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Physics Contribution

# Dosimetric Impact of Intrafraction Motion in Online-Adaptive Intensity Modulated Proton Therapy for Cervical Cancer

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**Summary**

Online-adaptive intensity modulated proton therapy is a promising approach for patients with cervical cancer, but intrafraction motion may limit its advantage. Focusing on patients subject to large uterus motion, intrafraction changes were found to occasionally cause substantial dose degradations. Relatively small margins (≤5 mm) around the mobile parts of the target are sufficient to address this issue in most

**Purpose:** A method was recently developed for online-adaptive intensity modulated proton therapy (IMPT) in patients with cervical cancer. The advantage of this approach, relying on the use of tight margins, is challenged by the intrafraction target motion. The purpose of this study was to evaluate the dosimetric effect of intrafraction motion on the target owing to changes in bladder filling in patients with cervical cancer treated with online-adaptive IMPT.

**Methods and Materials:** In 10 patients selected to have large uterus motion induced by bladder filling, the intrafraction anatomic changes were simulated for several prefraction durations for online (automated) contouring and planning. For each scenario, the coverage of the primary target was evaluated with margins of 2.5 and 5 mm.

**Results:** Using a 5- mm planning target volume margin, median accumulated D98% was greater than 42.75 $Gy_{RBE1.1}$ (95% of the prescribed dose) in the case of a prefraction duration of 5 and 10 minutes. For a prefraction duration of 15 minutes, this parameter deteriorated to 42.6 $Gy_{RBE1.1}$. When margins were reduced to 2.5 mm, only a 5-minute duration resulted in median target D98% above 42.75 $Gy_{RBE1.1}$. In addition, smaller bladders were found to be associated with larger dose degradations compared with larger bladders.

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cases. To limit dose degradations induced by intrafraction motion, it is recommended to treat with a full bladder.

**Conclusions:** This study indicates that intrafraction anatomic changes can have a substantial dosimetric effect on target coverage in an online-adaptive IMPT scenario for patients subject to large uterus motion. A margin of 5 mm was sufficient to compensate for the intrafraction motion due to bladder filling for up to 10 minutes of prefraction time. However, compensation for the uncertainties that were disregarded in this study, by using margins or robust optimization, is also required. Furthermore, a large bladder volume restrains intrafraction target motion and is recommended for treating patients in this scenario. Assuming that online-adaptive IMPT remains beneficial as long as narrow margins are used (5 mm or below), this study demonstrates its feasibility with regard to intrafraction motion. 

## Introduction

External beam radiation therapy (EBRT) is a crucial part of the standard treatment for patients with locally advanced cervical cancer (LACC) but can cause acute and late toxicities[1] due to the inevitable irradiation of organs at risk (OARs; bowel, rectum, bladder, and vagina).[2-7] The irradiation of the OARs partially results from the nonconformity of the dose distribution as well as from the use of the large margins necessary to handle the mobility of some parts of the target.

The primary clinical target volume (pCTV) is composed of the gross tumor volume (GTV), the remaining cervix, the uterus, and 2 cm of the upper vagina and is subject to interfractional motion during the course of EBRT. Interfractional target motion can result from changes in bladder or rectal filling.[8,9] A study by Heijkoop et al[10] showed that these anatomic changes may also be significant within the time-frame of a single fraction (ie, intrafraction motion). During a fraction, the group-mean systematic intrafraction cervix-uterus motion was found to be up to 5 mm in cranial and posterior directions, and this displacement was correlated with bladder inflow rate.

EBRT motion-compensating strategies include the use of internal target volume (ITV) margins or adaptive strategies such as a plan-of-the-day technique.[11-15] In contrast to ITV strategies, the plan-of-the-day approach requires smaller margins, reducing the dose to OARs.[13] The use of proton therapy, especially intensity modulated proton therapy (IMPT), can further reduce the dose received by surrounding organs compared with intensity modulated radiation therapy when narrow margins are used.[16-21] However, IMPT is sensitive to motion due to its sharp dose gradients and the physical characteristics of the proton dose deposition, which makes the use of tight margins particularly challenging.

