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## Original Article

## Inter-fraction motion robustness and organ sparing potential of proton therapy for cervical cancer



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## ABSTRACT

**Purpose:** Large-field photon radiotherapy is current standard in the treatment of cervical cancer patients. However, with the increasing availability of Pencil Beam Scanning Proton Therapy (PBS-PT) and robust treatment planning techniques, protons may have significant advantages for cervical cancer patients in the reduction of toxicity. In this study, PBS-PT and photon Volumetric Modulated Arc Therapy (VMAT) were compared, examining target coverage and organ at risk (OAR) dose, taking inter- and intra-fraction motion into account.

**Materials and methods:** Twelve cervical cancer patients were included in this in-silico planning study. In all cases, a planning CT scan, five weekly repeat CT scans (reCTs) and an additional reCT 10 min after the first reCT were available. Two-arc VMAT and robustly optimised two- and four-field (2F and 4F) PBS-PT plans were robustly evaluated on planCTs and reCTs using set-up and range uncertainty. Nominal OAR doses and voxel-wise minimum target coverage robustness were compared.

**Results:** Average voxel-wise minimum accumulated doses for pelvic target structures over all patients were adequate for both photon and proton treatment techniques (D98 > 95%, [91.7–99.3%]). Average accumulated dose of the para-aortic region was lower than the required 95%, D98 > 94.4% [91.1–98.2%]. With PBS-PT 4F, dose to all OARs was significantly lower than with VMAT. Major differences were observed for mean bowel bag  $V_{15Gy}$ : 60% [39–70%] for VMAT vs 30% [10–52%] and 32% [9–54%] for PBS-PT 2F and 4F and for mean bone marrow  $V_{10Gy}$ : 88% [82–97%] for VMAT vs 66% [60–73%] and 67% [60–75%] for PBS-PT 2F and 4F.

**Conclusion:** Robustly optimised PBS-PT for cervical cancer patients shows equivalent target robustness against inter- and intra-fraction variability compared to VMAT, and offers significantly better OAR sparing.

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One out of thirty cancer patients worldwide is diagnosed with cervical cancer [1] and the 5-year overall survival rate for the early stage group is 91% [2]. Half of all diagnosed cervical cancer patients is younger than 35 years [3], whereby late radiation-induced toxicities have a large influence on quality of life [4]. Thus, prevention of late radiation-induced side effects becomes increasingly relevant.

Currently, the standard treatment of cervical cancer consists of radiotherapy using photon Intensity Modulated Radiotherapy (IMRT) or Volumetric Modulated Arc Therapy (VMAT), combined with brachytherapy and concurrent chemotherapy [5]. Although radiotherapy contributes to high rates of loco-regional control, the dose to organs at risk (OARs) cannot be avoided and is

associated with acute and late bowel [6] and/or haematologic toxicity [7]. Proton therapy, in particular Pencil Beam Scanning Proton Therapy (PBS-PT), has resulted in clearly low or intermediate dose reductions compared to photon therapy for indications other than cervical cancer [8]. PBS-PT could therefore also play a role in the treatment of cervical cancer to reduce toxicity. Since larger treatment volumes lead to a higher dosimetric benefit with proton therapy, the greatest potential gain is expected for cervical cancer patients treated for pelvic and para-aortic nodal irradiation [9].

The main challenge in the treatment of cervical cancer is robust delivery of the dose in the presence of inter- and intra-fraction motion. The motion includes displacement and shape changes of the uterus and variation in filling of the bladder and rectum [10,11]. Inter- and intra-fraction motion may compromise target coverage and OAR sparing in photon treatment [12], but can be even more concerning in proton therapy due to the additional range uncertainty [13]. Due to the range uncertainty and the lack

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of high quality in-room imaging, proton therapy up until now has rarely been used to treat gynaecological malignancies.

The goal of this study was to investigate the robustness and organ-sparing potential of PBS-PT in comparison to VMAT for cervical cancer patients with an indication for pelvic and para-aortic nodal irradiation. The study took into account inter- and intra-fraction motion, using an intermediate Image Guided Radiotherapy (IGRT) approach.

## Materials and methods

### Patients and imaging

Twelve patients with primary cervical cancer treated in our centre between February 2017 and August 2018 were included in a prospective cohort study [NCT03022539]. They gave written informed consent to the acquisition of weekly repeated CT (reCT) scans. The study was approved by the local medical ethics committee. The inclusion criteria were cervical cancer patients, scheduled for curative photon radiotherapy, WHO score 0–2 and age  $\geq 18$  years. Five weekly CT scans were performed. In addition, one extra CT scan was acquired in week 1, 10 min after the first reCT was acquired (pre- and post-reCT). For each patient, a T2 weighted MRI, 4DCT and planning CT (planCT) scan in supine position were available. CT scans were acquired using a large bore 64-slice CT scanner (Somatom AS Open 64-RT Pro, Siemens Medical Systems, Erlangen, Germany), with a 2 mm slice thickness and an in-plane resolution of 1 mm. Patients were positioned using supports for the knees and feet.

