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Impact of interfractional target motion in locally advanced cervical cancer patients treated with spot scanning proton therapy using an internal target volume strategy

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ABSTRACT

Background and purpose: The more localized dose deposition of proton therapy (PT) compared to photon therapy might allow a reduction in treatment-related side effects but induces additional challenges to address. The aim of this study was to evaluate the impact of interfractional motion on the target and organs at risk (OARs) in cervical cancer patients treated with spot scanning PT using an internal target volume (ITV) strategy.

Methods and materials: For ten locally advanced cervical cancer patients, empty and full bladder planning computed tomography (pCT) as well as 25 daily cone beam CTs (CBCTs) were available. The Clinical Target Volume (CTV), the High Risk CTV (CTV_{HR}) (gross tumor volume and whole cervix), the non-involved uterus as well as the OARs (bowel, bladder and rectum) were contoured on the daily CBCTs and transferred to the pCT through rigid bony match. Using synthetic CTs derived from pCTs, four-beam spot scanning PT plans were generated to target the patient-specific ITV with 45 Gy(RBE) in 25 fractions. This structure was defined based on pre-treatment MRI and CT to anticipate potential target motion throughout the treatment. D98% of the targets and V40Gy(RBE) of the OARs were extracted from the daily anatomies, accumulated and analyzed. In addition, the impact of bladder volume deviations from planning values on target and bowel dose was investigated.

Results: The ITV strategy ensured a total accumulated dose >42.75 Gy(RBE) to the CTV_{HR} for all ten patients. Two patients with large bladder-related uterus motion had accumulated dose to the non-involved uterus of 35.7 Gy(RBE) and 41.1 Gy(RBE). Variations in bowel V40Gy(RBE) were found to be correlated (Pearson $r = -0.55$; p-value <0.0001) with changes in bladder volume during treatment.

Conclusion: The ITV concept ensured adequate dose to the CTV_{HR}, but was insufficient for the non-involved uterus of patients subject to large target interfractional motion. CBCT monitoring and occasional replanning is recommended along the same lines as with photon radiotherapy in cervical cancer.

1. Introduction

Using the characteristic Bragg peak, PT enables more localized dose deposition than photon therapy, and allows for additional sparing of healthy tissue and organs at risk (OARs) surrounding the target. The advantages of protons compared to photons have been shown in planning studies, which found that protons significantly reduced dose to the OARs [1–3]. Higher doses and larger irradiated volumes of the OARs are in general correlated with increased prevalence and grade of toxicity [4,5]. Therefore, substituting photons by protons for the External Beam Radiation Therapy (EBRT) phase of the treatment of locally advanced cervical cancer may allow patients to benefit from a lower prevalence of side effects.

However, before initiating PT for gynecological malignancies, some challenges need to be addressed. In particular, the impact of uncertainties related to density variations and/or organ motion needs to be evaluated and potentially mitigated [6,7]. With regard to organ motion, around one out of five cervical cancer patients experience substantial

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interfraction movement of the uterus, mainly depending on variable bladder and rectum filling [8,9]. Bladder and rectum volume variations during the radiotherapy course have previously been found to cause suboptimal target coverage in cervical cancer patients [9,10]. This target under-dosage may even be accentuated when PT and in particular spot scanning is used because of the steeper dose gradients obtained.

In photon therapy, a conventional strategy to mitigate the impact of interfraction motion is the use of ITV margins which are often defined based on pre-treatment imaging with the aim of including the most likely positions of the primary target during the treatment. Adaptive RT, by means of offline or online re-planning [11,12] modifies initial treatment plan parameters throughout the treatment to provide an optimized dose. Adaptive strategies have been proposed for pelvic malignancies in order to achieve with a limited treated volume an adequate target coverage despite interfractional motion [2,13–15]. Van de Schoot et al. [2] demonstrated the feasibility of an adaptive plan library strategy for cervical cancer patients with PT and showed its superiority over a similar approach with photons. Busch et al. demonstrated that on-line dose-guided PT better accounts for large interfractional organ motion in the pelvis than image guided PT [12]. ITV strategies can also be combined with adaptive replanning as demonstrated by Jensen et al. [16] with a CBCT monitoring strategy in photon radiotherapy. Furthermore, a recent study by Gort et al. [17] compared the robustness of ITV-based treatment plans with Pencil Beam Scanning PT (PBS-PT) and photon therapy. Based on the analysis of repeat CT scans they found PT to be equally robust to photons, in addition to significantly reducing the OARs doses. This study was based on simulations in weekly CBCT scans for twelve patients.

The purpose of our study was to validate, in an independent patient cohort, the findings of previous studies that an ITV approach can be used with spot scanning PT to compensate for interfractional anatomical variations occurring during the whole radiotherapy course. This purpose was addressed by quantifying the total accumulated dose on targets and OARs based on daily CBCTs acquired throughout 25 fractions of radiotherapy.

2. Materials and methods

2.1. Patient data

In this study, a data set of ten locally advanced cervical cancer patients previously treated with photons was utilized. Our cohort consisted in a retrospective planning study with fully anonymity, which is why neither Institutional Review Boards review nor patient consent was required according to local regulations. For each patient the following images were available: two CT scans in treatment position (empty and full bladder), pre-treatment magnetic resonance (MR) scan in treatment position, as well as 25 on-board acquired CBCT scans, which were used to position the patient prior to each fraction. EBRT was administered to all patients with a prescribed dose of 45 Gy in 25 fractions to the target related to the primary tumor and the elective lymph nodes. Three patients received a simultaneously integrated boost of 55 Gy to metastatic lymph nodes. All patients were contoured according to the EMBRACE II guidelines [18].

