomography (PET)-CT imaging (Philips Gemini, Eindhoven, The Netherlands). PET-CT imaging is performed with a full bladder in radiation therapy position. Eleven women with cervical cancer who received radiation therapy between January 2014 and December 2015 and showed a substantial (>4 cm) tumor free part of the uterus towards the fundus on pre-treatment MRI were selected retrospectively. Table 7.1 presents baseline characteristics of all patients including information regarding MRI acquisition and tumor extensions.

**Table 7.1** | Baseline characteristics.

Patient		Age (years)	FIGO stage	CC tumor extension (mm)	Uterine tumor free distance <sup>†</sup> (mm)	Treatment position
1	**	34	IA2 (N1)	0	55	prone
2	*	38	IIA2 (N1)	15	51	supine
3	**	54	IIIB	32	42	prone
4	**	28	IB2	20	64	prone
5	*	47	IIB	43	59	prone
6	**	49	IIIB	62	40	supine
7	**	53	IIIB	27	45	supine
8	**	36	IIB	35	46	supine
9	**	41	IB2	28	44	supine
10	**	39	IIA2	39	58	supine
11	*	42	IB1	35	89	supine

*Abbreviations:* FIGO = International Federation of Gynecology and Obstetrics; CC = craniocaudal.

\* MRI acquired using 1.5 T MRI system (Siemens Avanto, Erlangen, Germany).

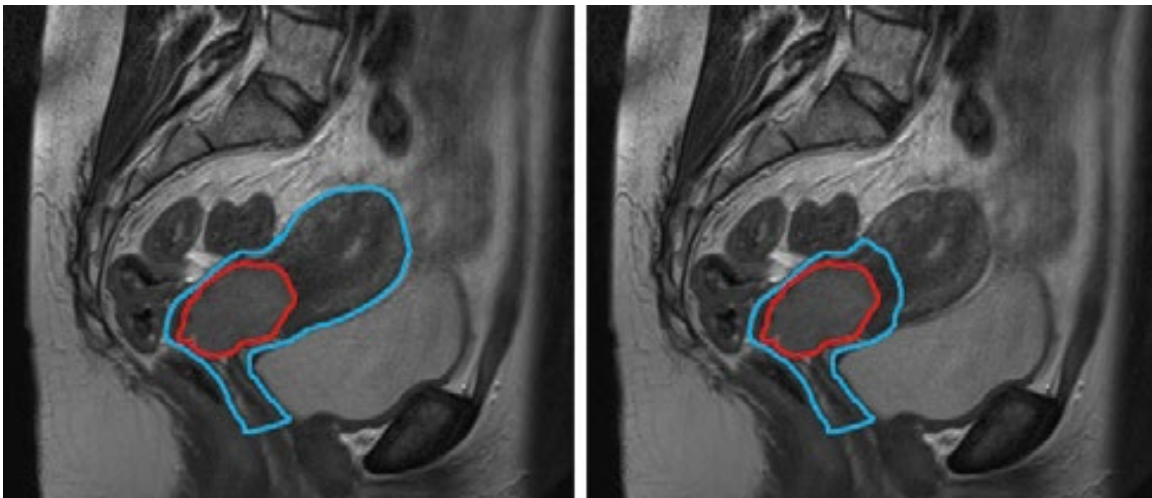
\*\* MRI acquired using 3.0 T MRI system (Philips Ingenia, Best, the Netherlands).

† Uterine tumor free distance is defined as the distance of tumor free uterine tissue cranial from the tumor.

## Structure definition

For each patient, the gross tumor volume (GTV) was delineated on the CT image after consensus between two experienced radiation oncologists. The GTV was defined as the visible tumor volume on the fused PET-CT image according to FDG-uptake and the visible tumor extend on MRI after co-registration to the CT image. Based on the delineated GTV, target volumes were defined using two different strategies: 1) the conventional definition strategy by including the entire uterus into the target volume (i.e. target volumes with the subscript ‘old’) and 2) the new definition strategy by defining the target volume based on MRI and excluding the uninvaded part of the uterus (i.e. target volumes with the subscript ‘new’).

The conventional target definition strategy recommended to define the primary clinical target volume ( $pCTV_{old}$ ) by including the GTV, the cervix, uterine corpus and upper part of the vagina [29,164,168]. The  $pCTV_{old}$  was enlarged by adding a 10 mm uniform margin to form the primary internal target volume ( $pITV_{old}$ ). In addition, the regional lymph node areas were delineated including parametric and lymph node areas around the iliac and obturator arteries/vessels ( $lnCTV$ ). The internal target volume ( $ITV_{old}$ ) was created by combining  $lnCTV$  and  $pITV_{old}$ . The  $ITV_{old}$  was expanded with an 8 mm isotropic margin to form the  $PTV_{old}$  (Figure 7.1).