To mitigate the effect of the anatomic displacements in IMPT, plan libraries similar to photon therapy have been proposed.[22] However, Jagt et al[23] showed that the target coverage of a plan-of-the-day strategy could still be unsatisfactory for proton therapy and proposed online-adaptive strategies such as daily replanning instead.[24,25] Jagt et al did not, however, take into account the intrafraction motion of the target due to bladder filling over the course of 1 single fraction. This intrafraction motion is expected to be larger in online-adaptive IMPT as additional time is required for online contouring, planning, and delivery. To conclude on the feasibility of online-adaptive IMPT approaches in the presence of intrafraction motion, further research is warranted.

This study aimed to evaluate the dosimetric effect of intrafraction motion due to changes in bladder filling in patients with cervical cancer subject to large cervix-uterus motion treated with online-adaptive IMPT. A motion model was used to simulate bladder-induced intrafraction motion on the pCTV position. Several prefraction durations (for online contouring and planning) were simulated, and for each scenario the dosimetric effect was assessed for different margins.

## Methods and Materials

Seventy-three consecutive patients with LACC, who were treated in 2 cohorts separated in time, were analyzed. A total of 10 patients for whom a wide range of bladder volumes caused significant uterus motion (ie, largest fundus displacement >4.5cm) during the radiation therapy course were selected. For each patient, a full-bladder planning computed tomography (pCT) was available as well as daily cone beam computed tomography (CBCTs) acquired for image guidance. The CBCTs were rigidly registered to the pCT based on the bony anatomy. Five different CBCTs, including the emptiest bladder, the fullest, and 3 bladders equally distributed in between, were selected to represent all possible bladder filling scenarios. The OARs, which included the outer extension of the bowels, the sigmoid, the bladder, and the rectum were contoured on the selected CBCTs by a radiation oncologist and verified by a senior site-expert. The pCTV, composed of the cervix, the uterus, the GTV, and the upper 2 cm of the vagina was also contoured on each CBCT.

The elective nodal target volume (CTV-E) included lymph nodes and was delineated on pCT. It followed the relevant vessels with a margin of ≥7 mm, unless safe anatomic barriers such as bone or uninvolved muscle/fascia allowed for a smaller margin. The number of lymph nodes with suspected metastases at imaging ranged from

0 to 5 in the patients. The cranial limit of the CTV-E was located for 7 patients at the aortic bifurcation while it reached the renal vessels, including the para-aortic region for 3 patients.

To account for the intrafraction motion, 2 planning target volume (PTV) margins, of 2.5 and 5 mm, were added isotropically to the pCTV. The pCTV from the CBCT was then combined with the CTV-E and the parametrium, which were both contoured on the pCT (and considered immobile) to form the PTV.

The Hounsfield units (HUs) of the CBCTs are not sufficiently accurate to determine the stopping power needed to calculate the proton beam range.[26] To solve this, synthetic CTs (sCT) that contain OARs and target contours from CBCTs with mapped HU from the pCT were generated. First, the body contours of the pCTs were filled with water HU except for the bones, which kept their original HU. Subsequently, the OARs and target contours were transferred from the CBCTs to the sCTs. Finally, the pCT HUs of the bladder and pCTV were mapped to the sCTs. To this end, the CBCT bladder and pCTV contours were nonrigidly registered to those in the pCTs, and the obtained transformations were used to map the HU in the contours from the pCTs to the sCTs.

In this study, the online-adaptive approach was assumed feasible and daily replanning was simulated. The contours from the CBCTs were considered as those obtained at imaging on the day of treatment delivery.

Using 'Erasmus-iCycle', a treatment planning system developed in house by Erasmus MC for fully automated plan generation,[27,28] 4-field IMPT dose-plans were generated[29] on the sCTs with 2 lateral-opposed and 2 posterior-oblique beams for the 5 fractions of the 10 patients. The EBRT schedule was 45 $Gy_{RBE1.1}$ in 25 fractions for the PTV. The boosted lymph nodes were planned using a simultaneous integrated boost with a dose of 55 $Gy_{RBE1.1}$. The dose and coverage criteria of the OARs and lymph nodes were according to the image-guided intensity modulated External beam radiochemotherapy and MRI-based adaptive BRAchytherapy in locally advanced CErvical cancer (EMBRACE) II protocol.[30] For the target, the V95% of the PTV was required to be $\geq$97.5% and pCTV V95% was $\geq$99.5% for all plans. All clinical constraints were fulfilled during the planning.

