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Original Article

Nine years of plan of the day for cervical cancer: Plan library remains effective compared to fully online-adaptive techniques

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ABSTRACT

Background and purpose: Since 2011, our center has been using a library-based Plan-of-the-Day (PotD) strategy for external beam radiotherapy of cervical cancer patients to reduce normal tissue dose while maintaining adequate target coverage. With the advent of fully online-adaptive techniques such as daily online-adaptive replanning, further dose reduction may be possible. However, it is unknown how this reduction relates to plan library approaches, and how the most recent PotD strategies relate to no adaptation. In this study we compare the performance of our current PotD strategy with non-adaptive and fully online-adaptive techniques in terms of target volume size and normal tissue sparing.

Materials and methods: Treatment data of 376 patients treated with the PotD protocol between June 2011 and April 2020 were included. The size of the Planning Target Volumes (PTVs) was reconstructed for different strategies: full online adaptation, no adaptation, and the latest clinical version of the PotD protocol. Normal tissue sparing was estimated by the difference in margin volume to construct the PTV and the volume overlap of the PTV with bladder and rectum.

Results: The current version of our PotD approach reduced the PTV margin volume by a median of 250 cm^3 compared to no adaptation. Bladder-PTV overlap decreased from a median of 142 to 71 cm^3, and from 39 to 16 cm^3 for rectum-PTV. Fully online-adaptive approaches could further decrease the PTV volume by 144 cm^3 using a 5 mm margin for residual errors. In this scenario, bladder-PTV overlap was reduced to 35 cm^3 and rectum-PTV overlap to 11 cm^3.

Conclusion: The current version of the PotD protocol is an effective technique to improve normal tissue sparing compared to no adaptation. Further sparing can be achieved using fully online-adaptive techniques, but at the cost of a more complex workflow and with a potentially limited impact. PotD-type protocols can therefore be considered as a suitable alternative to fully online-adaptive approaches.

Introduction

External beam radiotherapy (EBRT) is an important part of the treatment of locally advanced cervical cancer (LACC) patients. Inter-fraction deformations in pelvic anatomy are known to vary widely in size within this patient group [1–4], resulting in large inter-patient differences in target mobility. Consequently, population-based margins are undesirable as they disadvantage patients with low target mobility in terms of normal tissue sparing [5,6] or compromise the target coverage of the other patients, if chosen too small.

To account for highly variable target mobility, online-adaptive strategies based on a library-of-plans Plan-of-the-Day (PotD) – containing pre-treatment optimized plans – have been developed, as previously proposed and implemented by our institute [4]. In this strategy, an individualized non-rigid motion model is used to construct one or two internal target volumes (ITV) encompassing the position of the cervix and uterus as a function of bladder volume. In addition, a large margin back-up plan is added to the plan library as a safety measure that is applied if adequate target coverage cannot be achieved with the library plans. Plan selection is performed using daily acquired cone beam computed tomography (CBCT) scans.

This protocol was clinically implemented in 2011 and results for the

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first 64 patients were published in 2014 [8]. The protocol showed significant organ at risk (OAR) dose sparing, but at the cost of a more labor-intensive clinical workflow, as multiple treatment plans have to be made for each patient and the appropriate plan has to be selected at each fraction. Since then, fully automated planning of the library plans has helped to reduce the workload [9]. Furthermore, the protocol has been gradually improved. As an example, tighter ITV-to-PTV margins were implemented to further reduce the size of the Planning Target Volumes (PTVs). In 2017 it was reported that 25 % of all Dutch centers specialized in gynecological radiotherapy employed a library-of-plans-based approach for cervical cancer patients [10], meaning that 75 % of the Dutch centers still applied a non-adaptive, single-plan approach. In contrast, fully online-adaptive approaches, either MR- or CBCT-based, have been developed that include daily segmentation and re-optimization to make a new treatment plan fitting the anatomy of the day [11–14].

To support decision-making about the strategy to be implemented, information about the advantages of both adaptation methods compared to no adaptation approaches is crucial. However, this information is currently lacking. The performance in terms of OAR sparing of the currently implemented library-of-plans protocol has not yet been reported for substantial cohorts, nor the differences of such a protocol compared with fully online-adaptive workflows and no adaptation. Therefore, the aim of this study is to evaluate the capacity of the library-of-plans protocol to spare normal tissue, compared to non-adaptive and fully online-adaptive protocols. For this evaluation, the currently implemented PotD protocol was retrospectively applied to a historical cohort of PotD patients and the estimated normal tissue was compared with no adaptation and with fully online-adaptive approaches for the same patient cohort.