### Target and prescription

Targets were manually contoured by a radiation oncologist (JB) on planCTs and all reCTs using the EMBRACE intermediate IGRT protocol and for the planCT, the patient was scanned with a full bladder [14]. For the construction of the pelvic ITV, the GTV was expanded with an isotropic margin of 0.5 cm and (combined with both the uterus and 2 cm uninvolved part of the vagina) expanded using a 0.5 cm margin in the left–right, and 1 cm in all other directions, except the inferior direction. The parametria were included as part of the cervical region. According to the EMBRACE

intermediate IGRT protocol imaging on different timepoints was incorporated. The pelvic ITV was co-registered and further expanded if target structures on the diagnostic CT and MRI were positioned outside the ITV. For the final ITV, the pelvic and para-aortic lymph nodes CTVs were added to simulate irradiation of the primary target and para-aortic lymph nodes. For three patients, the cranial extent of the planCT scan volume was inadequate to include the full lymph node volumes. ITV volumes were cropped up to 1.5 cm from the cranial border for these three patients.

ReCT target delineation was based on reCTs only, and included the GTV, uterus, vagina and lymph nodes. The planCT GTV was rigidly copied to the reCTs and adjusted to the position within the cervical region when considered necessary. The prescription dose was 45 Gy<sub>RBE</sub> in 25 fractions of 1.8 Gy<sub>RBE</sub>.

### Organs at risk

OARs were delineated on the planCT and all reCTs according to the RTOG atlas [15]. The specific OAR parameters analysed for this study proved significant relationships with OAR toxicity specifically for cervical cancer patients in the present literature and were:

- Bowel bag  $V_{15Gy}$  [16]
- Bone marrow  $V_{10Gy}$ ,  $V_{20Gy}$ ,  $V_{30Gy}$ ,  $V_{40Gy}$ ,  $D_{mean}$  [7,17–19]
- Femoral heads  $D_{mean}$  [20]
- Sacrum  $D_{mean}$ ,  $D_{50\%}$  [20,21]

Additionally, dose volume histograms (DVHs) of bowel bag, bone marrow, femoral heads, sacrum, rectum and bladder were presented.

### Treatment planning

Treatment plans were made using RayStation Research v6.99 (RaySearch Laboratories, Stockholm, Sweden). Three types of treatment plans, VMAT, PBS-PT two-field (2F) and PBS-PT four-field (4F) were created (Fig. 1) using standardised objectives and constraints for treatment planning consistency and reproducibility reasons. For VMAT, two 6MV arcs were used with an ITV-PTV margin of 0.5 cm. For PBS-PT 2F, two posterior oblique beams (left and right) were used with directions of 150°–165° and 195°–210°.

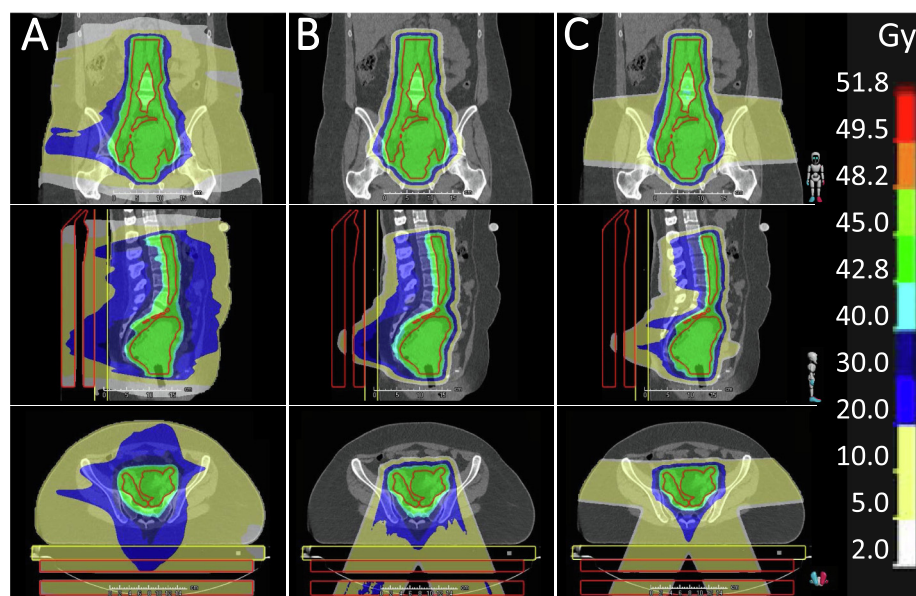


Fig. 1. Typical dose distributions for VMAT (A), PBS-PT 2F (B) and PBS-PT 4F (C) in axial, sagittal and coronal directions with ITV delineated in red.