**Figure 7.1** | Sagittal view of T2-weighted MRI for patient 8 with examples of the defined volumes according to the conventional definition strategy (left) and the novel definition strategy (right). In the conventional strategy, the  $pCTV_{old}$  (blue) included besides the GTV (red) the entire uterus and upper part of the vagina. The  $pCTV_{new}$  (blue) according to the novel strategy excluded the uninvaded part of the uterus.

The new target volume definition strategy was introduced to optimize the target volume in cervical cancer, as suggested previously. Instead of including the entire uterine corpus into the target volume, a margin of 10 mm in the direction of the uterine fundus was added to the MRI-based

GTV delineation and combined with the upper part of the vagina and cervix to form the  $pCTV_{new}$  [84,167]. Again, a 10 mm isotropic margin around the  $pCTV_{new}$  defined the  $pITV_{new}$  and the  $ITV_{new}$  was defined by combining the  $lnCTV$  and  $pITV_{new}$ . The PTV was formed by expanding the  $ITV_{new}$  with an 8 mm isotropic margin. Also, on all CTs, the bowel cavity as a surrogate for small bowel, rectum, bladder, and sigmoid were delineated according to RTOG guidelines [137].

## Treatment planning

For all patients, radiation therapy plans for both target definition strategies were generated using photons (Oncontra version 4.5, Elekta AB, Stockholm, Sweden) and protons (RayStation version 4.4, RaySearch Laboratories AB, Stockholm, Sweden). All treatment plans were created based on a prescribed target dose of 46 Gy (23 x 2 Gy) and were optimized on a 3 mm uniform dose grid using the planning CT. Both photon and proton plan optimizations were started with the clinically used planning objectives template (Table 7.2) and objective values were individually optimized to minimize OAR dose while maintaining ICRU-based target coverage ( $D_{98\%} \geq 95\%$ ,  $D_{2\%} \leq 107\%$ ) [169].

Treatment planning using photons was performed based on a dual-arc VMAT (356° per arc, fixed 20° collimator angle) treatment technique. The plan optimization process aimed at planning the prescribed PTV dose of 46 Gy using a 10 MV energy with the isocenter set to the PTV center of mass.

Table 7.2 | Planning objectives for photon (proton) therapy planning.

Structure	Planning objectives
PTV (ITV)	Minimum dose 46 Gy Maximum dose 46.8 Gy
Body	Dose fall-off: 46–30 Gy over 1.0 cm
Rectum	Maximum dose 43.7 Gy Maximum 30 Gy to 70% of the volume
Bladder	Maximum dose 43.7 Gy Maximum 30 Gy to 70% of the volume
Bowel cavity	Maximum dose 43.7 Gy

*Abbreviations:* PTV = planning target volume; ITV = internal target volume.

Intensity modulated proton therapy (IMPT) plans were generated based on pencil beam scanning (spot size in air:  $\sigma=2.5\text{--}7.0$  mm (226.7–70.0 MeV)) using four fixed beams (30°, 90°, 270°, 330° (prone); 90°, 150°, 210°, 270° (supine)) [138]. In proton therapy, the ITV instead of the PTV was used for robust optimization and evaluation. Assuming a proton relative biological effectiveness of 1.1 [139], plans were generated with a prescribed ITV dose of 46 Gy-equivalent. During robust optimization, a total of 21 scenarios were included. Next to the nominal isocenter position and

the six isocenter position shifts of 8 mm in the main directions also three range errors (-3%, 0%, 3%) were included. After optimization, target coverage robustness was evaluated using 28 error scenarios, consisting of two range error (-3%, 3%) and 14 position errors of 8 mm. The position errors were simulated by isocenter position shifts in the six main directions and the eight diagonal directions of each octant in three-dimensional space [138].

## Analysis

For all patients, first target volumes according to the conventional strategy as well as the new strategy were calculated and the effect of MRI-based target volume definition was determined in terms of target volume reductions. Secondly, plan quality was verified by quantifying the conformity index (CI) and target coverage (TC). The CI was defined as the volume of the body receiving 95% of the prescribed dose (body  $V_{95\%}$ ) divided by the  $V_{95\%}$  of the target volume. The PTV was used to calculate the CI for photon plans, but for proton plans the ITV was used for CI calculation. The maximum dose received by at least 98% of the volume ( $D_{98\%}$ ) determined the TC and was reported to support the CI [170].