Methods and materials

All cervical cancer patients treated with the PotD protocol from June 2011 until April 2020 were included under IRB study waiver MEC-2021–0338. Patients were treated with radiation therapy and concurrent chemotherapy, or with concurrent hyperthermia in case of contraindications to undergo chemotherapy. In case of bulky tumors beyond FIGO stage IIB or positive para-aortic lymph nodes, patients were treated with neo-adjuvant chemotherapy, and radiation therapy with concurrent hyperthermia. The initial version of the PotD protocol has been described previously [4]. Patients had four polymer markers implanted in the fornices of the vagina to aid in daily position verification on the CBCT scan. Patients were asked to follow a bladder-filling protocol before pre-treatment imaging and for each external beam radiotherapy (EBRT) fraction [8]. Delineations of bladder and low risk-clinical target volume (CTV, consisting of gross target volume, cervix, uterus, upper one-third of vagina, and parametrial tissue) were made on the full and empty bladder Computed Tomography (CT) scan. The CTV was contoured with the help of fused MR images. To construct the ITV, an in-house developed unidirectional thin plate spline robust point matching registration algorithm was used [15]. The algorithm is capable of describing the deformation of the bladder and uterus between the full and empty bladder CT scan, allowing interpolation of intermediate positions of bladder filling. For example, with the algorithm mid-full bladder and uterus position can be simulated.

In the current clinical PotD protocol, a tip-of-uterus displacement between full and empty bladder below 2 cm classifies a patient as a non-mover patient. For this type of patient one full-range ITV is constructed from the empty to the full bladder CTV position (full-bladder plan), followed by an ($\pm$x, $\pm$y, +z) 5 mm expansion. Above 2 cm, a patient is considered a mover and two sub-ITVs are constructed - one encompassing the target position from empty to half-full bladder (empty-bladder plan), and one encompassing the half-full to full-bladder target position (full-bladder plan). For both types of patients an isotropic 5 mm margin is then applied to the ITVs and elective nodal CTV to construct the different PTV structures.

In addition to these plan library PTV volumes, a motion-robust back-up plan was constructed. The procedure was the same for mover and non-mover patients, and comprised the full-range ITV from empty to full-bladder position with the elective volume and a margin expansion of 15 mm margin ($\pm$x, $\pm$y, +z) in all directions but caudal (10 mm) to the ITV, combined with an isotropic 5 mm-margin to the elective CTV. Historically, these margins have also been modified throughout the years, and an overview of the modifications is listed in Appendix A. Daily CBCT imaging is utilized on the linear accelerator to position the patient, and subsequently to allow for plan selection from the plan library. Patients were irradiated in 23 fractions of 2 Gy EBRT or 28 fractions of 1.5 Gy until 2019. After 2019 all patients were irradiated in 25 fractions of 1.8 Gy, in accordance with the EMBRACE II protocol [21].

The clinically-used full-bladder plan PTV at planning was collected for all patients and evaluated as $PTV_{POTD,\ hist}$. The retrospective application of the current clinical protocol, as described in the previous paragraph, was performed for all patients and evaluated as $PTV_{POTD,\ curr}$. As comparison, the current version of the motion-robust back up plan $PTV_{NONADAPT,\ curr}$ was retrospectively computed for the entire cohort. The clinically-used motion-robust back-up plan volumes were collected for analysis as $PTV_{NONADAPT,\ hist}$. All aforementioned volumes were evaluated on the full bladder planning CT scans, as patients were instructed from the drinking protocol. To further estimate the clinical performance of the PotD protocol, the starting date of treatment, the number of fractions given and the daily selected plan (full bladder, empty bladder, or back-up) were collected.

To simulate improvements to the historic and current clinical protocol, an expansion of the plan library from one to two, three and four plans was simulated for all patients, where the total ITV was equally divided according to the mover patient strategy – for example from 0 to 33 %, 33 %-67 % and 67 %-100 % bladder filling for the three-plan ITV – resulting in $PTV_{x\ ITV}$, with *x* being the number of ITVs. The ITVs were combined with the elective volume and expanded with the currently-implemented margins, and the ITV corresponding to the largest bladder filling was reported. Finally, fully online-adaptive scenarios were simulated, where 2.5 and 5 mm margins were applied to the CTV and the elective CTV, resulting in $PTV_{FA,\ 2.5mm}$ and $PTV_{FA,\ 5mm}$. To facilitate inter-patient comparison, the margin volume of all reported PTV volumes was computed by subtracting the elective and tumor CTV volumes from the PTV volumes.