The maximum hinge angle between the posterior beams was limited by the patient size and the treatment table width, to avoid beams travelling through the edges of the table. A range shifter was used in posterior beams if the ITV was located at depths shallower than 4 cm from the skin in the beam's eye view. The beam arrangement for PBS-PT 4F consisted of the PBS-PT 2F beams with the addition of two semi-lateral beams (gantry angles 85° and 275°, to avoid breathing motion in the anterior direction).

For PBS-PT 2F, full Intensity Modulated Proton Therapy (IMPT) was used. That is, the maximum dose per beam was not restricted. For PBS-PT 4F, all four beams contributed dose to the pelvic target, limited by the upper border of the sacrum. At this location a minimum dose of 10 Gy<sub>RBE</sub> per beam was requested for both posterior beams, to limit dose modulation and improve plan robustness. For PBS-PT, robust optimisation in RayStation was used with a 3% range and a 0.5 cm set-up uncertainty in all orthogonal directions [22,23]. Clinical dose distributions were calculated using the Monte Carlo dose calculation engine, with 1% uncertainty. In accordance with clinical practice to increase plan robustness to changes in gas, any air present in the bowel or rectum was overridden with a density of 1 g/cm<sup>3</sup> in the optimisation, thereafter the plan was recalculated without any air override. The same strategy was used for VMAT.

Robustness evaluation was performed using 0.5 cm set-up uncertainty with isocenter shifts in 14 directions; six in the cardinal directions and eight along the diagonal of each octant in 3D space [24]. For PBS-PT, 3% range uncertainty was added. This robustness evaluation produced 14 (28) scenarios and the voxel-wise minimum (vox min) dose was derived as the composite of minimum dose values per voxel from all scenarios [23,25]. Similar, voxel-wise maximum (vox max) dose was derived as the composite of maximum dose values.

Treatment plans were normalised to fulfil the clinical goals [23]:

- ITV D98  $\geq$  42.75 Gy<sub>RBE</sub> (95% of prescribed dose) in vox min
- Nominal ITV D50% =  $45 \pm 0.5$  Gy<sub>RBE</sub> between patients, range <0.5 Gy<sub>RBE</sub> per patient between the three techniques
- Vox max ITV D2% < 107% of prescribed dose

All final treatment plans were reviewed for clinical acceptability by a radiation oncologist (JB).

#### Evaluation of inter- and intra-fraction motion robustness

The reCTs were rigidly aligned with the planCT, allowing rotations up to  $-/+ 2^\circ$  using a pelvic reference box that included the pelvic bones and lower lumbar spine. The nominal plan was recalculated on the reCTs and robustness evaluation was done using an anisotropic set-up uncertainty of 0.15, 0.15 and 0.18 cm in the right-left, anterior-posterior and inferior-superior direction, following from an internal assessment accounting for systematic and random intra-fraction set-up error [10], re-positioning and isocenter versus imaging accuracy [23,26–28]. For PBS-PT, 3% range uncertainty was added. Again, vox min doses were derived for every reCT. The values for set-up uncertainty are lower than the 0.5 cm used for robustness evaluation during treatment planning, since by using reCTs the inter-fraction variability is already taken into account by the new anatomy.

Planning techniques were compared by evaluating the vox min D98 target dose ratio between the planCTs and reCTs for GTV, uterus, vagina and lymph nodes, and relating them to the bladder and rectum volume differences.

Accumulated doses were calculated using deformable image registration (DIR) between the planCT and reCT using the hybrid intensity and structure-based method in RayStation, with target

substructures as controlling regions of interest (ROIs). All vox min reCT doses were warped back to their planCT, assigning an equal number of fractions to each reCT. The resulting GTV, uterus, vagina and lymph nodes accumulated doses were evaluated. OAR doses were compared between techniques for nominal planCTs and reCTs. Differences were correlated to initial bowel bag volume and patient weight. Intra-fraction robustness was analysed by nominal dose differences between pre- and post-reCT in week 1 for targets ( $\Delta$ D98) and OARs. Statistical target coverage and OAR sparing differences among the techniques were tested using the Wilcoxon matched-pair signed-rank test in IBM SPSS Statistics 23, with a 0.05 significance level.