Differences in dose distributions corresponding to the generated treatment plans were calculated by evaluating DVH parameters for bladder, rectum, bowel cavity and sigmoid. Next to the mean dose ( $D_{\text{mean}}$ ) and maximum dose ( $D_{2\text{cc}}$ ), planned dose parameters for the volumes receiving 15 Gy ( $V_{15\text{Gy}}$ ), 30 Gy ( $V_{30\text{Gy}}$ ) and 45 Gy ( $V_{45\text{Gy}}$ ) were extracted as derivatives for volumes receiving low, intermediate and high dose, respectively. Patient-specific DVH differences with respect to the conventional definition strategy combined with photon therapy were tested pairwise for significance using a non-parametric statistical test (Wilcoxon signed-rank test).

## Toxicity

Differences in toxicity probabilities were estimated between both target definition strategies when applying photon therapy as well as proton therapy. Since NTCP models for bladder, sigmoid and rectum are only defined for dose levels above the prescribed dose of 46 Gy in cervical cancer EBRT, late toxicity probabilities cannot be determined for these OARs [171]. For small bowel, only acute toxicity models are available. Small bowel NTCP values associated with at least grade 2 acute small bowel toxicity were quantified using

$$NTCP = \frac{1}{1 + \left( \frac{V_{50}}{V_{45\text{Gy}}} \right)^k}$$

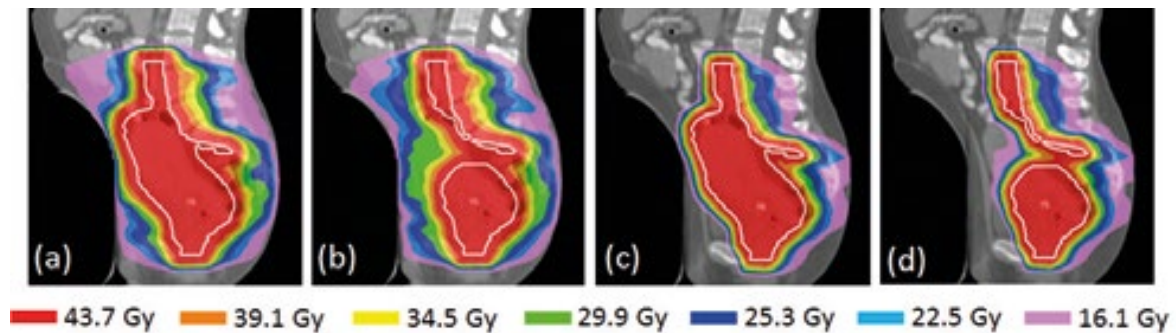
where  $V_{45\text{Gy}}$  represents the volume ( $\text{cm}^3$ ) receiving 45 Gy,  $V_{50}=410 \text{ cm}^3$  and  $k=3.2$  [141]. Improvements in NTCP between the use of photon therapy and proton therapy were calculated for each patient and correlated to  $V_{45\text{Gy}}$  of the small bowel. According to a model-based approach,

patient-specific NTCP differences were compared with the suggested 10% NTCP difference for individual patient selection who are expected to benefit from proton therapy [172].

### 7.3 | Results

For each patient, target volumes were defined according to the conventional strategy as well as our new strategy. Compared to the conventional volumes, excluding the uninvaded uterine corpus resulted in average reductions of the pITV and PTV by 37% (range, 17%–56%) and 8% (range, 3%–17%), respectively.

Photon-based VMAT plans showed consistency in CI with an average of 1.14 (range, 1.11–1.17) as well as in TC with an average of 44.2 Gy (range, 44.0 Gy – 44.5 Gy). Robustness evaluation for robustly optimized IMPT plans resulted in adequate ITV coverage ( $D_{98\%} \geq 98\%$ ;  $D_{2\%} \leq 107\%$ ) for all evaluated dose distributions. Further, nominal IMPT dose distributions showed consistency in both CI and TC, indicated by average values of 1.6 (range, 1.46–1.82) and 45.7 Gy (range, 45.5 Gy – 45.7 Gy), respectively. Figure 7.2 shows dose distribution examples for the different strategies.



**Figure 7.2** | Sagittal view of color wash map examples of dose distributions are shown for the use of  $PTV_{old}$  (a) and  $PTV_{new}$  (b) combined with photon therapy and for the use of  $ITV_{old}$  (c) and  $ITV_{new}$  (d) combined with proton therapy. All dose distributions indicated adequate target (white contour) coverage while differences in dose to surrounding healthy tissue are observed.