Comparison of all collected and computed PTV volumes was used to compare OAR sparing of the different adaptation strategies, and to assess potential gain by employing a fully online-adaptive strategy, where tip-of-uterus displacement was included to assess the target mobility of the entire cohort. Tip-of-uterus displacement was assessed with the 99th percentile of the Hausdorff distance (HD99) between the full and empty bladder position of the CTV. The incidences of replanning were reported, and the planning structures of CTVs and OARs (bladder, rectum) were collected. Replanning, consisting of new CT imaging and plan library creation during the treatment course, was generally carried out when back-up plans were selected more than three times during treatment. To estimate the radiation-induced toxicity burden of the different treatment approaches the overlap in cm^3 between PTV and collected OARs on the full bladder CT-scan was registered as a surrogate for the dose parameters (V_{45Gy}).

Results

A total of 376 patients was included in this study. For the whole cohort, 75.5 % of the chosen plans of during treatment was a full-bladder plan, 12.6 % an empty-bladder plan, and 11.9 % a back-up plan. A total of 67 out of 376 patients (18 %) required full replanning at one or more points during their treatment. The historically-employed $PTV_{POTD,\ hist}$ and $PTV_{NONADAPT,\ hist}$ margin volumes are depicted in Fig. 1, together

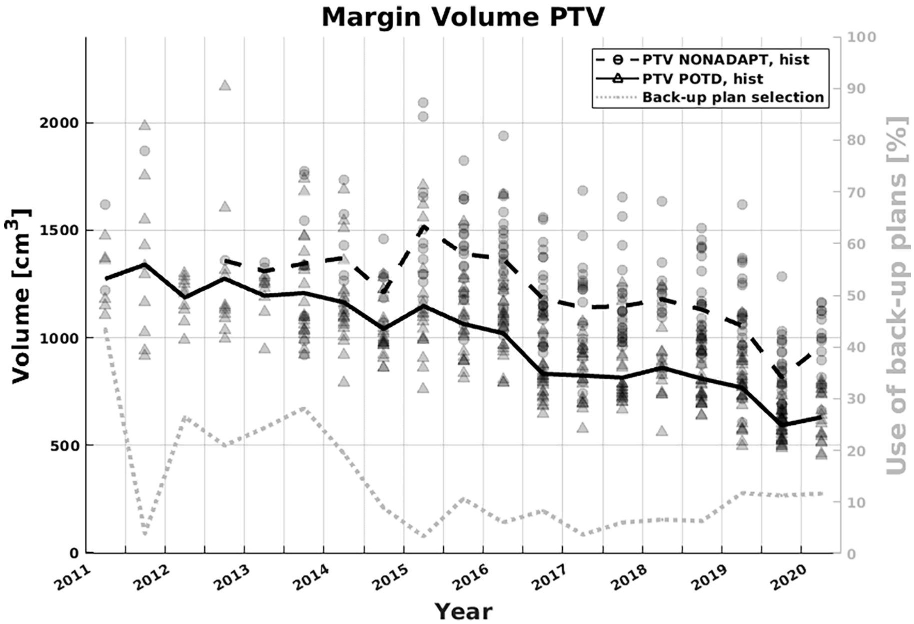

Fig. 1. On the left axis the margin volume is displayed in cm^3 of different PTV structures attributable to CTV-to-PTV expansions for historically used structures ($PTV_{NONADAPT,\ hist}$ and $PTV_{POTD,\ hist}$) through the years. On the right axis the usage of BU plans as a percentage of all treatment fractions is displayed. Data points were grouped per half year.

with the back-up plan selection throughout the years. $PTV_{POTD,\ hist}$ margin volumes have decreased with a median volume of 710 cm^3. From 2011 to 2013 no separate $PTV_{NONADAPT,\ hist}$ structure was constructed, but instead a four-field 3D conformal radiotherapy plan was planned upon the $PTV_{POTD,\ hist}$ structure, resulting in a larger V_{45Gy} volume and thus a more robust plan. Back-up plan selection has decreased and stabilized to 12 % in 2020.