Bladder expansion was estimated to simulate bladder-induced intrafraction motion based on data from 16 patients with LACC from Erasmus MC. These patients followed a drinking protocol and were asked to drink 300 mL of water 2 hours before treatment, to empty their bladders 1 hour later, and drink another 300 mL. Patients with bigger bladders tend to have larger urine inflows and faster bladder filling.[10] Therefore, to estimate the urine inflow in our patients, a linear regression of the bladder expansion rate (mL/min) as a function of initial bladder volume from the Erasmus MC patients was used. At each fraction, the bladder volume in the CBCT was used to determine the corresponding expansion rate using the aforementioned linear regression.

As the bladder expands between image acquisition and delivery,[10] this time interval needs to be estimated. To do so, 3 durations were considered for the completion of contouring and planning: 5, 10, and 15 minutes. In addition, the duration of the image guidance procedure from the clinical system was added. Moreover, an allocation time per beam of 1 minute 30 seconds was assumed and summed to account for treatments taking place concomitantly in other rooms as well as the beam shifting time. Finally, a program computing the number of spots, the number of energy layers, and the gantry rotation speed was used to estimate the time of delivery for each beam. In the end, by summing the aforementioned time intervals, the duration between imaging and the halfway of the delivery of each beam was calculated. By multiplying these durations and the urine inflow, the volume of the bladder at the halfway of each beam was estimated.

A motion model based on thin-plate-spline deformable image registration algorithms was used to simulate bladder-induced intrafraction pCTV motion.[31,32] It interpolates the shape of the uterus and bladder based on anatomic differences between pCT and CBCTs. A patient-specific pCTV position can thereby be simulated for any specific bladder volume or fraction duration. By applying this model for each fraction, the pCTV position halfway through each of the 4 beams was generated.

Using the newly generated pCTV, sCT images reflecting the patient anatomy at halfway through each beam were created. The contours were then visually assessed by the authors and the fractions with unrealistic anatomies (ie, uterus extrapolated in bony structures or too close to the external contour of the patient) were excluded from the analysis. The dose of each of the 4 beams was then recalculated on each corresponding sCT. Because the pCTV of each beam is different, the dose volume histogram (DVH) parameters cannot be calculated from a direct dose summation of each beam per fraction. The doses of each beam were therefore projected back to the pCT for each fraction using the deformable image registration algorithm previously described. The doses of all 4 beams were then accumulated, and a final fraction dose was computed. The dose was accumulated per fraction and not over a patient treatment as the 5 fractions selected per patient are not expected to be representative of the whole treatment course.

Three DVH parameters from the total pCTV dose per fraction were used for analysis: V42.75 $Gy_{RBE1.1}$ (%) corresponding to 95% of the prescribed dose, D98% ($Gy_{RBE1.1}$), and V48.15 $Gy_{RBE1.1}$ (%) corresponding to 107% of the prescribed dose.

To determine whether the bladder volume at imaging influences the dose degradation, the selected fractions were divided, based on their bladder volumes, into 4 groups (small, medium, large, or very large) of 8 to 9 fractions. Median bladder volumes and D98% were