For photon therapy, significant reductions in  $V_{15Gy}$ ,  $V_{30Gy}$ ,  $V_{45Gy}$  and  $D_{mean}$  for both bladder and bowel cavity were found after MRI-based target volume definition (Table 7.3, Figure 7.3). The dose to rectum and sigmoid was similar for both target definition strategies when applying photon therapy. Using conventional target volumes, the use of proton therapy instead of photon therapy was mostly pronounced in significant reductions in  $V_{15Gy}$ ,  $V_{30Gy}$ ,  $V_{45Gy}$  and  $D_{mean}$  for sigmoid and bowel cavity. Moreover, the combination of proton therapy and MRI-based target volumes resulted in additional dosimetric benefits compared to the current clinical standard, resulting in significant

reductions in bladder  $V_{15\text{Gy}}$ ,  $V_{30\text{Gy}}$ ,  $V_{45\text{Gy}}$  and  $D_{\text{mean}}$ . Compared to proton therapy using  $\text{ITV}_{\text{old}}$ , the application of proton therapy with  $\text{ITV}_{\text{new}}$  resulted in significant reductions in  $V_{30\text{Gy}}$ ,  $V_{45\text{Gy}}$  and  $D_{\text{mean}}$  for bladder, sigmoid and bowel cavity (Table 7.3).

**Table 7.3** | Comparison of the mean (standard deviation) dosimetric parameters of all patients for the dose distributions corresponding to the specific target volume and treatment modality. Statistical significant improvements ( $p < 0.05$ ) compared to current clinical practice (i.e. photon therapy,  $\text{pCTV}_{\text{old}}$ ) and proton therapy using conventional target volumes are indicated by an asterisks (\*) and a dagger (†), respectively.

	Photon therapy			Proton therapy		
	$\text{pCTV}_{\text{old}}$	$\text{pCTV}_{\text{new}}$		$\text{pCTV}_{\text{old}}$	$\text{pCTV}_{\text{new}}$	
<b>Bladder</b>						
$V_{15\text{Gy}}$ (%)	95.3 (7.8)	88.4 (10.3)	*	86.8 (7.7)	81.3 (15.2)	* *
$V_{30\text{Gy}}$ (%)	74.0 (8.4)	64.5 (10.5)	*	62.0 (10.7)	50.8 (16.0)	* †
$V_{45\text{Gy}}$ (%)	35.8 (7.2)	27.6 (6.8)	*	30.2 (11.3)	21.9 (13.8)	†
$D_{\text{mean}}$ (Gy)	37.2 (2.6)	34.0 (3.4)	*	33.0 (3.4)	29.3 (5.8)	* †
$D_{2\text{cc}}$ (Gy)	47.1 (0.6)	47.1 (0.6)		48.1 (0.9)	48.0 (0.9)	*
<b>Rectum</b>						
$V_{15\text{Gy}}$ (%)	100.0 (0.0)	100.0 (0.0)		99.7 (1.0)	99.8 (0.6)	
$V_{30\text{Gy}}$ (%)	99.7 (0.3)	99.6 (0.6)		84.3 (5.9)	81.5 (7.5)	* †
$V_{45\text{Gy}}$ (%)	47.1 (19.2)	51.7 (16.6)		40.9 (5.9)	40.3 (5.7)	
$D_{\text{mean}}$ (Gy)	43.5 (0.9)	43.5 (0.9)		39.7 (1.4)	39.2 (1.5)	* †
$D_{2\text{cc}}$ (Gy)	46.0 (0.3)	46.1 (0.4)		46.4 (0.2)	46.5 (0.2)	*
<b>Sigmoid</b>						
$V_{15\text{Gy}}$ (%)	96.0 (6.1)	92.0 (16.3)		83.7 (27.0)	82.6 (27.2)	*
$V_{30\text{Gy}}$ (%)	81.1 (27.1)	78.6 (28.3)		71.6 (25.3)	68.1 (26.3)	* †
$V_{45\text{Gy}}$ (%)	55.9 (21.7)	50.1 (23.2)	*	44.3 (18.2)	33.3 (15.6)	* †
$D_{\text{mean}}$ (Gy)	39.6 (6.8)	38.2 (8.4)	*	34.7 (10.7)	33.2 (10.9)	* †
$D_{2\text{cc}}$ (Gy)	46.9 (0.5)	46.9 (0.6)		46.9 (0.7)	46.8 (0.9)	
<b>Bowel cavity</b>						
$V_{15\text{Gy}}$ (cm <sup>3</sup> )	899.1 (287.3)	838.6 (320.7)	*	559.4 (207.0)	530.9 (212.1)	*
$V_{30\text{Gy}}$ (cm <sup>3</sup> )	501.4 (199.9)	460.3 (202.8)	*	382.3 (170.0)	337.9 (154.1)	* †
$V_{45\text{Gy}}$ (cm <sup>3</sup> )	268.0 (146.3)	226.3 (123.7)	*	227.7 (117.4)	173.4 (88.8)	* †
$D_{\text{mean}}$ (Gy)	20.7 (11.4)	16.9 (6.3)	*	12.8 (5.8)	11.8 (5.6)	* †
$D_{2\text{cc}}$ (Gy)	47.8 (0.5)	47.9 (0.5)		47.9 (0.4)	47.7 (0.4)	