Retrospective reconstruction of the current protocol and the calculation of plan library expansions was possible for 243 patients (65 % of the full cohort), due to differences in delineation practices before and after 2016. Fig. 2 displays the collected PTV volumes ($PTV_{POTD,\ hist}$ and $PTV_{NONADAPT,\ hist}$) of all 376 patients and reconstructed PTV volumes ($PTV_{POTD,\ curr}$, $PTV_{NONADAPT,\ curr}$, $PTV_{x\ ITV}$, $PTV_{FA\ 2.5mm}$ and $PTV_{FA\ 5mm}$) of 243 out of 376 patients. The results of the mover patient subgroup (uterine displacement of equal or more than 2.5 cm) can be found in Appendix B. A median theoretical margin volume decrease from 841 to 593 cm^3 was achieved by employing the current version of the PotD library ($PTV_{POTD,\ curr}$) instead of a non-adaptive approach ($PTV_{NONADAPT,\ curr}$). Taking a weighted average of 12 % back-up plan selection ($PTV_{NONADAPT,\ hist}$) and 88 % daily Plan-of-the-Day selection ($PTV_{POTD,\ hist}$) resulted in an achieved median 208 cm^3 decrease compared to a non-adaptive approach. Expansion of the PotD library did not yield large margin reductions for the whole patient cohort beyond the currently-employed two-ITV plan libraries ($PTV_{2\ ITV}$). With a fully online-adaptive strategy without the need of a back-up scenario, the median $PTV_{FA\ 5mm}$ margin volume was 449 cm^3 compared to a 233 cm^3 median volume of $PTV_{FA\ 2.5mm}$.

The uterine mobility (HD99) within the full cohort is displayed in Fig. 3. The median movement was equal to 16 mm between full and empty bladder position, while 75 % all patients displayed movement of less than 25 mm. A total of 95 % of the population had uterine movement below 42 mm. The overlap between bladder or rectum and different PTV volumes ($PTV_{POTD,\ curr}$, $PTV_{NONADAPT,\ curr}$ and $PTV_{FA\ 2.5mm}$) for individual patients as a function of HD99 is displayed in Fig. 4.

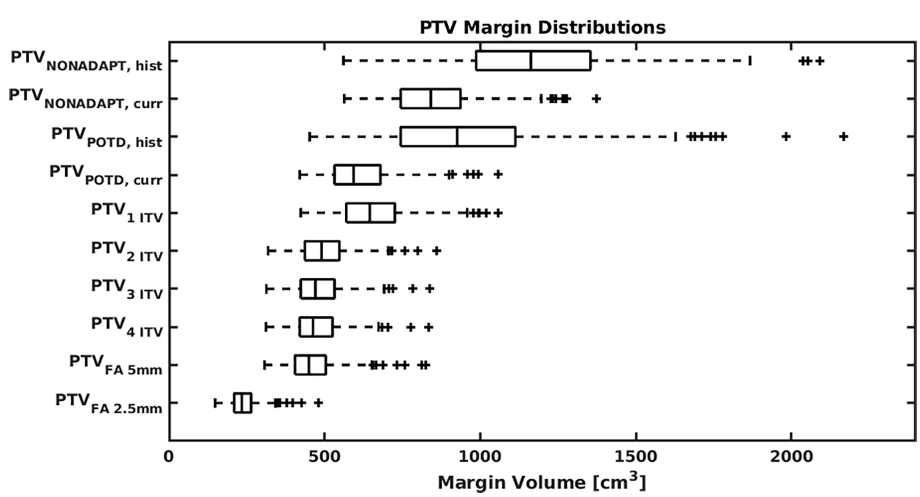

Fig. 2. Distributions in cm^3 of collected PTV volumes ($PTV_{POTD,\ hist}$ and $PTV_{NONADAPT,\ hist}$) of 376 patients and reconstructed PTV volumes ($PTV_{POTD,\ curr}$, $PTV_{NONADAPT,\ curr}$, $PTV_{x\ ITV}$, $PTV_{FA\ 2.5mm}$ and $PTV_{FA\ 5mm}$) of 243 out of 376 patients. Boxes depict 25th percentile, median, and 75th percentile. Outliers are defined as points below or above 1.5 times the interquartile ranges from median.

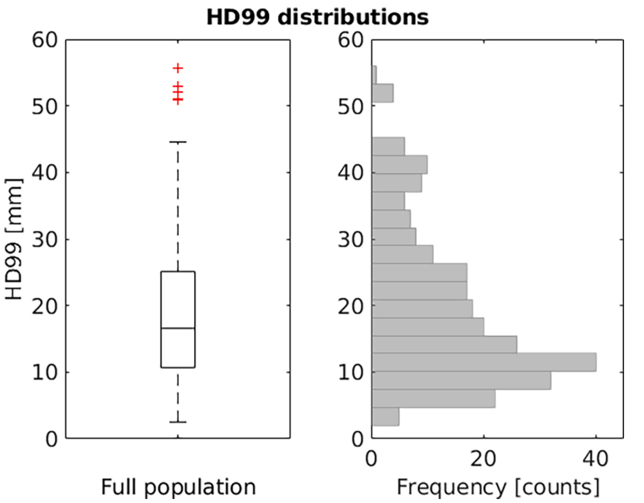

Fig. 3. Distribution of 99th percentile Hausdorff distance (HD99) of the CTV as an assessment of tip-of-uterus displacement between full and empty bladder CT scan. Left panel depicts boxplot with HD99 values in the population, the right panel a histogram of the distribution. The distribution is skewed towards lower HD99 and thus smaller displacements.