2.2. Treatment planning

The CT numbers of CBCT scans do not accurately predict the relative stopping power ratios for proton dose calculation. In order to compensate for this, synthetic CTs (sCTs) were generated based on information from the CBCT scans and the pCTs. For each patient, two sCTs were created: one for planning purposes, reflecting the anatomy of the patient on the full bladder pCT. In addition, a sCT was generated to reflect the anatomy of the patient at each fraction and extract fractional dose parameters. The sCTs were generated by taking the full bladder pCT outer body contour which was filled with water CT numbers, except for bones, which kept their original CT values. In addition, as shown in Fig. 1 (right), the primary CTVs and bladder contours taken from the CBCT scans were filled with their corresponding CT numbers from the full bladder pCT. The use of sCTs ensured that no uncertainties other than interfractional motion of the pelvic organs influenced our study. As such, interfractional density variations were not included in the analysis. This approach was chosen in order to study one particular aspect of the problem, i.e. interfractional internal organ motion and not diluting the findings with other effects. An example of cervix-uterus interfraction motion is shown in Fig. 1 as well as a planned dose distribution for comparison.

The simulations were performed using a generic machine in the proton Eclipse treatment planning system (v 13.7, Varian Medical Systems, Palo Alto, USA) as a representation of a Varian ProBeam spot scanning system. A four-beam configuration was used: two lateral opposed and two posterior oblique (90°, 150°, 210°, and 270°) with multi-field optimization (MFO). The contribution of each field to the total dose was not constrained. The same ITV target volume as the one defined for the clinical photon plans was utilized, and a plan was optimized on the planning sCTs to the same dose prescription as for photon treatment with the assumption of Relative Biological Effectiveness (RBE) of 1.1. The beam parameters of the resulting plans were thereafter applied on the sCTs and the dose recalculated for all treatment fractions with their respective OARs from CBCTs.

The target volumes related to the primary tumor were identified on MRI and included: gross tumor volume (GTV-T), CTV_{HR} (GTV-T plus whole cervix), and low risk CTV (CTV_{LR}) (CTV_{HR}, whole uterus, whole parametria, upper vagina, and a margin towards bladder and rectum). For the purpose of this study, the non-involved uterus CTV (CTV_{uterus_noninv}) was contoured on MRI. Radiation oncologists contoured the ITV from the CTV_{LR} based on current clinical practice according to the EMBRACE II protocol [18]: the ITV related to the primary tumor (ITV-T) accounts for cervix-uterus motion expected throughout the treatment [19]. The ITV margin was determined individually for each patient according to rectal filling and from the location of the CTV_{LR} on full/empty bladder treatment planning CT scans as well as on the MRI which was also acquired in treatment planning position. The full/empty bladder CTs were fused with MRI based on bony structures. The ITV was constructed according to the physician's expectations of motion during treatment, e.g. additional ITV margin was added in the posterior direction in case rectum was not empty on the planning scan, as it may appear empty during EBRT. The construction of the ITV is described in more detail in Jensen et al. [16] as well as in the EMBRACE II protocol [18]. An elective nodal CTV (CTV-E) was also delineated. The so-called ITV45 was then composed of the CTV-E and the ITV-T. The planning target volume (PTV) was obtained by adding a 5 mm isotropic margin to the ITV45.

On each CBCT the combined CTV_{HR} and uterus, bladder, bowel and rectum were contoured by radiation oncologists. As the volume of the GTV shrinks in response to the treatment, the CTV_{HR} becomes smaller, whereas the non-involved uterus region is not normally changing in volume. Using the assumption that the length of the non-involved uterus is stable in relation to the most distal fundus, we measured this distance on the pre-treatment MRI to delineate the non-involved uterus on all CBCTs. All CBCT contours, reflecting the anatomical location of the target and OARs just prior to the dose delivery were propagated to the sCTs using a rigid bony match used in clinical practice.

2.3. Plan evaluation

The CTV_{HR} is a region sensitive to dose degradation as it could reduce local control [20] and according to EMBRACE II, a minimum of 95% of the prescribed dose was considered as threshold for an acceptable dose, i.e. 42.75 Gy (RBE). For the non-involved uterus, 40 Gy (RBE) was considered as threshold for acceptable dose, since the non-involved uterus is associated with lower risk of recurrence (microscopic spread)