*Abbreviations:* pCTV = primary clinical target volume; Gy = gray.

Figure 7.4 shows patient-specific NTCP values associated with small bowel acute toxicity for both the conventional and reduced target volumes, and for both photon therapy and proton therapy. Conventional photon therapy without the new target volume definition strategy ( $PTV_{old}$ ) resulted in an average toxicity probability of 25% (Table 7.4). Either MRI-based target volume definition or proton therapy yielded an average small bowel acute toxicity probability of 18% and the combination of both strategies resulted in an average 9% small bowel acute toxicity probability (Table 7.4).

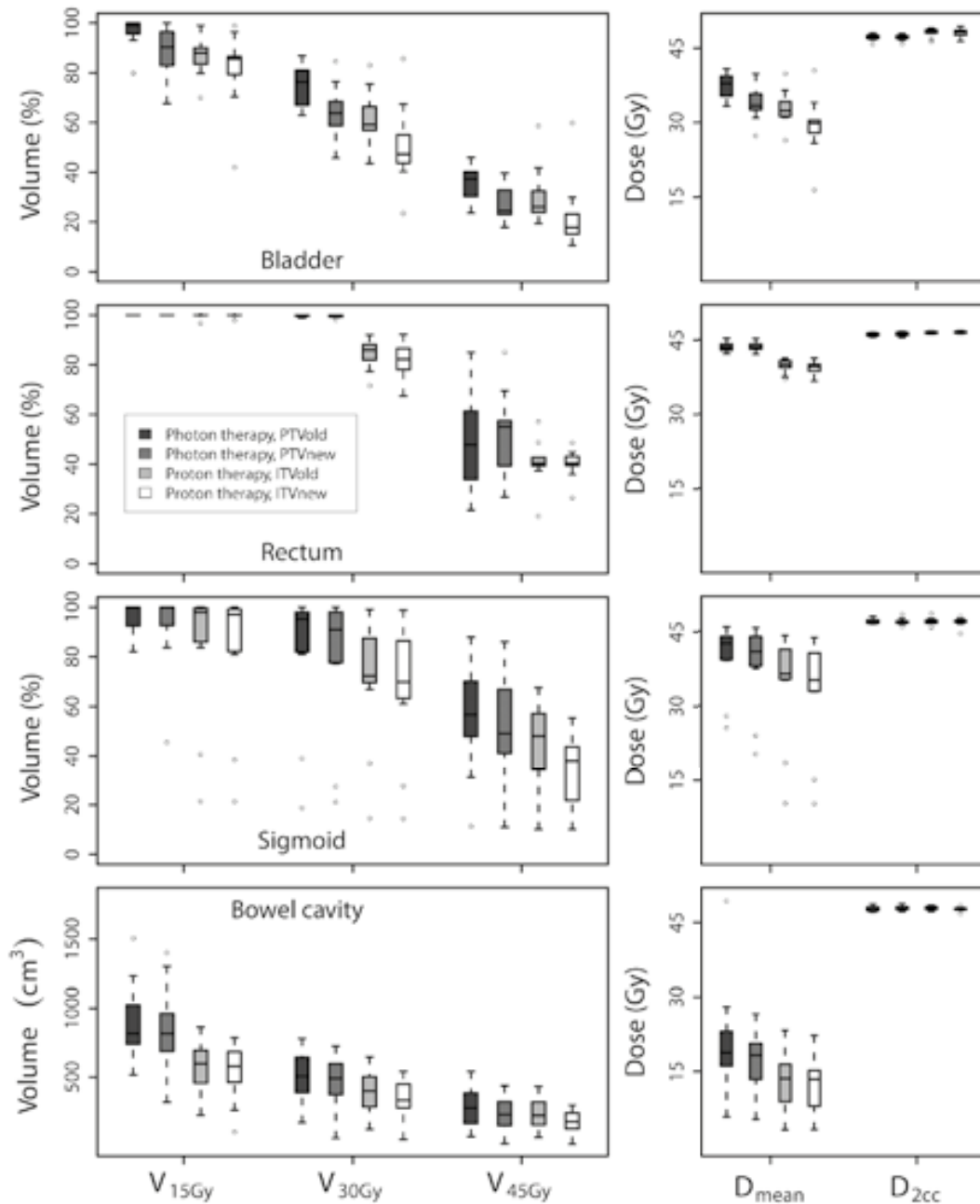


Figure 7.3 | Boxplots of DVH parameters over all planned dose distributions of all patients are shown for bladder, rectum, sigmoid and bowel cavity. Boxes represents upper and lower quartiles (IQR), the band inside the box the median value and the whiskers the highest (lowest) value within 1.5 IQR of the upper (lower) quartile.