For $PTV_{NONADAPT,\ curr}$ and $PTV_{POTD,\ curr}$ a median decrease in overlap from 142 to 71 cm^3 was present for bladder, and from 39 to 16 cm^3 for rectum. Fully online-adaptive approaches $PTV_{FA\ 5mm}$ and $PTV_{FA\ 2.5mm}$ could further decrease the overlap to 35 or 17 cm^3 for bladder and to 11 or 5 cm^3 for rectum, demonstrating a major gain for bladder specifically for fully online-adaptive techniques.

Overlap of bladder and $PTV_{NONADAPT,\ curr}$, $PTV_{POTD,\ curr}$ or $PTV_{FA\ 5mm}$ volume was shown to correlate to HD99, as higher HD99 values corresponded to higher overlap volumes. As an example, a specific patient with a HD99 value of 44 mm would have had 420 cm^3 bladder-$PTV_{NONADAPT,\ curr}$ overlap, 160 cm^3 bladder- $PTV_{POTD,\ curr}$ overlap and 35 cm^3 bladder- $PTV_{FA\ 5mm}$ overlap. For a patient with a HD99 value of 2.5 mm this would have been 48 cm^3 bladder-$PTV_{NONADAPT,\ curr}$ overlap, 29 cm^3 bladder- $PTV_{POTD,\ curr}$ overlap and 14 cm^3 bladder- $PTV_{FA\ 5mm}$ overlap. For rectum this HD99 dependency was not present, and differences between $PTV_{POTD,\ curr}$ and $PTV_{FA\ 5mm}$ overlap volumes were generally smaller (Fig. 4B).

Discussion

In this paper we have reported a comprehensive analysis of our library-of-plans-based PotD protocol for cervical cancer patients in the context of the clinical implementation of expanded plan libraries and fully online-adaptive techniques. We believe this to be the first study of its size demonstrating the performance of PotD protocol for cervical cancer patients compared to non-adaptive and fully online-adaptive techniques. The dataset used in this study extends the work published by Heijkoop et al. in 2014 by displaying the historic development and current performance of the PotD protocol by itself and compared to other techniques.