#### Clinical re-planning

According to our IGRT (CBCT) protocol, in case of systematic changes in the position of the vagina and/or uterus compared to the PTV, dose on an extra reCT is evaluated and a clinical plan adaptation is performed if necessary. This was the case for three patients due to large rectal filling changes (patient 3), uterus fluid accumulation (patient 4) and large weight reduction (patient 5). Re-planning was performed on reCT week 2 (patient 3) and week 3 (patient 4 and 5). The same strategy was used for the photon and proton plans in this study.

#### Results

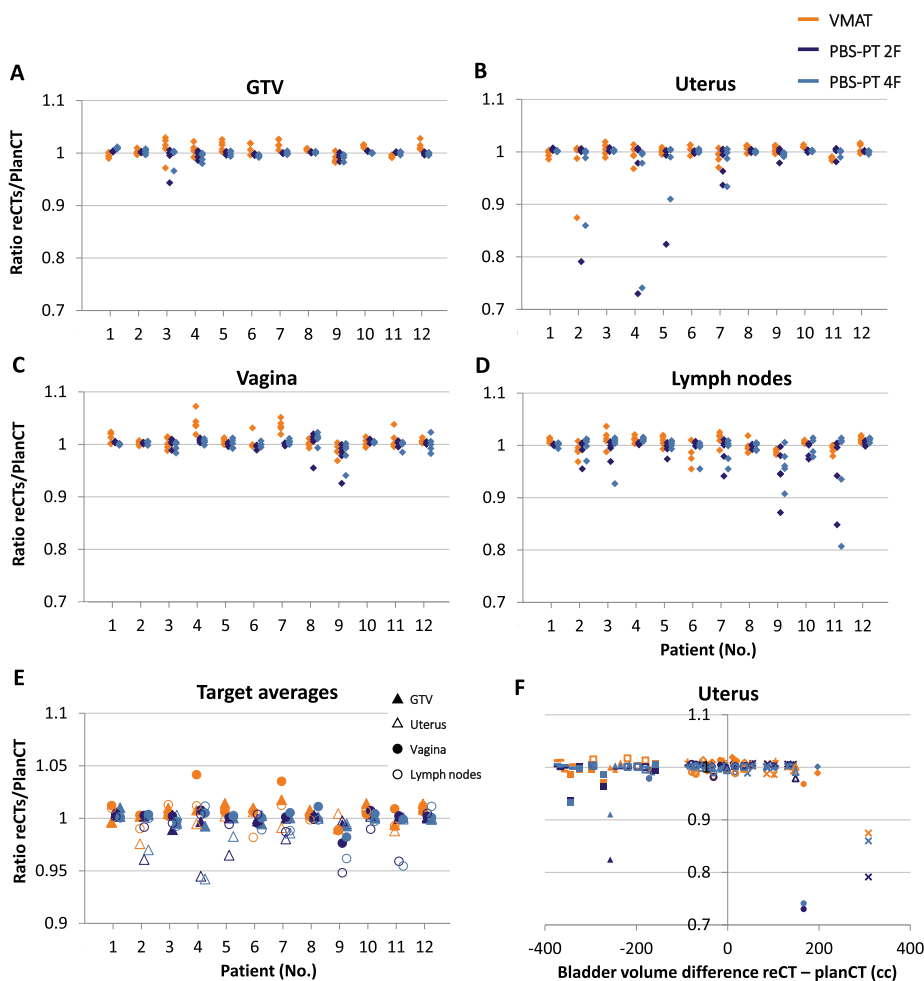
In total, 58 reCTs of twelve patients were included in the analysis, for two patients only four reCTs were acquired. Patient and target volume characteristics can be found in Fig. 1. ITV conformity indices for all initial treatment plans can be found in Fig. 2.

For the GTV and vagina, the reCTs vs planCT vox min D98 target dose ratio was >0.95 for all plans, except for one reCT resulting in a ratio <0.95 for GTV for PBS-PT 2F (94.3%) and vagina PBS-PT 2F and 4F (>92.6%) (Fig. 2A, patient 3 and Fig. 2C, patient 9, respectively). For the uterus, four reCTs (patients 2, 4, 5, 7) resulted in a reCT/planCT ratio <0.95, 1× VMAT and 4× PBS-PT 2F and 4F (Fig. 2B). For the lymph nodes, four reCTs also had a reCT/planCT ratio <0.95 (patient 3, 7, 9, 11), 3× PBS-PT 2F and 3× PBS-PT 4F (Fig. 2D).