Improvements in acute small bowel toxicity probability are mostly observed in patients with a high NTCP for standard treatment (Figure 7.4), caused by a consequently large volume of the bowel cavity receiving at least 45 Gy in current clinical practice (Figure 7.5). The proposed 10% NTCP reduction threshold as an acceptable indication for proton therapy was observed in four patients when using conventional target volumes. For these patients, the bowel cavity  $V_{45Gy}$  was at least 275 cm<sup>3</sup> in the standard treatment. If additionally the non-invaded uterine corpus was excluded from the target volume, a 10% NTCP reduction was expected in 6 out of the 11 patients of whom the bowel cavity  $V_{45Gy}$  was at least 200 cm<sup>3</sup>.

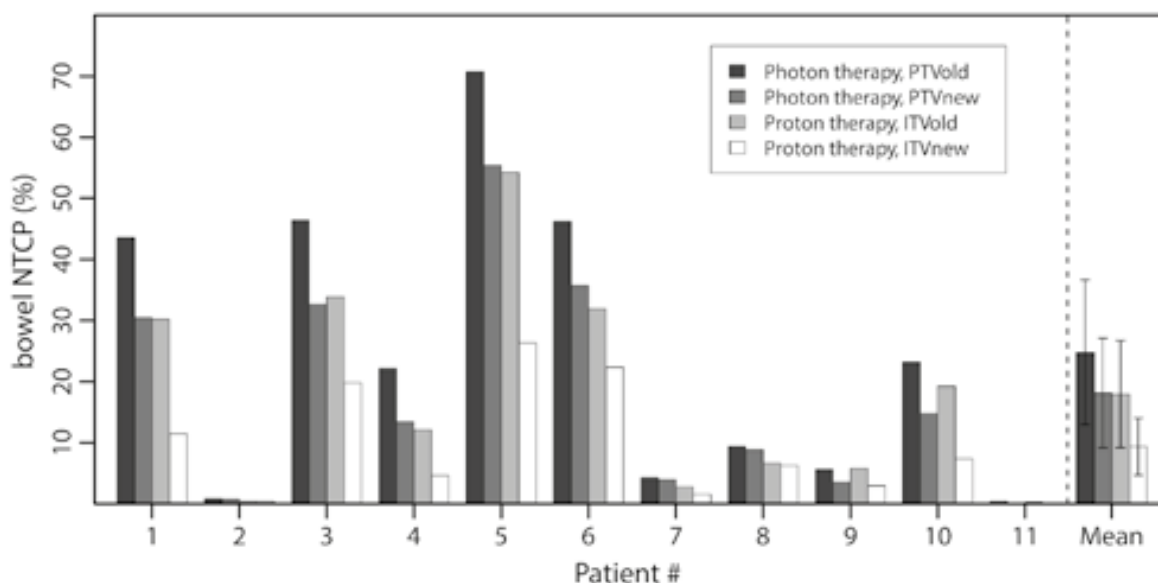
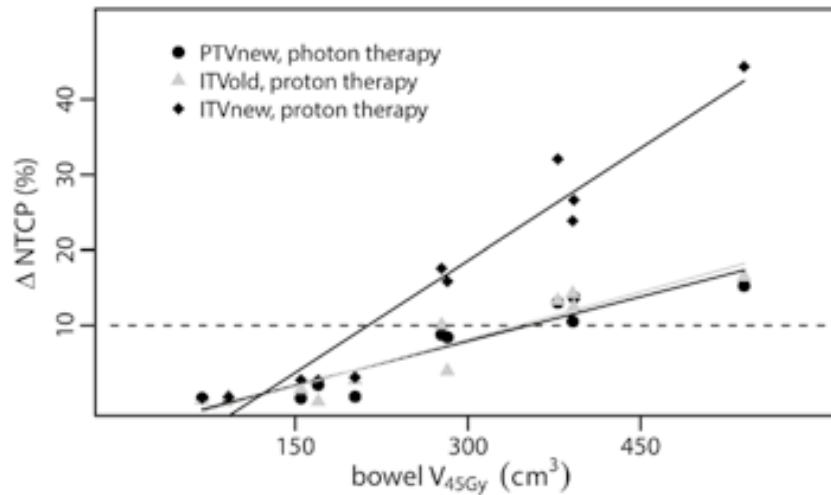


