

# Influence of Interfractional Variations of Bladder and Rectal Filling on Vaginal Cuff Movement and the Role of Rectal Balloons in Gynecological Pelvic Proton Beam Therapy

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## Abstract

**Introduction:** Postoperative active raster-scanning intensity modulated proton beam therapy (IMPT) for gynecological cancers requires precise target coverage, yet interfractional motion of the vaginal cuff and adjacent pelvic organs may compromise dosimetric robustness. This study retrospectively assessed interfractional organ movement and evaluated the clinical need for rectal balloon (RB) use to ensure adequate target coverage. **Methods:** 23 patients, 17/6 with/without RB, received postoperative IMPT between 2017 and 2020 at Heidelberg Ion-beam Therapy Center (HIT). Positioning verification computed tomography (pv-CT) and treatment planning CT (tp-CT) images were retrieved and rectum, bladder and the vaginal cuff (VC) were contoured. The clinical target volume (CTV) and planning target volume (PTV) were mapped from tp-CT to the pv-CT images and forward dose calculation was performed. To assess the volume of the VC not covered by the CTV or PTV, the region of interest (ROI), VC outside of CTV (VC-CTV) and outside of PTV (VC-PTV) were created. Volume differences ( $\Delta$ ) to the tp-CT images and dose parameters for each ROI were evaluated. **Results:** 139 pv-CTs were analysed. The use of RB significantly reduced VC displacements, resulting in fewer pv-CTs with the VC located outside the CTV (40% vs. 91%,  $p = 0.0252$ ) and PTV (28% vs. 68%,  $p = 0.0362$ ). CTV/PTV coverage and ROI doses remained stable across all fractions and there was no significant difference between groups. The applied PTV margins ensured robust dose coverage despite interfractional anatomical variations. **Conclusion:** RB application effectively reduced interfractional VC motion and there was no significant  $\Delta$  in target coverage or ROI doses. Using tp-CT images with full and empty bladder for definition of the CTV and standardized PTV margins contributed to stable dosimetry outcomes, confirming the robustness of the used IMPT treatment protocol. However, the use of RB may be beneficial, especially in patients with known gastrointestinal comorbidities or trapped air in the rectum.

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**Keywords**

endometrial cancer, cervical cancer, vaginal cuff, interfractional organ movement, proton beam therapy, rectal balloon

Received: 2 December 2025; Revised: 24 February 2026; Accepted: 9 March 2026

**Introduction**

Postoperative pelvic radiotherapy is a cornerstone of adjuvant management in patients with cervical or endometrial cancer who present with adverse pathological features following hysterectomy.<sup>1-3</sup> Randomized trials have shown that adjuvant pelvic irradiation improves local control and survival in selected patients, yet treatment-related gastrointestinal and genitourinary toxicities remain a major concern.<sup>4-7</sup> The implementation of intensity-modulated radiation therapy (IMRT) in clinical practice and, more recently, intensity-modulated proton beam therapy (IMPT) has allowed for more conformal treatment delivery, reducing incidental dose to surrounding organs-at-risk (OAR), especially the bowel, bladder, and rectum.<sup>8-10</sup> However, the dosimetry advantages of conformal techniques can be compromised by internal organ motion and variations in organ filling, which directly impact the position of the target volume, the vaginal cuff, and the dose distribution.<sup>11</sup>

The extent of organ motion, tumour regression, and anatomical deformation observed in patients with cervical and endometrial cancer is often considerably greater than that seen in prostate cancer.<sup>12-16</sup> After hysterectomy, the vaginal cuff is located adjacent to the bladder anteriorly and the rectum posteriorly, and its position is highly sensitive to variations in bladder filling and rectal distension.<sup>11,16,17</sup> Several studies have demonstrated substantial interfractional displacement of the vaginal cuff during adjuvant pelvic irradiation<sup>8,12,17</sup> and large variations in bladder and rectal filling correlate with displacement of the vaginal cuff.<sup>12</sup> The vaginal cuff can move up to 28 mm in the Anterior-Posterior (AP) direction, with rectal distension strongly correlating with anterior displacement.<sup>18</sup> In a prospective image guided (IG) IMRT study, a mean displacement of 1.2 mm (mediolateral), 4.0 mm (superior-inferior), and 2.8 mm (anterior-posterior) was measured, with required internal target volume (ITV) margins in the range of 10 mm to encompass 95% of excursions.<sup>17</sup> These studies highlight the unpredictable nature of vaginal cuff motion and its dependence on dynamic bladder and rectal conditions. Such interfraction variability is challenging for reliable target coverage in highly conformal treatments. If not properly accounted for, organ motion risks miss of the vaginal cuff and underdosage of high-risk regions.<sup>18</sup> Conversely, the use of large margins to compensate for motion increases dose to the bladder, rectum, and bowel, undermining the sparing advantage of IMRT and IMPT.