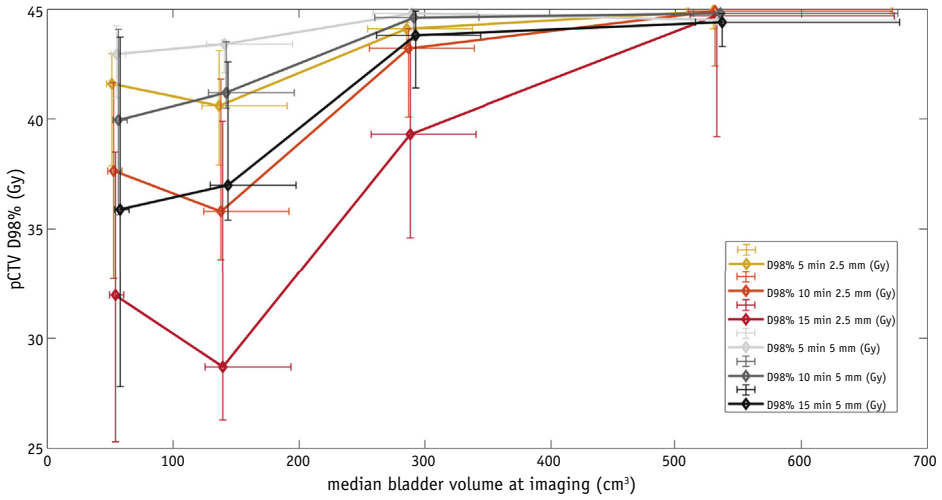


**Fig. 1.** Median values of accumulated primary clinical target volume (pCTV) D98% ($Gy_{RBE1.1}$) as a function of median values of bladder volume at imaging ($cm^3$). Error bars indicate first and third quartiles.

calculated for the 4 groups and plotted (Fig. 1). Mann-Whitney U-tests were performed (*P*-value threshold of .01) to compare the D98% of 2 groups composed of 17 and 18 fractions with bladder volumes of 42 to 207 $cm^3$ and 240 to 724 $cm^3$, respectively.

To assess whether the excluded fractions significantly affected the bladder volume distribution, a 2 sample Kolmogorov-Smirnov test was used with a threshold for statistical significance of 0.01. In addition, the anatomic location of the pCTVs subject to dose degradations (<42.75 $Gy_{RBE1.1}$) was visually inspected by a physicist.

## Results

Of the 50 CBCT scans initially selected, 35 with realistic anatomies and evenly distributed among patients (3 to 4 per patient) were further analyzed. The other cases were excluded mainly because of a too small anatomic difference between pCT and CBCTs, which made the use of the motion model inappropriate. The median (Q1-Q3) bladder volume was 240 (113-431) $cm^3$ at the time of daily image acquisition. The estimated time between the end of the prefraction procedure (for contouring and planning) and halfway of the last beam ranged between 10 and 19 min with a median value of 13 minutes. In a scenario with 5 minutes dedicated to contouring and dose-planning, median bladder volume increased to 299 (155-545) $cm^3$ at the halfway of the last beam. For the 10- and 15-minute scenarios, median bladder volume increased to 318 (168-574) and 336 (181-602) $cm^3$, respectively.

The longer prefraction durations were associated with lower V42.75 $Gy_{RBE1.1}$ and D98%. Median D98% and V42.75 $Gy_{RBE1.1}$ were found to be close to or above 40 $Gy_{RBE1.1}$ and 98%, respectively, in all scenarios studied except with a 2.5-mm margin and a 15-minute prefraction duration. In this scenario, the median D98% dropped to 38.9 $Gy_{RBE1.1}$ and V42.75 $Gy_{RBE1.1}$ to 94.1%. Despite tolerable median DVH parameters for most scenarios, considerable dose degradation was still found for some fractions. In 1 particular case, D98% dropped to 25 $Gy_{RBE1.1}$ with a 5-mm margin and a 5-minute prefraction duration. The target coverage parameters are provided as boxplots in Figures 2 and 3 for 6 scenarios (3 prefraction durations and 2 different margins). The median values are summarized in Table 1.

Figure 4 shows that prefraction duration had very limited effect on median V48.15 $Gy_{RBE1.1}$ when margins of 5 mm are used. Decreasing the margin from 5 mm to 2.5 mm slightly reduced the V48.15 $Gy_{RBE1.1}$.

As illustrated in Figure 1 and confirmed by the Mann-Whitney U-tests, higher initial bladder volumes (assessed at daily image acquisition) are associated with lower D98% dose degradations in all scenarios tested ($P <$ .01). In a scenario with a 2.5-mm margin and 15-min prefraction duration, the group with the lowest CBCT bladder volume (median of 56 $cm^3$) had a median pCTV D98% of 32.0 $Gy_{RBE1.1}$. For the group with a median CBCT bladder volume of 290 $cm^3$, the median D98% was 39.3 $Gy_{RBE1.1}$, and for the 1 with the largest volume (median of 534 $cm^3$), the D98% was 44.7 $Gy_{RBE1.1}$. For a bladder volume of 290 $cm^3$ or more, all scenarios led to a median accumulated D98% > 42.75 $Gy_{RBE1.1}$ apart from if a 2.5-mm margin was combined with a 15 min prefraction duration.