Figure 7.4 | Bar plots of the small bowel NTCP values are shown per patient according to different target volume definition strategies and different treatment modalities. The grouped bars at the right side represent mean NTCP values and the error bars indicate one standard deviation.

Table 7.4 | Comparison of the mean (range) bowel NTCP values (%) for the planned dose distributions of all patients, including the absolute NTCP differences.

	pCTV <sub>old</sub>	pCTV <sub>new</sub>	Absolute difference (%)
Photon therapy	25.0 (1.0–71.0)	18.0 (1.0–55.0)	7.0
Proton therapy	18.0 (1.0–54.0)	9.0 (1.0–26.0)	9.0
Absolute difference (%)	7.0	9.0	–

Abbreviations: pCTV = primary clinical target volume.



**Figure 7.5** | Absolute improvements in normal tissue complication probability ( $\Delta$  NTCP) compared to conventional high precision photon therapy without target volume reduction ( $PTV_{old}$ ) as a function of bowel cavity volume receiving 45 Gy in current clinical practice. Each dot represents a measurement for an individual patient and linear fits are added for visualization purposes. The dotted horizontal line indicates the 10%  $\Delta$  NTCP threshold above which proton therapy is indicated [172].

## 7.4 | Discussion

In this paper, we estimated the effect of two approaches on toxicity reduction for cervical cancer radiation therapy: 1) target definition improvement by excluding the non-invaded uterine corpus from the target volume using MRI and 2) the application of proton therapy. We found that, compared to current clinical standard EBRT, both approaches yielded an absolute NTCP reduction for acute small bowel toxicity of 7%. However, an absolute 16% reduction in acute small bowel toxicity probability may be obtained by combining MRI-based target volume definition with proton therapy. It is up to the radiation oncologist and the patient to decide on an individual basis which approach is desirable. As mentioned previously, the model-based approach suggested a 10% NTCP reduction threshold as an acceptable indication for taking proton therapy into consideration [172]. We estimated a NTCP reduction of at least 10% by proton therapy for 6 patients (55%) in whom the initial bowel cavity  $V_{45Gy}$  was above 200 cm<sup>3</sup> for MRI-based target volumes and in 4 patients (36%) above 275 cm<sup>3</sup> for the conventional target volumes. However, some aspects of both strategies for toxicity reduction in cervical cancer radiation therapy deserve some further discussion.

### MRI-based target volume definition

There is little clinical evidence about the safety of target volume reduction and about the benefit in terms of reduction of toxicity. Especially now advanced adaptive strategies combined with either

photon therapy or proton therapy are making precise dose delivery increasingly possible, methods for improved OAR sparing are warranted.

What we do know is that the uterus and the cervix is an embryological unit without a separating fascial plane, including interconnected lymphatics and the risk of cervical cancer growth into the uterine body is well known [173]. Since this infiltration was hard to detect for decades [174], guidelines continue to recommend inclusion of the uterine body within the CTV [92].

Nowadays with modern MRI techniques, uterine invasion can be assessed prior to treatment and is already widely used for brachytherapy planning [167,168]. Therefore, CTV concepts in EBRT derived from old times may possibly benefit from a modern reappraisal. If there is no sign of invasion into the uterine body, experts suggest that the uterine body can be excluded from the CTV, however, this could not be recommended due to the lack of evidence [29].

On the other hand, studies after trachelectomy have shown a higher risk of recurrences for tumors larger than 2 cm, however, these tumors typically recurred regional and not in the remaining uterine corpus [175,176]. These studies also indicate that histopathological characteristics such as lymph vascular space invasion (HR=3.2,  $P=0.03$ ) and deep stromal invasion (HR=4.5,  $P=0.005$ ) are the most important independent predicting factors for recurrence after surgery [177]. Furthermore, previous studies validated MRI-based tumor volume delineations with histopathology in cervical cancer and demonstrated the feasibility of accurate tumor definition on MRI [84,167].