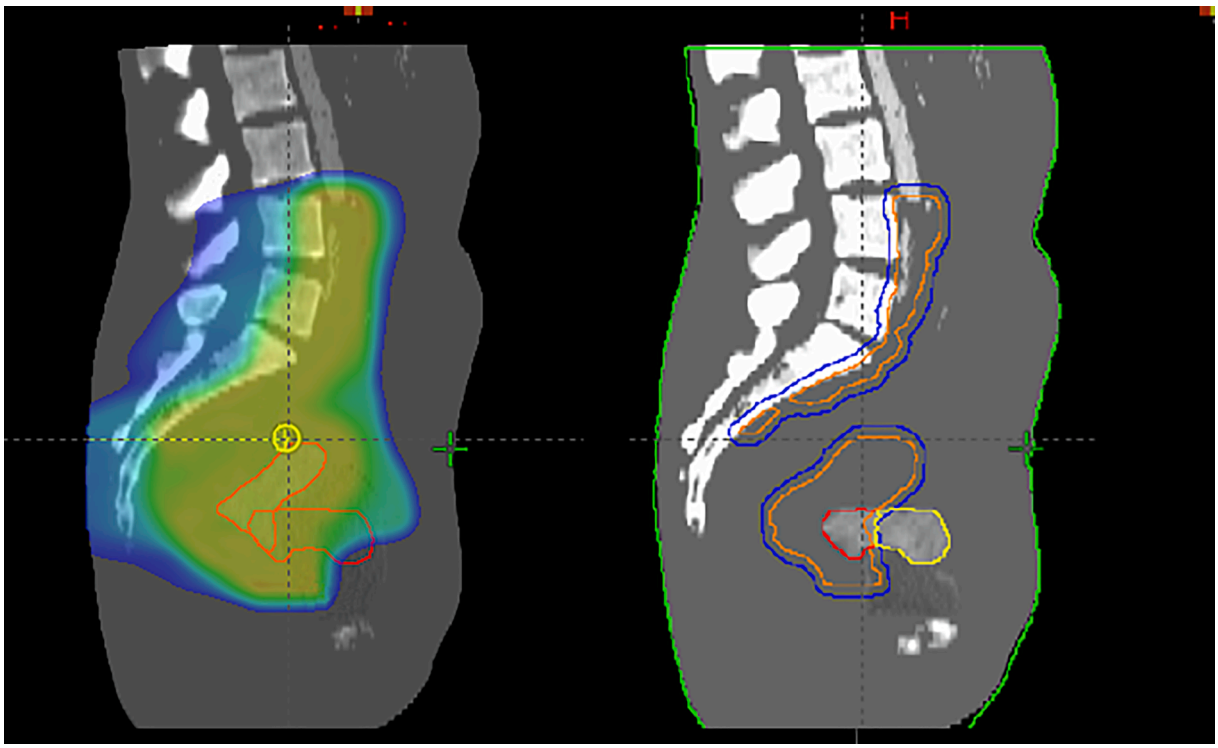

Fig. 1. Sagittal view of a synthetic CT for patient 8 showing the planned dose distribution on the left as well as planning target contours (ITV contour in orange, PTV in blue), and cervix-uterus position at fraction 7 (CTV_{HR} in red and non-involved uterus in yellow) on the right. For this fraction, D98% was 43.1 Gy(RBE) and 2.7 Gy (RBE) on the CTV_{HR} and CTV_{uterus_noninv}. Dose colorwash indicates doses between 30 Gy[RBE] and 48.1 Gy[RBE]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

and since a typical brachytherapy dose contribution of 5–10 Gy brings the total dose to the uterine body above >45 Gy (RBE) [21].

Dose-volume histogram (DVH) parameters were extracted from sCTs for all the targets which were propagated from the daily CBCTs: CTV_{HR}, CTV_{uterus_noninv}. Accumulated D98% was estimated for each patient by averaging D98% across all treatment fractions (DVH addition). Estimation of accumulated dose through DVH addition can be considered as a worst-case scenario, when considering hot spots and cold spots (e.g. D98%) [22]. The accumulated target D98% was compared to the planned values. In addition, relative bladder V40Gy (RBE) was extracted for all patients on the daily sCTs.

In order to investigate how variations in bladder volume impact the target dose degradation, the change in bladder volume between CBCTs and pCTs was calculated for all fractions of the ten patients and related to the target dose degradation. Furthermore, daily bowel V40Gy (RBE) and V30Gy (RBE) in cm^3 were extracted and related to bladder volume change from planning CT, and Pearson's correlation coefficients were calculated.

3. Results

The average planned D98% was 43.9 ± 0.3 Gy (RBE) for the CTV_{HR} and 43.8 ± 0.3 Gy (RBE) for the CTV_{uterus_noninv}. Planned dose to the OARs can be found in Supplementary Table S1.

For all ten patients, the minimum accumulated CTV_{HR} D98% was 43.0 Gy (RBE) which in all cases met the 42.75 Gy (RBE) dose threshold (95%). As shown in Supplementary Table S2, the accumulated D98% to the CTV_{uterus_noninv} was >40 Gy (RBE) (90% of prescribed dose) and >42.75 Gy (RBE) (95% of prescribed dose) in 9/10 and 8/10 patients, respectively. In the two patients receiving less than 95% of prescribed dose, the D98% was 35.7 Gy (RBE) (79%) and 41.1 Gy (RBE) (91%) to the CTV_{uterus_noninv} and 36.5 Gy (RBE) (81% of prescribed dose) and 41.9 Gy (RBE) (93% of prescribed dose) to the CTV, respectively.