Average reCT vs planCT vox min D98 target dose ratio was >0.94 for all patients for all target structures [94.2–104.2%] (Fig. 2E). For the uterus, the lower coverage was related to a larger difference in reCT bladder volume compared to the planCT (Fig. 2F). The uterus coverage was maintained if the bladder volume difference was within 166 cc. The vox min D98 target doses on the reCTs and average reCT target doses per patient showed similar target coverage for all three techniques (Fig. 3, Supplementary Fig. 4). No significant difference in planCT-reCT dose differences was found for the uterus (Table 1). For the other targets, the dose difference was significantly larger for the proton techniques.

The vox min D98 accumulated dose was >95% for GTV and vagina for all patients and for uterus in 10/12 patients (2 patients >91.7%, Table 2). For lymph nodes, the D98 accumulated dose was >91.1% in all patients. Vox min D98 doses for the target substructures of the initial accepted plans are found in Supplementary Fig. 3.

The nominal OAR doses calculated on the planCT and reCTs showed significantly lower OAR doses for both PBS-PT techniques compared to VMAT, except for sacrum PBS-PT 2F (Table 3, Supplementary Fig. 5). Comparing reCT and planCT, the  $V_{15Gy}$  (%) of the bowel bag and  $V_{10Gy}$  (%) of the bone marrow showed similar OAR robustness for all techniques. However, plans based on VMAT provided less OAR sparing than those based on PBS-PT (Fig. 3A and B). The mean DVHs (i.e. composite DVHs constructed by averaging dose to volume over



**Fig. 2.** Target coverage ratio reCT/planCT (voxel-wise minimum D98%) for 12 patients (GTV (A), uterus (B), vagina (C) and lymph nodes (D)). Average reCT/planCT ratio per patient per target structure (E). Uterus target coverage ratio vs bladder volume difference (reCT–planCT) (F), different symbols represent the 12 different patients.

**Table 1**  
D98% reCT target dose difference compared to planCT (dose reCT–dose planCT) for 12 patients (voxel-wise minimum).

Target		Target dose differences (Gy)			Difference		
		VMAT	PBS-PT 2F	PBS-PT 4F	VMAT – PBS-PT 2F p value	VMAT – PBS-PT 4F p value	PBS-PT 2F – PBS-PT 4F p value
GTV	Mean	0.3	0.0	0.0	<0.001	<0.001	0.340
	IQR	0.8	0.2	0.3			
Uterus	Mean	–0.1	–0.5	–0.4	0.058	0.017	0.088
	IQR	0.7	0.2	0.3			
Vagina	Mean	0.4	0.0	0.0	0.002	0.003	0.772
	IQR	0.7	0.2	0.3			
Lymph nodes	Mean	0.1	–0.4	–0.3	<0.001	0.009	<0.001
	IQR	0.9	0.5	0.8			

all patients) for bowel bag and bone marrow for the planCT and reCTs showed that both PBS-PT techniques provided better OAR sparing than VMAT (Fig. 3C and D). PBS-PT 2F showed slightly better bowel bag sparing than PBS-PT 4F, and PBS-PT 4F provided sparing gain in the higher dose regions for bone marrow compared to PBS-PT 2F. The mean DVHs for the femoral heads and the bladder showed better OAR sparing for both PBS-PT techniques compared to VMAT and mean sacrum PBS-PT 4F DVH was in favour over VMAT (Supplementary Fig. 6). The mean rectum DVHs were similar for both PBS-PT 4F and VMAT

and the DVHs for the femoral heads showed a similar trend as for the bone marrow DVH. The smaller the bowel bag volume and patient’s weight, the smaller the  $V_{15Gy}$  (%) bowel bag sparing capabilities of PBS-PT compared to VMAT (Fig. 3E and F). With the other OARs, no relationship was found between OAR sparing and bowel bag volume or body mass parameters.

PBS-PT and VMAT showed similar target robustness against intra-fraction motion:  $\Delta D98$  was within 1 Gy (Supplementary Fig. 7). Intra-fraction robustness was comparable for all specific OAR parameters (Supplementary Fig. 8).



**Table 2**

Target D98% accumulated dose for 12 patients (voxel-wise minimum).