Because the full bladder CTs were not all acquired with similar bladder volumes, the bladder volumes of the excluded CBCTs ranged from 103 $cm^3$ up to 543 $cm^3$. The exclusion of these fractions was found not to significantly affect the distribution of bladder volumes ($P = .879$).

As illustrated in Figure 5, the anatomic region subject to repeated dose reductions (<42.75 $Gy_{RBE1.1}$) was for all patients the fundus and more specifically the cranial posterior part of the uterus.

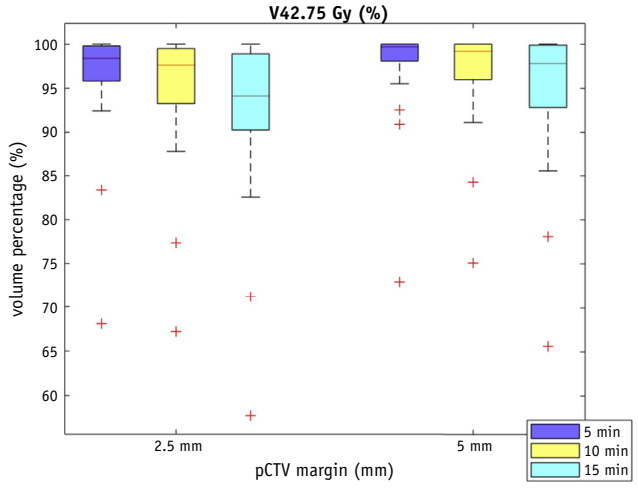


**Fig. 2.** Boxplots of accumulated primary clinical target volume (pCTV) V42.75 $Gy_{RBE1.1}$ (%) for both 2.5 and 5 mm and 3 durations dedicated to contouring and dose-planning (5, 10, and 15 min). The bottom edge, the central mark, and the top edge of the box indicate the 25th, the 50th, and 75th percentiles, respectively. The whiskers extend to the most extreme data points not considered outliers [<Q3 + 1.5 × (Q3-Q1) or >Q1-1.5 × (Q3-Q1)], and the outliers are plotted individually using the + symbol.

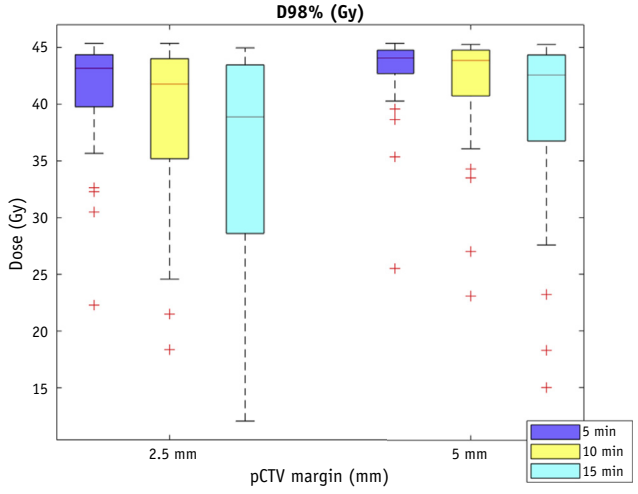


**Fig. 3.** Boxplots of accumulated primary clinical target volume (pCTV) D98% ($Gy_{RBE1.1}$) for both 2.5 and 5 mm margins and the 3 durations dedicated to contouring and dose planning (5, 10, and 15 min). The bottom edge, the central mark, and the top edge of the box indicate the 25$^{th}$, the 50$^{th}$, and 75th percentiles, respectively. The whiskers extend to the most extreme data points not considered outliers [<Q3 + 1.5 × (Q3-Q1) or >Q1-1.5 × (Q3-Q1)], and the outliers are plotted individually using the + symbol.