The distribution of the D98% for all individual fractions is illustrated in Fig. 2 for all ten patients. For the two patients (patient 5 and 8) with suboptimal coverage on the CTV, the CTV_{HR} D98% was >42.75 Gy (RBE) for all fractions but one in both patients, whereas the CTV_{uterus_noninv}, D98% was <40 Gy (RBE) in six fractions for the first patient and seven fractions for the second patient. As illustrated in Fig. 2, for a third patient (patient 9), the D98% of the CTV_{uterus_noninv} was <40 Gy (RBE) in two fractions. It can be noticed that for the two patients that were subject to major interfractional motion (patient 5 and patient 8), the daily bladder volumes were repeatedly smaller than at planning. The fractions in which they experienced major dose degradation all corresponded to bladders smaller by 120–300 cm^3 compared to pCT (Fig. 3 panel B and panel C). The opposite pattern was observed for patient 9 who had minor dose degradations in two fractions on the non-involved uterus (Fig. 3 panel C). The bladder volume of the fractions in question exceeded the value on pCT by 180–200 cm^3. This difference in volume pushed the fundus towards the superior-posterior direction and outside the D98% isodose. As seen on Fig. 3, several patients experienced similar bladder volume variations that did not induce target dose degradation. This is particularly the case for patient 10 who had 20 fractions delivered with a bladder smaller than on pCT by −265 cm^3 and up to −307 cm^3.

Variations in irradiated volume of the bowel were found to be correlated ($r = -0.60$ and $r = -0.55$ with p-value <0.0001 for V30Gy (RBE) and V40Gy (RBE), respectively) with changes in bladder volume between full bladder pCT and sCTs (Fig. 4 and Supplementary material Fig. S1). Two patients that were subject to major interfractional motion had on average higher fractional V40Gy (RBE) of the bowel compared to planning values (upper left corner of Fig. 4).

The difference in bladder V40Gy (RBE) [%] between accumulated dose and planned dose ranged between −13% and 3% for patients 1–9 while it was 50% for patient 10. For this patient, the bladder volume was on average 275 cm^3 smaller compared to the planning value.

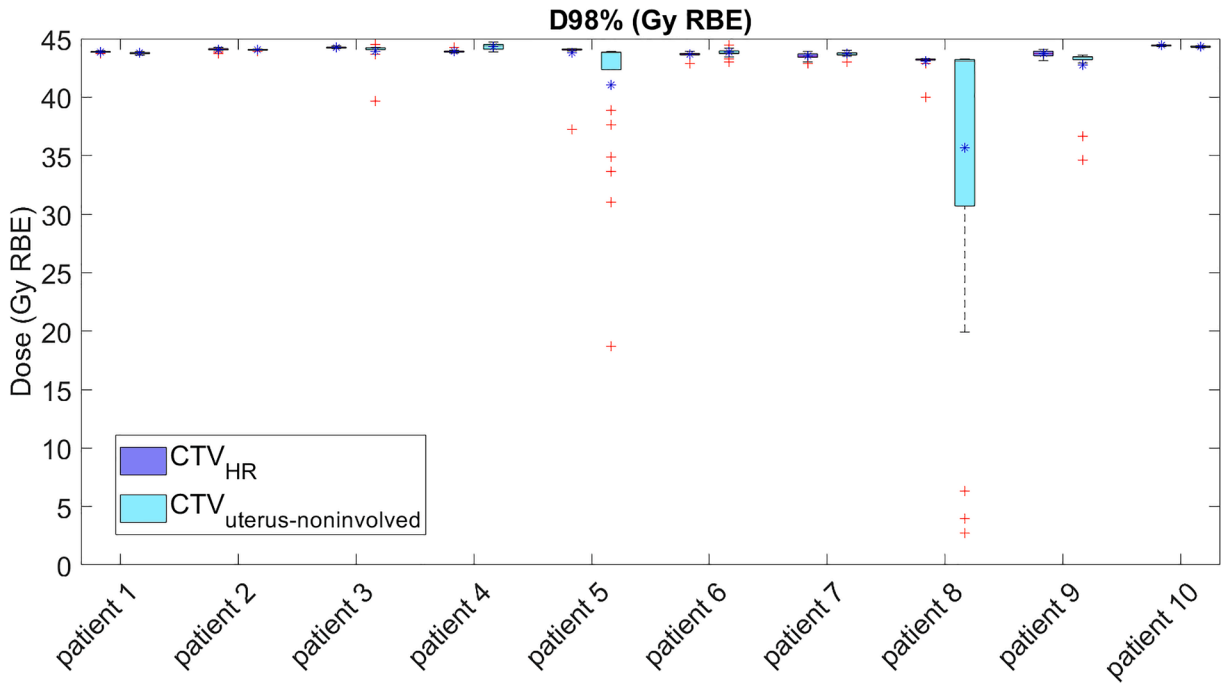

Fig. 2. Boxplots showing D98% Gy (RBE) on CTV_{HR} and CTV_{uterus_noninv} across all fractions for the ten patients studied. The bottom edge, the central mark and the top edge of the box indicate the 25th, the 50th and 75th percentiles, respectively. The blue asterisks show the total accumulated D98%. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

In the present study an ITV strategy commonly used in photon radiotherapy practice was applied to PT and its performance in compensating cervix-uterus interfractional motion was evaluated. The study showed that the use of individualized ITV margins plus a 5 mm PTV margin, ensured an acceptable total accumulated dose to the CTV_{HR} in all ten patients analyzed. Furthermore, the non-involved uterus, region particularly prone to interfractional motion, was sufficiently covered in all patients but one.