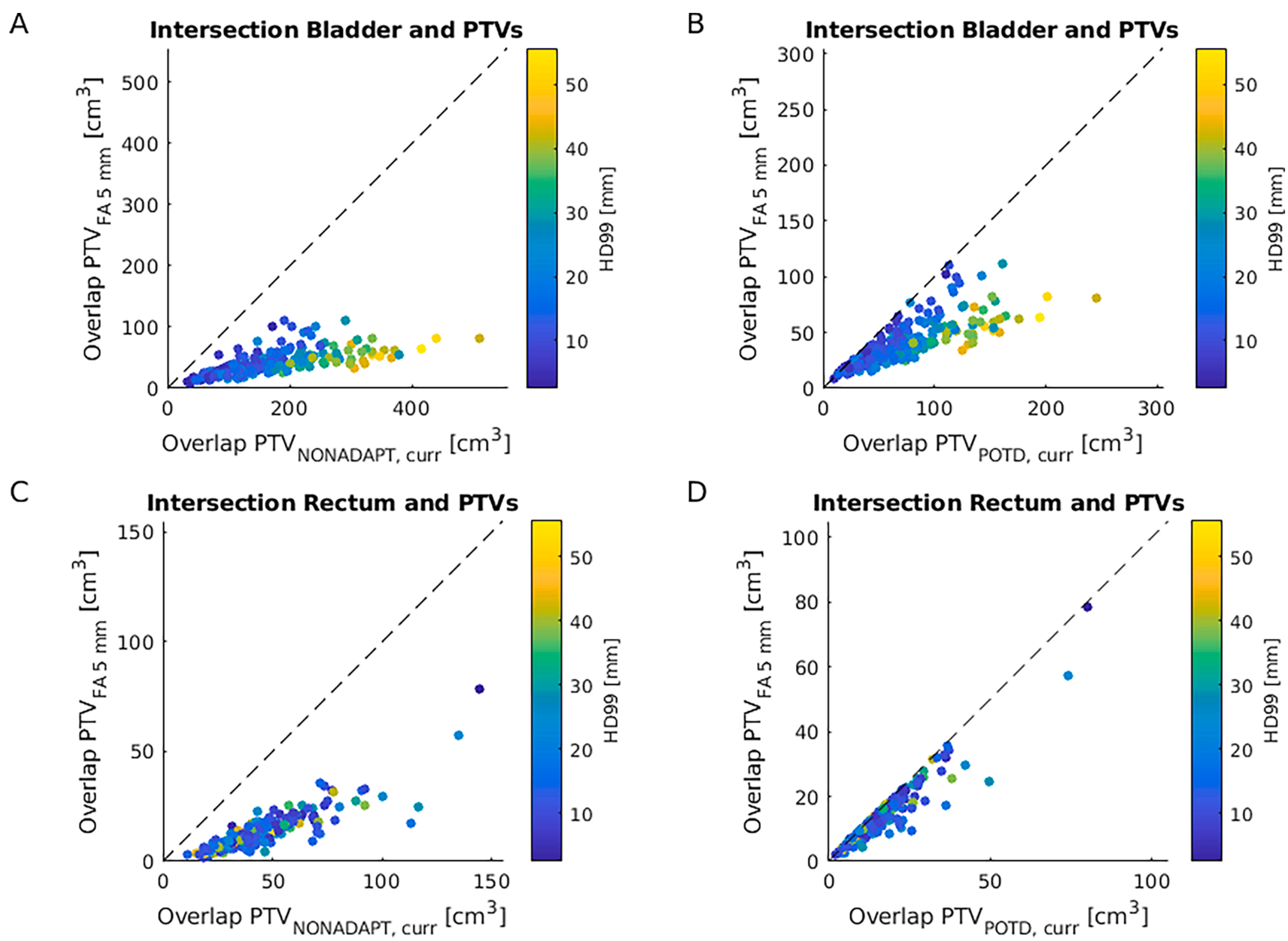

Fig. 4. Distributions of the overlap of bladder as a function of HD99 between $PTV_{FA\ 5mm}$ and $PTV_{NONADAPT,curr}$ and between $PTV_{FA\ 5mm}$ and $PTV_{POTD,\ curr}$ in panel A and B. Distributions of the overlap of rectum as a function of HD99 between $PTV_{FA\ 5mm}$ and $PTV_{NONADAPT,\ curr}$, and between $PTV_{FA\ 5mm}$ and $PTV_{POTD,\ curr}$ are displayed in panel C and D. Data point color corresponds to the HD99 distance in mm (colorbar).

As an overview, a total of 18 % of the treated patients required replanning one or more times within the PotD protocol. Replanning is performed in case the back-up plan ($PTV_{NONADAPT}$) is selected too frequently, in case persistent deviations from the library are present, or in case of noticeable anatomy changes, such as weight loss or substantial tumor shrinkage (in case of bulky tumors at planning). Back-up plan selection could occur due to image quality problems or due to target coverage problems with PTV_{POTD}. In addition, in this study PTV margin volumes are considered as a surrogate for V_{45Gy} volumes. As dose deformation and dose accumulation for this treatment site are by themselves difficult to perform reliably, plan selection and adaptation complicate these analyses even further. With the arrival of better daily imaging in MR and CBCT technology such analyses can be performed to better estimate accumulated target and OAR doses.

After the initial publication by Heijkoop et al. in 2014, smaller margins were gradually implemented, inducing less plan robustness to pelvic mobility that is not currently included in the bladder-based motion-model. In 2019, the ITV-to-PTV margins were enlarged again for non-mover patients in an attempt to mitigate the amount of replanning that was observed for this patient group, and reduce back-up plan selection for this cohort. A thorough analysis to determine whether this attempt was successful has yet to be carried out. The 12 % back-up plan selection and incidences of replanning could indicate that the current margin-limit with the bladder-uterus motion model has been reached. Bladder-induced motion represents the majority of uterus displacement [16], but margins remain necessary to account for other types of pelvic motion. Bondar et al. demonstrated that a 7-mm CTV margin was necessary for the currently-used motion model to obtain sufficient coverage within a fourteen-patient study population [4]. The currently-used margin for mover patients is smaller (5 mm), and the incidence of back-up plan selection and replanning seems to demonstrate that an optimum has been reached for the current clinical situation. Nevertheless, our results demonstrate that protocol modifications have resulted in substantially lower PTV volumes.