Proton therapy, with its sharp distal fall-off and reduced dose behind the target volumes, provides further opportunities to reduce dose to the bladder, rectum, and small bowel compared to photon-based IMRT.<sup>10,19,20</sup> However, the precision of proton therapy makes it especially sensitive to interfraction organ motion and density variations, which can alter the proton beam path and degrade target coverage.<sup>21,22,23</sup> Recent developments in offline adaptive workflows and magnetic resonance image (MRI) guided therapy have shown that interfractional adaptations can improve robustness against motion.<sup>24</sup> Nevertheless, these methods are resource-intensive, and reproducible strategies to minimize motion—such as bladder filling protocols and potentially rectal balloons (RB)—remain important to optimize dosimetry without excessive adaptation.

To address vaginal cuff displacement during radiotherapy, consensus guidelines recommend simulation with both empty- and full-bladder CT images to generate an ITV that encompasses both extremes of bladder filling.<sup>25</sup> This strategy captures some of the variability but often leads to expansion of the PTV and increased OAR doses.<sup>25</sup> This demonstrates a fundamental trade-off: ensuring coverage of target motion versus minimizing OAR exposure.<sup>26</sup> Rectal distension correlates especially with AP displacement of the vaginal cuff.<sup>18</sup> In prostate cancer, rectal balloons have been successfully used to stabilize rectal volume, reduce interfraction motion, and improve dosimetry.<sup>27,28</sup> Whether such an approach can improve stability of the vaginal cuff in gynaecologic patients is not well established. By controlling rectal distension, rectal balloons may reduce anterior-posterior shifts of the vaginal cuff and thereby improve reproducibility of its position relative to the bladder and rectum. Given the high conformality and steep dose gradients achievable with IMPT, the potential of rectal balloons to reduce target motion and protect OARs is particularly relevant.<sup>11</sup>

Despite increasing evidence of substantial interfraction motion of the vaginal cuff and variable bladder/rectal volumes, there is debate on optimal strategies to mitigate these effects in postoperative radiotherapy settings. Current bladder-filling protocols achieve inconsistent results, and rectal distension remains uncontrolled.<sup>12</sup> Evidence in prostate radiotherapy suggests that endorectal balloons can improve positional reproducibility and may reduce rectal doses in selected settings; however, dosimetry benefits are variable across techniques, and routine use is not currently guideline-mandated.<sup>29,30</sup> However, the rectal balloon value in gynaecologic cancer patients is largely unexplored.

The present study investigates interfraction motion of the vaginal cuff and variations in bladder and rectal volumes during postoperative IMPT, comparing patients treated with and without rectal balloons. By quantifying organ motion and assessing

dose distribution to the vaginal cuff, bladder, and rectum, this work aims to determine whether rectal balloon use enhances the stability of target coverage and improves the therapeutic ratio of proton beam therapy in postoperative radiotherapy of gynaecological cancer patients.

## Patients and Methods

Patients with either uterine cervical or endometrial cancer who have been treated at Heidelberg Ion-beam Therapy Center (HIT) have been screened. All patients fulfilling the following criteria were included in this retrospective analysis: postoperative radiotherapy with a total dose of 45 or 50.4 Gy relative biological effectiveness (RBE) in 5 to 6  $\times$  1.8 Gy RBE fractions weekly using active raster-scanning IMPT and available planning CT and positioning verification CT scans. All in all, 23 patients were included in the analysis.

Radiotherapy planning was performed with two CT scans (full and empty bladder), using an immobilization ProSTEP (Innovative Technologie Völp e.U., Innsbruck, Austria) device for patient positioning. All in all, in 17 patients a RB (RectalPro™75, QLRAD) was used during IMPT treatment. 6 patients were treated without a RB. If a RB was applied, it was inserted to a consistent depth shortly before the planning CT scan and before every single fraction of IMPT. We inflated the balloon with 20 mL of fluid Natrium Chloride (NaCl) – this volume was chosen to gently distend the rectum without causing discomfort and without extensive compression of the VC. The CTV was defined according to the RTOG consensus guidelines.<sup>25</sup> Dose was prescribed to the CTV aiming at a PTV coverage of 95%. For plan design, two posterior oblique fields (160° and 200°) were applied using single field optimization. For larger target volumes, a third field (180°) was used, if necessary. Further details of IMPT planning and application at our institution have been described previously.<sup>10</sup> Patients were requested to have a full bladder during radiotherapy (RT). Isocenter and patient positioning were checked daily in-room pre-treatment by orthogonal x-ray-imaging and by regularly performed off-line position verification CT scans, the number depending on the decision of the treating radiation oncologist.