Our results are in line with the ones of Gort et al. [17] which showed by analyzing repeat CT scans, that ITV-based treatment plans with PBS-PT and photon therapy were equally robust to interfractional motion. However, it is interesting to note that their worst D98% dose degradation of the uterus was of less than 30%, while in our study fractions with dose degradation greater than 80% was observed in one patient. Despite these occasional large underdosages of the uterus observed in our study, the CTV_{HR} remained well covered with a total accumulated dose meeting the recommended constraints. Considering the pattern of underdosage of this patient (patient 8), the target dose could have been improved with a library-based plan. However, exceptionally large anatomical variations, as seen for this patient, illustrate the interest of daily online treatment adaptation. One further patient received more than 95% of the prescribed dose on the CTV_{HR}, but two fractions had less than 40 Gy(RBE) on the $CTV_{\_uterus\_noninv}$, which despite being tolerable in regard to the accumulated dose on the $CTV_{\_uterus\_noninv,}$ still would have benefited from one re-plan with an updated ITV for two fractions. Patients with suboptimal coverage illustrate the need for alternative approaches. Individualized ITV margins for the mobile target related to the primary tumor combined with a CBCT-monitoring-based offline re-planning may be efficient without requiring excessive resources [16]. A plan of the day concept as proposed by van de Schoot et al. [2] or a real-time re-planning strategy as reported by Jagt et al. [11] for cervix cancer with a prior plan-library may further improve target coverage and OARs sparing for patients subject to large interfractional anatomical variations. Nevertheless, the workflow of the latter strategy is still not clinically available and some challenges remain to be addressed before implementation of on-line adaptive RT/PT in clinical routine: improved image quality and automatic contouring would be required for this approach to become feasible and cost-effective [23,24].

Consistent with several studies [8,9] on photon therapy, our results indicated the need of a bladder filling protocol during treatment. Our study showed that large differences in bladder volume between the day of planning and the delivery could cause target dose degradation as well as bowel dose deviations compared to planned values. The largest overdosage of the bowel was found for bladders that were smaller during dose delivery compared to pCT. This indicates, similarly to what was demonstrated in conventional photon therapy [16] that large bladder volumes achieved on the day of planning CT acquisition and difficult to reproduce on the day of dose delivery can induce higher dose to the bowel than expected at planning.

Robust optimization, such as the worst-case algorithm, is designed to anticipate the impact of patient positioning errors and range uncertainties on the proton beams and is currently seen as a standard requirement in PT. In a real scenario in which all sources of uncertainty disregarded in the present study, combine, such a planning strategy, robust to density changes and patient shifts would lead to improved delivered doses to the patients.

The results of planning studies evaluating the impact of uncertainties for a specific modality depend on several parameters, which for protons would include the beam configuration and plan optimization. The beam configuration chosen in the present study (two lateral opposed and two posterior oblique) places the distal fall off region, associated with the steepest dose gradient, mainly in the anterior part of the patient. This arrangement was chosen, in order for the beams not to pass through the bowels hence minimizing the irradiation of this organ as well as the likelihood of crossing gas pockets. As the pCT was aimed to be acquired with a full bladder, the patients subject to bladder-filling induced uterus motion would likely experience it with emptier bladders, inducing an anterior-inferior displacement of the fundus, towards the low dose region. Therefore, beam configurations associated with shallower dose gradients in the anterior part of the patient could have reduced the dose