Besides margin reduction, expanding the current plan library would theoretically benefit patients with large motion in terms of normal tissue sparing. However, as demonstrated in Fig. 3, the number of patients with large motion is low. Most of the patients (75 %) had tip-of-uterus displacement smaller than 2.5 cm, for which a single-ITV plan library might suffice, and 95 % of the patients had a uterine displacement below 4.8 cm. Taking the abovementioned limitations of the current strategy into account, a plan library expansion might not be effective for the whole patient cohort. On an individual basis however, patients with large uterine movement could still greatly benefit from this. A possible increase in back-up plan selection due to the expansion of the library is not taken into account in this study, but might negate the intended normal tissue sparing. Other retrospective studies have reported on the results of three- to seven-plan libraries for 10 to 14 patients, but employed different and larger CTV-to-ITV or ITV-to-PTV margins, making a translation to our results difficult [6,17]. Potentially an update of the motion model to incorporate other pelvic motions (such as rectum filling) could also benefit non-mover patients, but no clinical results for such motion models have been reported yet [16]. No matter the preferred type of plan library, additional clinical workload has to be considered when creating multiple treatment plans to construct the library.

Without plan libraries, the next step to further reduce the PTV volume and potentially radiation-induced toxicity could be the application of a fully online-adaptive strategy. For fully online-adaptive strategies, both a 2.5 and 5 mm margin were simulated in this work. The 2.5 mm margin appears to be too optimistic especially for patients displaying bigger movement within the current capabilities and timeframes of fully online-adaptive replanning [1,17,18], but was included in this study as an ultimate goal. Especially for relatively large mover patients the overlap volume for bladder and $PTV_{POTD,\ curr}$ would decrease when employing a fully online-adaptive strategy. As the current PotD strategy includes bladder filling as foundation for the ITV construction to create the plan library, it is a logical consequence that omitting the bladder-based ITV for a CTV-based approach spares the bladder. The ITV approach ensures target coverage when bladder filling displaces the target, but increases overlap with bladder compared to fully online-adaptive strategies. For rectum the overlap volume also decreases when employing the fully online-adaptive approach, but does not appear to correlate with uterine mobility (HD99).

Taking all results into account, a fully online-adaptive approach with tight margins would yield the most significant improvements for our patient cohort in terms of normal tissue sparing. However, the execution of a fully online-adaptive strategy on an MR-linac is not easily applicable to LACC-patients, due to the long fields and longer treatment times, requiring multi-isocenter plans or larger margins to overcome intra-fraction motion [19,20]. Alternatively, fully online-adaptive treatments could be executed through CBCT-based workflows. For consideration, soft tissue contrast is worse compared to MR-linac imaging, which could potentially limit the desired margin reduction [14]. Recent advances in the development of CBCT-based fully online-adaptive planning, demonstrate a median of 18 min between acceptance of reconstructed CBCT to treatment delivery for different pelvic treatment sites, which is shorter than MR-based strategies [14]. Regardless of the technique, intra-fraction motion between imaging and dose delivery, contouring uncertainties, and less optimal treatment plans due to time constraints could limit the potential of tissue sparing for fully online-adaptive strategies [1,18].

The clinical significance of the reported techniques can be quantified by normal tissue complication probabilities. Models reported in literature are not suitable for this study, due to the use of plan libraries and use of smaller fully online-adaptive PTV volumes that require significant model extrapolation. As an alternative, PTV volume was found to correlate with higher incidences of patient-reported diarrhea symptoms for the PotD protocol in previous work [7]. A 17 % odds increase of patient-reported diarrhea symptoms was found per 100 cm^3 increase of PTV volume in a univariate analysis, in a cohort where 61 out of 103 patients had reported diarrhea symptoms. Switching from $PTV_{NONADAPT,\ curr}$ to $PTV_{POTD,\ curr}$ could lead to a hypothetical median 42 % odds reduction in patient-reported diarrhea symptoms, and an additional 24 % odds reduction might be found when employing a fully online-adaptive approach compared to a library of plans approach. This is under the assumption that a PTV volume reduction directly corresponds to a V_{45Gy} volume reduction. Large-scale international studies such as the EMBRACE II collaboration, can potentially better quantify the impact of PTV reductions on toxicity, such that the impact of protocol improvements can be better estimated [21]. Nevertheless, the approximate 50 % reduction in overlap volume for both bladder and rectum after implementing a PTV_{POTD} approach over $PTV_{NONADAPT}$ approach will likely have benefitted this patient cohort.