Dose target (Gy)	Treatment technique	PT01	PT02	PT03	PT04	PT05	PT06	PT07	PT08	PT09	PT10	PT11	PT12
GTV	VMAT	43.9	43.8	44.1	44.6	44.3	43.9	44.3	44.1	42.9	44.3	43.7	44.3
	PBS-PT 2F	43.9	44.1	43.6	44.0	44.0	43.9	44.1	44.0	44.0	44.1	44.0	43.9
	PBS-PT 4F	43.9	43.8	43.9	43.9	44.1	43.9	44.1	44.0	43.9	44.0	44.0	43.9
Uterus	VMAT	44.1	42.9	44.1	44.0	44.7	43.9	44.2	44.5	43.7	44.3	43.8	44.4
	PBS-PT 2F	43.7	<b>42.2</b>	43.9	<b>41.3</b>	43.9	43.8	43.9	43.9	43.5	43.9	43.8	43.8
	PBS-PT 4F	43.9	42.9	44.0	<b>41.3</b>	44.0	44.0	44.0	44.0	43.8	44.0	43.9	43.9
Vagina	VMAT	43.5	44.0	44.1	44.5	44.2	43.6	44.4	44.0	43.3	43.8	42.9	43.5
	PBS-PT 2F	43.7	43.6	43.8	43.7	43.8	43.7	43.8	43.8	42.9	43.8	43.7	43.6
	PBS-PT 4F	43.6	43.7	43.8	44.0	43.7	44.0	44.0	44.1	43.3	43.9	43.6	43.2
Lymph nodes	VMAT	43.2	42.8	43.7	44.2	43.8	42.9	43.9	43.0	<b>42.4</b>	44.0	43.1	43.7
	PBS-PT 2F	43.2	<b>42.6</b>	<b>42.7</b>	43.3	42.8	43.0	<b>42.4</b>	43.2	<b>41.0</b>	<b>42.5</b>	<b>41.3</b>	43.2
	PBS-PT 4F	43.2	<b>42.6</b>	<b>42.6</b>	43.1	43.1	<b>41.8</b>	<b>42.7</b>	42.9	<b>41.3</b>	<b>42.5</b>	<b>41.0</b>	43.2

≥95%.

**91–95%.****Table 3**

Organ at risk dose; VMAT vs PBS-PT 2F and 4F, all planCTs and reCTs of 12 patients.

OAR	Parameter		OAR doses			OAR dose differences		
			VMAT	PBS-PT 2F	PBS-PT 4F	VMAT – PBS-PT 2F p value	VMAT – PBS-PT 4F p value	PBS-PT 2F – PBS-PT 4F p value
Bowel bag	$V_{15\text{Gy}}$ (%)	Mean	60	30	32	<0.001	<0.001	<0.001
		IQR	12	21	23			
Bone marrow	$V_{10\text{Gy}}$ (%)	Mean	88	66	67	<0.001	<0.001	0.620
		IQR	9	5	7			
	$V_{20\text{Gy}}$ (%)	Mean	69	59	41	<0.001	<0.001	<0.001
		IQR	5	5	5			
	$V_{30\text{Gy}}$ (%)	Mean	45	40	24	<0.001	<0.001	<0.001
		IQR	5	5	6			
	$V_{40\text{Gy}}$ (%)	Mean	19	15	9	<0.001	<0.001	<0.001
		IQR	4	3	2			
	$D_{\text{mean}}$ (Gy)	Mean	26.6	21.4	18.4	<0.001	<0.001	<0.001
		IQR	2.1	1.9	2.6			
Femoral heads	$D_{\text{mean}}$ (Gy)	Mean	21.7	6.6	9.5	<0.001	<0.001	<0.001
		IQR	6.2	4.9	3.9			
Sacrum	$D_{\text{mean}}$ (Gy)	Mean	36.0	36.0	24.2	0.950	<0.001	<0.001
		IQR	2.7	1.0	3.3			
	$D_{50\%}$ (Gy)	Mean	35.8	36.6	21.0	0.014	<0.001	<0.001
		IQR	3.2	1.4	4.5			

IQR, interquartile range.

## Discussion

This in-silico planning study of cervical cancer patients with an indication for pelvic and para-aortic nodal irradiation showed that target coverage for both VMAT and robustly optimised PBS-PT 2F and 4F was robust to inter- and intra-fraction motion. PBS-PT planned significantly lower doses in the bowel bag and bone marrow, potentially resulting in fewer side effects for patients, and consequently an improvement in their quality of life.