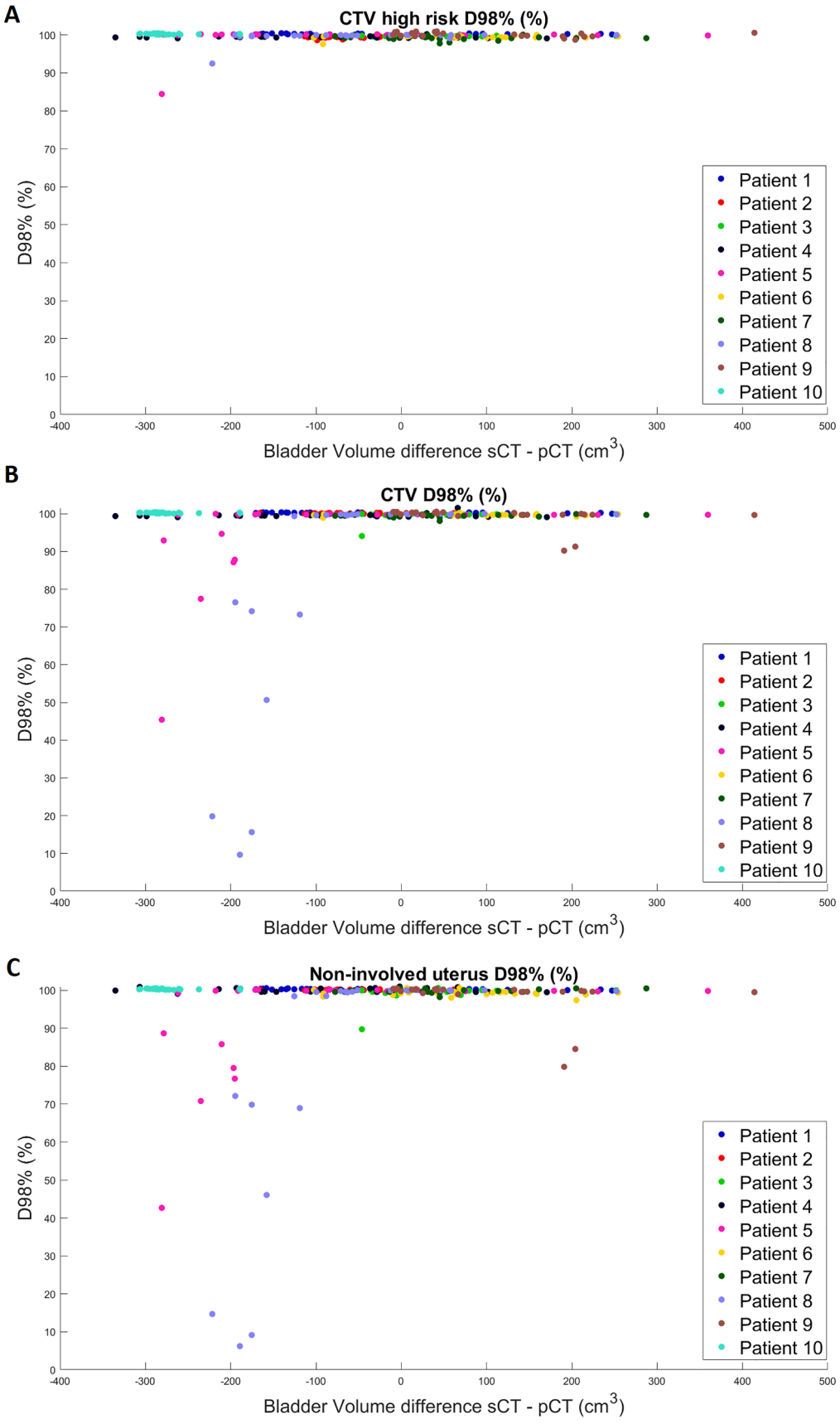

Fig. 3. Target D98% (Gy RBE) relative to planned dose (sCT/pCT) as a function of bladder volume difference (Panel A: $CTV_{HR,}$ Panel B: CTV, Panel C: $CTV_{\_uterus\_noninv}$).

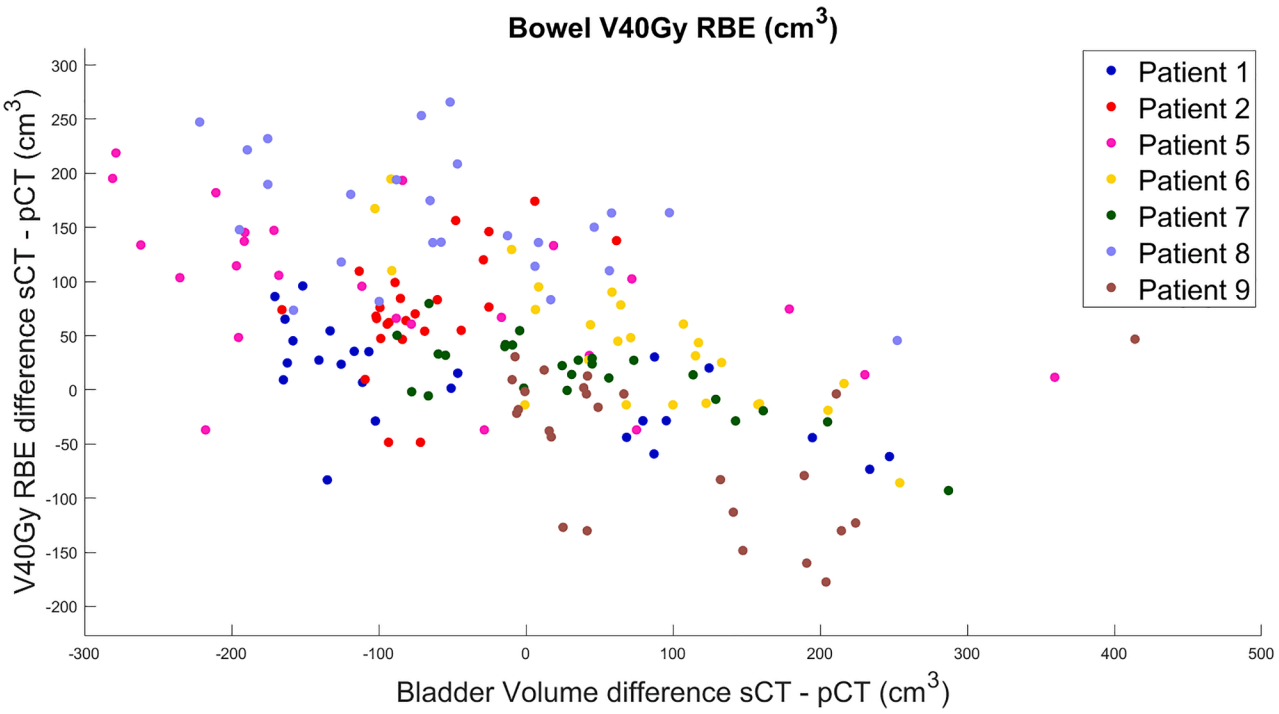

Fig. 4. Bowel V40Gy[RBE] (cm^3) difference (sCT-pCT) as a function of bladder volume difference.

degradations observed in this study.