**Table 1** Median accumulated pCTV V42.75 $Gy_{RBE1.1}$ and D98% ($Gy_{RBE1.1}$) for durations of 5, 10, and 15 minutes and margins of 2.5 and 5 mm

| V42.75 $Gy_{RBE1.1}$ (%) | 5 min | 10 min | 15 min |
|---|---|---|---|
| 2.5 mm | 98.4 | 97.6 | 94.1 |
| 5 mm | 99.7 | 99.2 | 97.8 |
| D98% ($Gy_{RBE1.1}$) | | | |
| 2.5 mm | 43.2 | 41.8 | 38.9 |
| 5 mm | 44.1 | 43.9 | 42.6 |

*Abbreviation:* pCTV = primary clinical target volume.
Cells with a D98% > 42.75 $Gy_{RBE1.1}$ and V42.75 $Gy_{RBE1.1}$ > 98% are highlighted in green, others in yellow.

## Discussion

Intrafraction anatomic changes in patients subject to large uterus motion may induce substantial dose degradations. However, in most cases, relatively small margins (≤5 mm) are sufficient to compensate for this dose degradation. The proportion of patients encountering large bladder-filling−induced uterus-cervix motion was found to be 14% in our study, as the 10 patients analyzed were selected from a group of 73 patients. This category of patients is expected to represent between 10% and 20% of all patients with cervical cancer. Therefore, median values in our selected population could be considered as the 90 to 95th percentile for the whole population. An increased

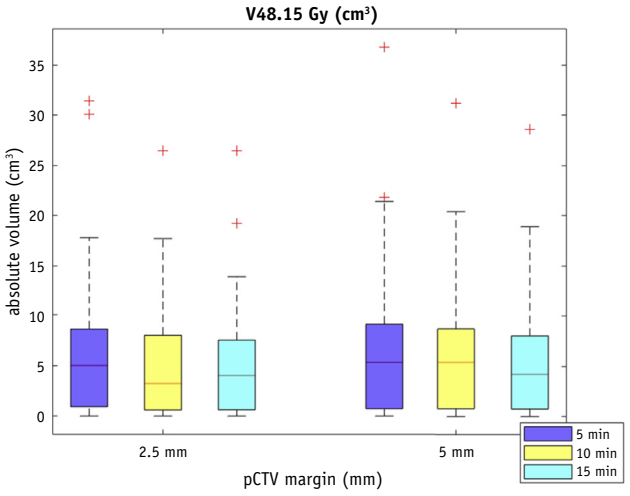


**Fig. 4.** Boxplots of accumulated primary clinical target volume (pCTV) V48.15 $Gy_{RBE1.1}$ ($cm^3$) for both pCTV-to-planning target volume (PTV) margins (2.5 and 5 mm) and the 3 durations dedicated to contouring and dose planning (5, 10, and 15min). For boxplots, the bottom edge, the central mark, and the top edge of the box indicate the 25$^{th}$, the 50$^{th}$, and 75th percentiles, respectively. The whiskers extend to the most extreme data points not considered outliers [<Q3 + 1.5 × (Q3-Q1) or >Q1-1.5 × (Q3-Q1)], and the outliers are plotted individually using the + symbol.