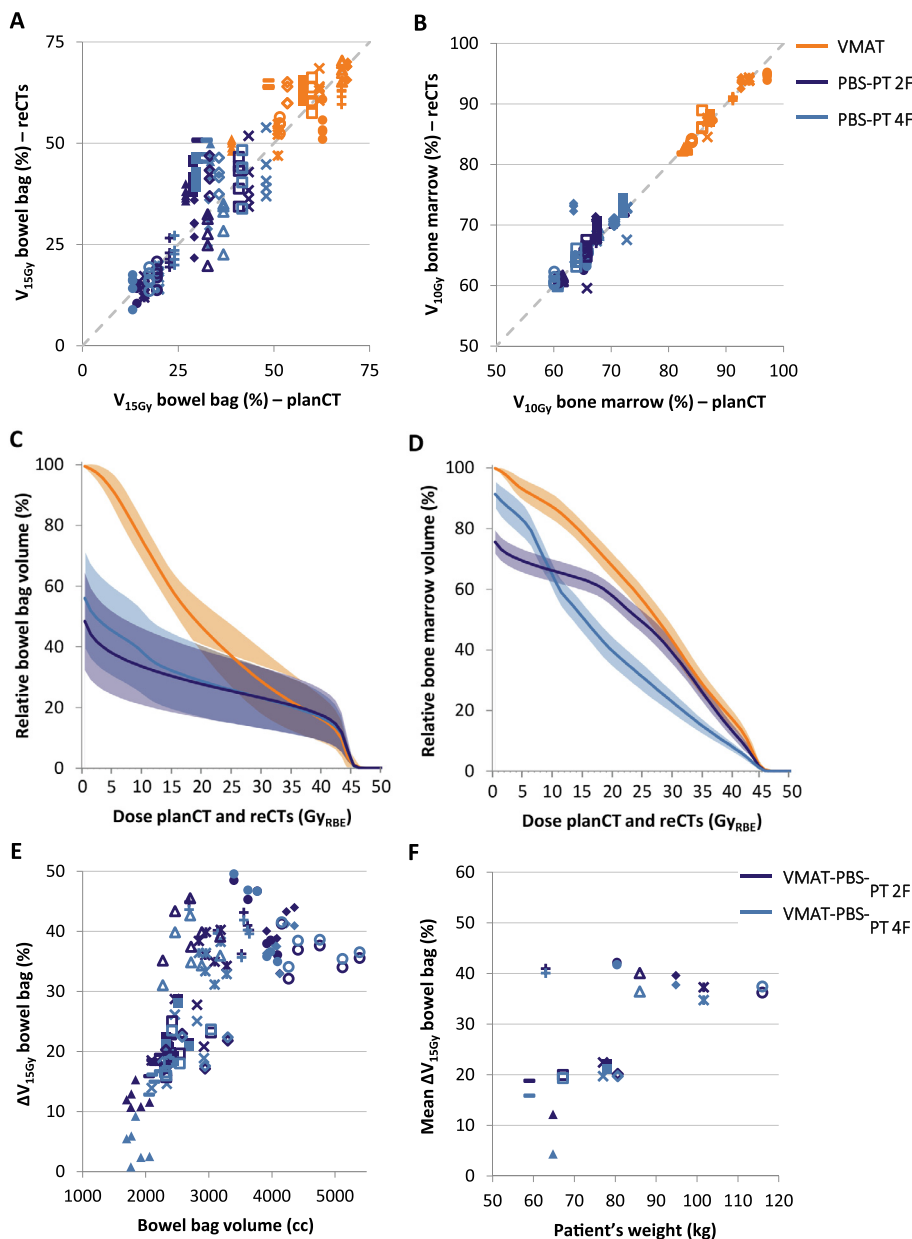
Several studies have shown the benefit of potential OAR sparing using protons (entirely or in part) [24,29–32]. Nevertheless, these studies did not investigate robust planning and/or robustness against the effects of inter- and intra-fraction motion, and did not take into account relevant OARs such as bowel bag and bone marrow. We investigated robust optimised PBS-PT including robustness evaluation for set-up errors and anatomical changes, using manual contouring of targets and OARs based on multiple CT datasets.

Van de Schoot et al. [24] showed the benefit of protons over photons using a plan of the day strategy, with a mean photon bowel cavity  $V_{15\text{Gy}}$  of 1673 cm<sup>3</sup>, compared to the 1795 cm<sup>3</sup> bowel bag in our study. In that study, ten out of twelve patients were treated with pelvic radiotherapy only, resulting in lower bowel

bag doses than for our pelvic and para-aortic nodal irradiation. The mean proton bowel cavity  $V_{15\text{Gy}}$  was 1013 cm<sup>3</sup> compared to our 852 cm<sup>3</sup> and 899 cm<sup>3</sup> using PBS-PT 2F and 4F. Although we did not apply a plan of the day concept, our  $V_{15\text{Gy}}$  bowel cavity volumes were lower for both proton techniques. Plan of the day strategies are not widely used because of the labour-intensive workflow and sub-optimal (CBCT) online image quality. In addition, this strategy mainly reduces the effect of uterus position difference but does not account for anatomical (range) changes such as rectum volume differences and intra-fraction motion. In our study, instead of using plan of the day strategies, inter- and intra-fraction target robustness is demonstrated with the use of robust optimisation and an intermediate IGRT strategy [14].