The relatively small number of patients is a clear limitation of this study, since it is not representative of the whole cervical cancer patients' population. However, the analyzed cohort includes patients with occasional large interfractional uterus motion and the analysis of all daily fractions allowed us to estimate total accumulated dose for several parts of the target each associated with different risk of recurrence. In addition to the dose degradation found in this study which is only due to interfractional target motion, additional sources of uncertainties should be combined and taken into account, such as interfractional density variations, gas cavities, body outline variations [6] stopping power ratio (SPR)-to-HU correspondence, set up and contouring uncertainties [25,26]. Berger et al. [6] showed that gas cavities and outline variations had minor impact on target and OARs doses. In addition, the study by Gort et al. [17] indicated that, with all sources of uncertainties considered, robustly optimized PBS-PT was equally robust against inter- and intrafraction variability compared to photon therapy and provides better OARs sparing.

In conclusion, our study validates that the use of individualized ITV margins, as proposed in the EMBRACE II protocol, ensures satisfactory total accumulated dose to the CTV_{HR} for all analyzed patients despite occasional large interfractional displacement. Our results also highlight the importance of bladder filling protocols to avoid target underdosage or increased dose to OARs as compared to at pre-treatment planning. In addition, our results show the interest of alternative approaches, such as replanning and adaptive strategies for the patients subject to large interfractional motion.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.phro.2021.01.010.

References

[1] Marnitz S, Wlodarczyk W, Neumann O, Koehler C, Weihrauch M, Budach V, et al. Which technique for radiation is most beneficial for patients with locally advanced cervical cancer? Intensity modulated proton therapy versus intensity modulated photon treatment, helical tomotherapy and volumetric arc therapy for primary radiation – an intraindividual comparison. Radiat Oncol 2015;10. https://doi.org/10.1186/s13014-015-0402-z.

[2] van de Schoot AJAJ, de Boer P, Crama KF, Visser J, Stalpers LJ, Rasch CR, et al. Dosimetric advantages of proton therapy compared with photon therapy using an adaptive strategy in cervical cancer. Acta Oncol 2016;55:892–9. https://doi.org/10.3109/0284186X.2016.1139179.

[3] Wang D, Bhatia SK, Felderman NK, Dinges E, Patel SC, Buatti J, et al. The effect of anatomical changes on target coverage in intensity modulated proton therapy for cervical cancer. Int J Radiat Oncol Biol Phys 2015;93. https://doi.org/10.1016/j.ijrobp.2015.07.1207. E262–E262.

[4] Ramlov A, Pedersen EM, Røhl L, Worm E, Fokdal L, Lindegaard JC, et al. Risk factors for pelvic insufficiency fractures in locally advanced cervical cancer following intensity modulated radiation therapy. Int J Radiat Oncol Biol Phys 2017;97:1032–9. https://doi.org/10.1016/j.ijrobp.2017.01.026.

[5] Kirchheiner K, Nout RA, Lindegaard JC, Haie-Meder C, Mahantshetty U, Segedin B, et al. Dose-effect relationship and risk factors for vaginal stenosis after definitive radio(chemo)therapy with image-guided brachytherapy for locally advanced cervical cancer in the EMBRACE study. Radiother Oncol 2016;118:160–6. https://doi.org/10.1016/j.radonc.2015.12.025.

[6] Berger T, Petersen JBB, Lindegaard JC, Fokdal LU, Tanderup K. Impact of bowel gas and body outline variations on total accumulated dose with intensity-modulated proton therapy in locally advanced cervical cancer patients. Acta Oncol 2017;56:1472–8. https://doi.org/10.1080/0284186X.2017.1376753.

[7] White I, McQuaid D, McNair H, Dunlop A, Court S, Hopkins N, et al. Geometric and dosimetric evaluation of the differences between rigid and deformable registration to assess interfraction motion during pelvic radiotherapy. Phys Imag Radiat Oncol 2019;9:97–102. https://doi.org/10.1016/j.phro.2019.02.005.

[8] Jadon R, Pembroke CA, Hanna CL, Palaniappan N, Evans M, Cleves AE, et al. A systematic review of organ motion and image guided strategies in external beam radiotherapy for cervical cancer. Clin Oncol (R Coll Radiol) 2014;26:185–96. https://doi.org/10.1016/j.clon.2013.11.031.

[9] Eminowicz G, Rompokos V, Stacey C, Hall L, McCormack M. Understanding the impact of pelvic organ motion on dose delivered to target volumes during IMRT for cervical cancer. Radiother Oncol 2016;122:116–21. https://doi.org/10.1016/j.radonc.2016.10.018.

[10] Heijkoop ST, Langerak TR, Quint S, Bondar L, Mens JW, Heijmen BJ, et al. Clinical implementation of an online adaptive plan-of-the-day protocol for nonrigid motion management in locally advanced cervical cancer IMRT. Int J Radiat Oncol Biol Phys 2014;90:673–9. https://doi.org/10.1016/j.ijrobp.2014.06.046.