Even in cervical cancer patients with FIGO stage IIB and IIIB, a local control of 96% and 86% can be achieved using image-guided adaptive brachytherapy with interstitial needles [161]. Although determined for brachytherapy, our findings suggest that the coverage of the high risk CTV, indicated by the  $D_{90\%}$ , is one of the most determining factors in successful local control for chemoradiation. The cause of recurrence in these patients is more likely due to the more challenging coverage of the tumor spread in direction of the parametria, without unacceptable exceeding OAR dose levels, rather than not reaching high dose levels in de uterine fundus.

If a large part of the uninvaded uterus can be safely excluded from the CTV, an adaptive strategy to compensate for the interfraction motion of the uterus may no longer be necessary for a subset of patients. However, target volume reduction will not necessarily results in a negligible benefit of an adaptive strategy. Substantial anatomical changes during the course of treatment may still influence dose delivery and requires an adaptive approach, especially during proton therapy. Therefore, an hybrid strategy including target volume reduction and treatment adaptations should be considered as a future solution.

## Proton therapy

Proton therapy is subject to delivery uncertainties caused by the sensitivity of protons to inter- and intra-fraction anatomical variations. To anticipate on day-to-day anatomical changes, our proton plans were robustly optimized and subsequently evaluated on robustness. Moreover, dose delivery

according to an adaptive strategy can be considered to avoid incorrect dose delivery due to large anatomical deformations [54,77].

The comparison between photon therapy and proton therapy in cervical cancer was performed previously based on the conventional target definition strategy [69,77]. Van de Schoot *et al.* [77] compared both treatment modalities combined with an adaptive strategy based on recalculated dose distributions and showed relative reductions in  $V_{15\text{Gy}}$ ,  $V_{30\text{Gy}}$  and  $V_{45\text{Gy}}$  for bladder, rectum and bowel cavity. Also, similar absolute reductions in small bowel NTCP of 7% were found. The comparison between photon therapy and proton therapy presented by Marnitz *et al.* [69] also showed similar results in favor of proton therapy. However, both model based studies compared the effect of different treatment modalities using conventional target volumes including the whole uterus.

In this study, we also estimated the additional benefit of excluding the uninvaded part of the uterine body combined with proton therapy. Since our results are solely based on planned dose distributions, the actual consequences of daily anatomical variation on DVH parameters were not taken into account. However, van de Schoot *et al.* [77] showed the feasibility of accurate dose delivery using an adaptive strategy under image guidance while maintaining the high-quality dose distributions. Given these results, it is expected that planned dose distributions presented in this study can be delivered accurately without additional deteriorations. Therefore, the NTCP reductions found in our study can be considered reliable, even when the non-invaded uterine fundus will be excluded from the CTV.

## Toxicity estimation

There is a fair consensus amongst radiation oncologists that uninvaded organs and healthy tissue should be avoided, and that new imaging techniques have become indispensable to distinguish healthy uterine tissue from tumor tissue. However, there is little clinical evidence about the safety of only including the invaded part of the uterine corpus and the associated reductions in toxicity. Late toxicity for bladder, sigmoid and rectum is mainly induced by the delivery of high doses and available NTCP models predicting these late toxicities require high dose levels. As a consequence, no NTCP differences will be observed for these OARs after cervical cancer EBRT with a prescribed dose of 46 Gy. Differences in NTCP corresponding to late toxicity are therefore not presented in this study. Nevertheless, acute toxicities already occur at lower dose levels and acute small bowel toxicity probabilities were estimated after cervical cancer EBRT.

Other available NTCP models for rectum, sigmoid, and bladder address toxicity probabilities in relation to the brachytherapy boost by using the  $D_{2cc}$  as independent variable [178,179]. However, in this study only the contribution of EBRT on toxicity probabilities is estimated without including the brachytherapy dose distribution. The accumulation of EBRT and brachytherapy dose distributions including associated toxicity probabilities will be explored in future.

## 7.5 | Conclusion

Improvements in target volume definition and proton therapy both lead to significant OAR dose reductions in cervical cancer radiation therapy as well as a significant decrease in small bowel toxicity. Moreover, the combination of both strategies resulted in an additional reduction of acute small bowel toxicity. The estimated benefit from target volume improvements combined with proton therapy is at least 10% for patients with bowel cavity  $V_{45\text{Gy}}$  above  $200\text{ cm}^3$ .