Song et al. [30] and Lin et al. [31] showed lower bone marrow  $V_{30\text{Gy}}$  and  $V_{35\text{Gy}}$  for IMRT compared to proton therapy. This is in contrast with our study where bone marrow dose is lower for PBS-PT compared to VMAT for the entire DVH, especially for the 4F technique (Fig. 3D). This could be explained by the use of passive scattering proton therapy and an extra anterior-inferior oblique beam as used by Song et al. Also, both of these studies used enlarged margins for nodal targets and excluded vertebrae.

Van de Schoot et al. [33] analysed the optimal PBS-PT beam set-up. They showed that PBS-PT 4F potentially improves planCT CTV



**Fig. 3.** Comparison of nominal OAR doses for bone marrow and bowel bag.  $V_{15Gy}$  (%) bowel bag (A) and  $V_{10Gy}$  (%) bone marrow (B) reCTs vs planCT. Average bowel bag (C) and bone marrow (D) DVH on planCT and reCTs + standard deviation. PlanCT and reCT difference  $V_{15Gy}$  (%) bowel bag (E) vs bowel bag volume (cc) and mean difference  $V_{15Gy}$  (%) bowel bag (F) vs patient's weight (kg). Different symbols represent the 12 different patients.

coverage as well as rectum and bladder sparing when compared to PBS-PT 2F. The authors used beam angles of 90° and 270° for PBS-PT 2F, with an additional beam angle of 0° for PBS-PT 3F, and two additional angles of 30° and 330° for PBS-PT 4F. However, no inter-fraction motion analysis was performed. We chose to use posterior beam angles, since 4DCTs revealed breathing and bowel motion in the anterior direction (Supplemental Material 9). While PBS-PT 2F showed the lowest bowel bag doses, PBS-PT 4F showed both lower sacrum doses and reduction of relative bone marrow receiving higher dose. In our study, in-house clinical settings and beam models for VMAT and PBS-PT were used, resulting in clinically deliverable plans. Estimated delivery time of all fields was approximately 5 minutes for both VMAT and PBS-PT 2F and 8 minutes for PBS-PT 4F. Since PBS-PT 2F will reduce radiation time significantly, this can possibly lead to a reduction of intra-fraction

motion resulting in better target coverage and is therefore a favourable PBS-PT technique to use [34].

Our study has some limitations. Patient position and anatomy during reCT imaging could be suboptimal. In the treatment room, bladder and rectum filling will be checked using CBCT, and optical surface scanning and orthogonal X-rays will be used to set-up the patient and reduce rotational errors in positioning. ReCT positioning was performed based on isocenter markings only. The positioning was only done on the pelvic region since in clinical practice, patients had no indication for para-aortic nodal irradiation. Therefore, the position of the upper body was not adjusted, which could result in misalignments due to, for example, spine flexion, causing loss in para-aortic lymph node coverage and OAR dose robustness. Therefore, inter-fraction changes might be overestimated in this study. For reCT robustness evaluation, uterus intra-fraction

set-up errors [10] were applied, while these errors for the lymph node region are smaller in reality (limited movement with respect to the bones). This led to a pessimistic para-aortic target coverage. If proton therapy will be implemented in clinical practice, the use of light surface scanning during treatment will allow correct positioning of both the pelvic and the para-aortic region and daily CBCT imaging will avoid treatment in extreme anatomical deviations. Future research could aim to improve robust planning optimisation and evaluation strategies including different uncertainties for uterus and lymph nodes [35].

We calculated accumulated dose by summing and weighting of voxel-wise minimum doses of the weekly reCTs. Voxel-wise minimum doses represent robustness against intra-fraction set-up errors, including errors for re-positioning and isocenter versus imaging accuracy, as well as 3% range uncertainty. This might be too pessimistic since the voxel-wise minimum dose is not a real dose scenario, and in reality dose distributions will be more favourable.

Furthermore, the interpretation of the accumulated dose is not straightforward, since it includes uncertainties due to different target and OAR volumes over reCTs. We therefore extensively evaluated dose distributions, including manual delineations, for every reCT. Also, the manual delineations were used to control the deformation vector field and minimise the influence of inaccuracies in the DIR. Overall, the average reCT voxel-wise minimum target doses per patient showed a trend similar to that of accumulated doses (Table 2, Supplementary Fig. 4).

This study demonstrates the feasibility of robust PBS-PT for cervical cancer patients with an indication for pelvic and para-aortic nodal irradiation, using the EMBRACE intermediate IGRT protocol. Presented techniques are in accordance with our standard operational procedures and ready to use in clinical practice. This study shows that target coverage robustness of PBS-PT plans is similar as that of our current clinical VMAT treatment plans, while proton treatment offers similar or significantly better OAR sparing. Attention should be paid to patient alignment of the para-aortic lymph node area to warrant sufficient lymph node coverage during proton therapy.

## Conflicts of interest

None.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.radonc.2020.09.022>.

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