[11] Jagt TZ, Breedeveld S, van Haveren R, Nout RA, Astreinidou E, Heijmen BJM, et al. Plan-library supported automated replanning for online-adaptive intensity-modulated proton therapy of cervical cancer. Acta Oncol 2019;58:1440–5. https://doi.org/10.1080/0284186X.2019.1627414.
[12] Busch K, Muren LP, Thörnqvist S, Andersen AG, Pedersen J, Dong L, et al. On-line dose guidance to account for inter-fractional motion during proton therapy. Phys Imag Radiat Oncol 2018;9:7–13. https://doi.org/10.1016/j.phro.2018.11.009.
[13] van de Schoot AJAJ, de Boer P, Visser J, Stalpers LJA, Rasch CRN, Bel A. Dosimetric advantages of a clinical daily adaptive plan selection strategy compared with a non-adaptive strategy in cervical cancer radiation therapy. Acta Oncol 2017;56:667–74. https://doi.org/10.1080/0284186X.2017.1287949.
[14] Byskov CS, Nyvang L, Guren MG, Splindler K-LG, Muren LP. The normal tissue sparing potential of an adaptive plan selection strategy for re-irradiation of recurrent rectal cancer. Phys Imag Radiat Oncol 2017;3:43–8. https://doi.org/10.1016/j.phro.2017.09.001.
[15] Thornqvist S, Hysing LB, Tuomikoski L, Vestergaard A, Tanderup K, Muren LP, et al. Adaptive radiotherapy strategies for pelvic tumors – a systematic review of clinical implementations. Acta Oncol 2016;55:943–58. https://doi.org/10.3109/0284186x.2016.1156738.
[16] Jensen NBK, Assenholt MS, Fokdal LU, Vestergaard A, Schouboe A, Kjaersgaard EB, et al. Cone beam computer-based monitoring and management of target and organ motion during external beam radiotherapy in cervical cancer. Phys Imag Radiat Oncol 2019;9:14–20. https://doi.org/10.1016/j.phro.2018.12.002.
[17] Gort EM, Beukema JC, Matysiak W, Sijtsema NM, Aluwini S, Langendijk JA, et al. Inter-fraction motion robustness and organ sparing potential of proton therapy for cervical cancer. Radiother Oncol 2020;154:194–200. https://doi.org/10.1016/j.radonc.2020.09.022.
[18] Potter R, Tanderup K, Kirisitis C, de Leeuw A, Kirchheiner K, Nout R, et al. THE EMBRACE II study: the outcome and prospect of two decades of evolution within the GEC-ESTRO GYN working group and the EMBRACE studies. Clin Transl Radiat Oncol 2018;9:48–60. https://doi.org/10.1016/j.ctro.2018.01.001.
[19] Bondar ML, Hoogeman MS, Mens JW, Quint S, Ahmad R, Dhawtal G, et al. Individualized nonadaptive and onlineadaptive intensity-modulated radiotherapy treatment strategies for cervical cancer patients based on pretreatment acquired variable bladder filling computed tomography scans. Int J Radiat Oncol Biol Phys 2012;83:1617–23. https://doi.org/10.1016/j.ijrobp.2011.10.011.
[20] Tanderup K, Fokdal LU, Sturdza A, Haie-Meder C, Mazeron R, van Limbergen E, et al. Effect of tumor dose, volume and overall treatment time on local control after radiochemotherapy including MRI guided brachytherapy of locally advanced cervical cancer. Radiother Oncol 2016;120:441–6. https://doi.org/10.1016/j.radonc.2016.05.014.
[21] Sapru S, Mohamed S, Fokdal L, Nkiwane K, Swamidas J, Mahantshetty U, et al. Dose to the non-involved uterine corpus with MRI guided brachytherapy in locally advanced cervical cancer. Radiother Oncol 2013;107:93–8. https://doi.org/10.1016/j.radonc.2013.02.005.
[22] Andersen ES, Noe KO, Sørensen TS, Nielsen SK, Fokdal L, Paludan M, et al. Simple DVH parameter addition as compared to deformable registration for bladder dose accumulation in cervix cancer brachytherapy. Radiother Oncol 2013;107:52–7. https://doi.org/10.1016/j.radonc.2013.01.013.
[23] Andersen AG, Park Y-K, Elstrom UV, Petersen JBB, Sharp GC, Winey B, et al. Evaluation of an a priori scatter correction algorithm for cone-beam computed tomography based range and dose calculations in proton therapy. Phys Imag Radiat Oncol 2020;16:88–94. https://doi.org/10.1016/j.phro.2020.09.014.
[24] Taasti VT, Klages P, Parodi K, Muren LP. Developments in deep learning based corrections of cone beam computed tomography to enable dose calculations for adaptive radiotherapy. Phys Imag Radiat Oncol 2020;15:77–9. https://doi.org/10.1016/j.phro.2020.07.012.
[25] Laursen LV, Elstrøm UV, Vestergaard A, Muren LP, Petersen JB, Lindegaard JC, et al. Residual rotational set-up errors after daily cone-beam CT image guided radiotherapy of locally advanced cervical cancer. Radiother Oncol 2012;105:220–5. https://doi.org/10.1016/j.radonc.2012.08.012.
[26] Eminowicz G, Rompokos V, Stacey C, McCormack M. The dosimetric impact of target volume delineation variation for cervical cancer radiotherapy. Radiother Oncol 2016;120:493–9. https://doi.org/10.1016/j.radonc.2016.04.028.