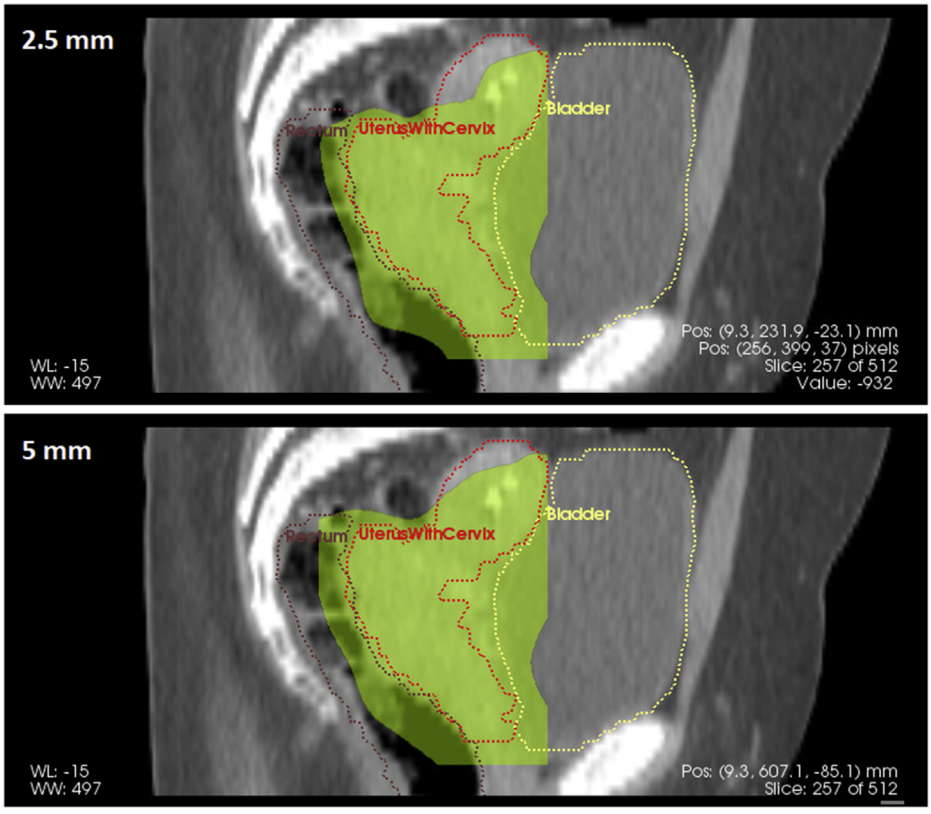


**Fig. 5.** Accumulated V42.75 Gy (colored regions) from the 4 beams of 1 fraction on sagittal view of the planning computed tomography (CT) with 2.5 mm (top) and 5 mm (bottom) margins. The red contour is the primary clinical target volume (pCTV) and the yellow one the bladder. (A color version of this figure is available at https://doi.org/10.1016/j.ijrobp.2020.11.037.)

prefraction duration (from 5-10 and 15 minutes) corresponds to larger target dose degradations, as shown in Figure 2. In a scenario in which 5 minutes are dedicated to contouring and dose planning, a 2.5-mm margin is sufficient to maintain the median pCTV D98% above 42.75 $Gy_{RBE1.1}$ (95% of prescription). For longer prefraction durations, a margin of 5 mm is required to secure a median D98% close to or greater than 95% of the prescribed dose. This finding suggests that the online-adaptive IMPT approach is feasible with a tight margin, even for prefraction durations of 10 or 15 min.

Because large bladder volumes are associated with smaller dose degradations (Fig. 1), choosing a margin based on the bladder volume at imaging is a sensible strategy to minimize the dose to the OARs. Patients with bladders around 534 $cm^3$ seem not to require margins greater than 2.5 mm for all prefraction durations. For bladders of 290 $cm^3$, a 2.5-mm margin maintains the pCTV dose coverage up to a 10-min prefraction duration. For 15-min durations, a 5-mm margin is required. For smaller bladders ($<141$ $cm^3$), however, a 5-mm margin can only compensate for intrafraction motion in a 5-min prefraction duration. For this small bladder group, a margin larger than 5 mm is required for a prefraction duration of 10 or 15 min. This may limit the benefit of an online-adaptive approach for these patients.

It is currently recommended to treat patients with a full bladder to push the bowel away from the irradiated area.[33,34] Based on our results, we can conclude that patients with a fuller bladder are also less subject to dose degradation induced by intrafraction motion and therefore require smaller margins. This is partly due to the fact that a uterus resting on a small expanding bladder will preferably move cranially and posteriorly. When the uterus reaches a straight position, we have observed that the bladder continues to expand predominantly cranially while affecting less the uterus position. Geometric aspects reinforce this effect: A same bladder volume increase induces a larger radius change in a smaller bladder compared with a bigger one. However, the inflow of larger bladders is greater than that of smaller ones and slightly mitigates this effect.[10]

As larger bladder volumes are associated with a smaller dose degradation, bladder volumes as high as comfortably achieved by the patient can be recommended. It is important to keep in mind that the benefits associated with a bladder volume strongly depend on the duration during which intrafraction motion occurs (ie, the planning and treatment phase). In addition, as bladder volume tends to decrease during the treatment course,[35] larger margins are expected to be required toward the end of the course. DVH parameters allow evaluation of the coverage but do not take

into account anatomic information that may be essential. It is of particular interest for targets composed of subregions associated with different risks of recurrence, such as the pCTV. An underdosage on the GTV has more clinical effect compared with an underdosage on the uterus fundus. In our study, the anatomic region repeatedly subject to dose degradation was found to be the fundus. Incidentally, the EMBRACE II protocol tolerates a 40 Gy delivered dose to the fundus while recommending a planning aim of $\geq$42.75 Gy for the ITV-45 including the uterus. The small underdosages (eg, D98% $\approx$ 40 $Gy_{RBE1.1}$) found in our study are within the thresholds recommended in the EMBRACE II protocol.