Conclusion

This work demonstrates that the over the years optimized library-of-plans based PotD strategy has resulted in an effective protocol to reduce normal tissue irradiation compared to a non-adaptive protocol. Further reduction of the PTV could be achieved by fully online-adaptive radiotherapy, but this will only result in a notable reduction if the residual margin can be kept small enough. Plan libraries should be strongly considered as an alternative to improve normal tissue sparing, as long as the availability of fully online-adaptive radiotherapy is not widespread.

Conflicts of interest

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Accuray Inc, Sunnyvale, USA and Varian Medical Systems Particle Therapy GmbH & Co. KG, Troisdorf, Germany. Dr. Hoogeman reports a membership of the advisory board Accuray, Sunnyvale, USA.

CRediT authorship contribution statement

Dominique Reijtenbagh: Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Visualization, Project administration. **Jérémy Godart:** Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft, Writing – review & editing, Supervision, Project administration. **Joan Penninkhof:** Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **Sandra Quint:** Conceptualization, Resources, Writing – review & editing. **András Zolnay:** Methodology, Software, Investigation, Resources, Data curation, Writing – review & editing. **Jan-Willem Mens:** Conceptualization, Methodology, Formal analysis, Writing – review & editing. **Mischa Hoogeman:** Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition.

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.

Appendices A and B. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2023.110009.

References

[1] Heijkoop ST, et al. Quantification of intra-fraction changes during radiotherapy of cervical cancer assessed with pre- and post-fraction Cone Beam CT scans. Radiother Oncol 2015;117:536–41.

[2] Haripotepornkul NH, et al. Evaluation of intra- and inter-fraction movement of the cervix during intensity modulated radiation therapy. Radiother Oncol 2011;98:347–51.

[3] Ahmad R, et al. Increasing treatment accuracy for cervical cancer patients using correlations between bladder-filling change and cervix-uterus displacements: proof of principle. Radiother Oncol 2011;98:340–6.

[4] Bondar ML, et al. Individualized nonadaptive and online-adaptive 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.

[5] Gordon JJ, et al. The effect of uterine motion and uterine margins on target and normal tissue doses in intensity modulated radiation therapy of cervical cancer. Phys Med Biol 2011;56:2887.

[6] van de Schoot A, et al. 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.

[7] Reijtenbagh DMW, et al. Patient-reported acute GI symptoms in locally advanced cervical cancer patients correlate with rectal dose. Radiother Oncol 2020;148:38–43.

[8] Heijkoop ST, 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.

[9] Sharfo AWM, et al. Comparison of VMAT and IMRT strategies for cervical cancer patients using automated planning. Radiother Oncol 2015;114:395–401.

[10] de Boer P, et al. Patterns of care survey: Radiotherapy for women with locally advanced cervical cancer. Radiother Oncol 2017;123:306–11.

[11] Kerkhof EM, et al. Online MRI guidance for healthy tissue sparing in patients with cervical cancer: an IMRT planning study. Radiother Oncol 2008;88:241–9.

[12] de Muinck Keizer DM, et al. Prostate intrafraction motion during the preparation and delivery of MR-guided radiotherapy sessions on a 1.5 T MR-Linac. Radiother Oncol 2020;151:88–94.

[13] McPartlin AJ, et al. MRI-guided prostate adaptive radiotherapy–A systematic review. Radiother Oncol 2016;119:371–80.

[14] Sibolt P, et al. Clinical implementation of artificial intelligence-driven cone-beam computed tomography-guided online adaptive radiotherapy in the pelvic region. Phys Imaging Radiat Oncol 2021;17:1–7.

[15] Bondar L, et al. A symmetric nonrigid registration method to handle large organ deformations in cervical cancer patients. Med Phys 2010;37:3760–72.

[16] Rigaud B, et al. Statistical shape model to generate a planning library for cervical adaptive radiotherapy. IEEE Trans Med Imaging 2019;38:406–16.

[17] Visser J, et al. Dosimetric comparison of library of plans and online MRI-guided radiotherapy of cervical cancer in the presence of intrafraction anatomical changes. Radiat Oncol 2019;14:126.

[18] Berger T, et al. Dosimetric impact of intrafraction motion in online-adaptive intensity modulated proton therapy for cervical cancer. Int J Radiat Oncol Biol Phys 2021;109:1580–7.

[19] Chuter RW, et al. Investigating the impact of field size on patient selection for the 1.5 T MR-Linac. Med Phys 2017;44:5667–71.

[20] Klüter S. Technical design and concept of a 0.35 T MR-Linac. Clin Transl Radiat Oncol 2019;18:98–101.

[21] Pötter 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.