The fractions selected for each patient are not expected to be representative of the whole EBRT course, but to depict the widest range of bladder volumes. The median results are thereby expected to provide a reasonable approximation of most of the fractions. In addition, we analyzed patients subject to substantial bladder-filling-induced uterus motion. As they represent the most challenging group that would require the largest margins, this allows us to conclude on the feasibility of the online-adaptive approach for all patients with cervical cancer.

The uterus motion that was simulated is likely not to have accurately reflected the anatomic changes that occurred in the patients in all situations. In particular, the urine inflow varies depending on hydration, and the bladder expansion parameters used were based on an average of patients who followed a specific drinking protocol. The effect of this uncertainty may be estimated if one considers the different prefraction durations of this study as a modulation of the inflow. Despite this imprecision, the shape of the growing bladder as well as the subsequent uterus motion can be considered realistic. In this study, only intrafraction motion due to bladder filling was simulated despite the presence of other organs with variable filling in the pelvic region. The filling of the rectum is known to cause GTV/cervix interfraction motion, but Heijkoop et al[10] found an average variation of 5 $cm^3$ of the rectum in a 21-minute fraction and an absence of correlation with intrafraction motion, which justifies our approach. However, further studies are needed to confirm these results and to determine whether an extra margin is required to account for this.

The method to generate the sCT is described in the Methods and Materials section. We also tested an alternative method, which uses intensity-based deformable registration to deform the pCT to the CBCT and map the HU accordingly. However, this resulted in disproportionately stretched gas pockets in the sCT, which interfered with the dose calculation. The advantage of our approach is that the results are not distorted by other factors, but only gives the dosimetric effect of the intrafractional movement of the cervix-uterus.

Most studies evaluating plan-library strategies are based on an analysis of repeat CTs and disregard the dosimetric contribution of intrafraction motion. Our study indicates that this aspect should be considered for patients subject to large intrafraction motion. On the other hand, in our study, uncertainties other than intrafraction motion, such as change in patient position from pCT to delivery, pencil beam misalignment, couch misalignment, or range uncertainties, were not included and should be evaluated and compensated for separately. Our results indicate that for intrafraction motion alone, small margins ($\leq$5 mm) are sufficient in most cases. However, in a realistic treatment scenario the other uncertainties should be accounted for by an additional margin or robust optimization.

In the present study, the lymph nodes were considered static, but possible intrafraction motion should be assessed and included when devising margins for this part of the target volume.

The implementation of online-adaptive strategies in clinical practice still requires some challenges to be addressed, such as the development of a fast and reliable auto-contouring tool as well as a way to generate a treatment plan rapidly. The durations for contouring and treatment planning (5, 10, and 15 minutes) were chosen in the present study assuming that reliable automated solutions will become available for both tasks. Research groups and also vendors have made significant progress in this direction. For example, Liu et al[36] have developed a tool based on a convolutional neural network for automatic segmentation of the OARs of patients with cervical cancer and have achieved acceptable results in less than 5 seconds. For target contours, Bondar et al[37] investigated different strategies with minimal user intervention, which satisfactorily delineated daily cervix−uterus shapes in less than 1 minute. Regarding automatic IMPT replanning for patients with cervical cancer, Jagt et al[23] recently reported on a method that successfully adapts the treatment plan from a plan-library in the order of minutes. Therefore, we believe that the durations chosen in the present study are realistic for the near future.

## Conclusions

In conclusion, intrafraction motion can have a substantial dosimetric effect for patients with cervical cancer treated with online-adaptive IMPT. Margins of 2.5-5 mm were found to limit this effect in most scenarios for patients subject to large interfractional uterus motion. Note that an additional margin or robustness may be needed to account for other treatment uncertainties. In addition, it is recommended to treat patients with a full bladder to minimize the dose degradation.

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