For this analysis, we retrieved all planning CT scans and position verification CT scans from hospital databases. Rigid registrations were performed between the initial planning CT scan with full bladder and all position verification scans of each patient. On each of these CT images, OARs like rectum and bladder and additionally the vaginal cuff were contoured using RayStation version 2024B (RaySearch Laboratories, Stockholm, Sweden). All images were contoured by the same radiation oncologist to avoid inter-observer variability. The initial CTV and PTV were then mapped from the planning CT onto the position verification CT images and new ROIs, vaginal cuff subtracted by CTV (VA-CTV) and PTV (VA-PTV) respectively, were created. These ROIs represent the volume of the vaginal cuff that is not covered by the CTV and PTV, respectively. The initial IMPT treatment plan was used for forward dose calculation onto each position verification CT scan. Dose parameters from each CT scan were extracted. The following data were collected: volumes of bladder, rectum, vaginal cuff and the newly created ROI VA-CTV/VA-PTV. Volume Differences ( $\Delta$ ) in comparison to the planning CT scan for each of the mentioned ROIs were calculated. Furthermore, dose parameters like mean dose (DMean), Dose in 95% volume (D95) and highest dose of defined volumes (D0.03cm<sup>3</sup>) for each ROI were extracted.

## Statistical Analysis

For statistical analysis, patients were divided into 2 groups depending on the use of a rectal balloon. Statistical analysis was performed using GraphPad Prism version 10.5 (GraphPad Software, Boston, Massachusetts USA). Univariate analyses comparing groups were performed using independent t-tests on aggregated subject means. Spearman's correlation was employed to evaluate associations between OAR volumes and vaginal cuff dose coverage. A p-value of < 0.05 was considered statistically significant.

All data was collected retrospectively and in accordance with institutional ethical policies. The study was granted ethical approval by the local ethics committee of Heidelberg University.

The reporting of this study conforms to STROBE guidelines.<sup>31</sup>

## Results

Between June 2017 and April 2020, 23 patients with uterine cervical or endometrial cancer received postoperative IMPT at Heidelberg Ion-beam Therapy Center (HIT).

Of the 23 patients analyzed, 17 (74%) were treated with a RB and 6 (26%) without. In total, 139 pv-CT scans were evaluated, comprising 98 (71%) in the RB group and 45 (29%) in the non-balloon group. The median number of pv-CTs per patient was 6 (range 3–9) overall, with 6 (3–8) in the RB and 7 (4–9) in the non-balloon group.

**Table 1.** Data of Position Verification CT Scans (Pv-CTs), Vaginal Cuff (VC) Outside of the Clinical Target Volume (CTV) and Planning Target Volume (PTV), Median, SD and Range are Specified Where Applicable; Number of Cases and Percentage are Stated.  $p < 0.05^*$ ;  $p < 0.01^{**}$ ;  $p < 0.0001^{****}$

|                                                                   | Total    | RB       | No RB    | p-value               |
|-------------------------------------------------------------------|----------|----------|----------|-----------------------|
| Number of patients                                                | 23       | 17 (74%) | 6 (26%)  |                       |
| Number of pv-CT                                                   | 139      | 98 (71%) | 45 (29%) |                       |
| pv-CTs Median (range)                                             | 6 (3-9)  | 6 (3-8)  | 7 (4-9)  |                       |
| VC ROI outside CTV in all pv-CTs                                  | 69 (50%) | 39 (40%) | 30 (66%) | <b>0.0006***</b>      |
| VC ROI outside PTV in all pv-CTs                                  | 31 (22%) | 11 (11%) | 20 (44%) | <b>&lt;0.0001****</b> |
| Patients with at least one VC ROI outside CTV                     | 22 (96%) | 16 (94%) | 6 (100%) | 0.4024                |
| Patients with at least one VC ROI outside PTV                     | 10 (43%) | 6 (35%)  | 4 (66%)  | 0.1992                |
| Percentage of pv-CTs with VC ROI outside CTV per affected patient | 48%      | 40%      | 91%      | <b>0.0252*</b>        |
| Percentage of pv-CTs with VC ROI outside PTV per affected patient | 43%      | 28%      | 68%      | <b>0.0362*</b>        |

Across all pv-CTs the VC ROI was located outside the CTV in 69 (50%) scans, occurring in 39 (40%) of pv-CTs with RB and 30 (66%) without RB ( $p = 0.0006$ ). The VC ROI outside the PTV was observed in 31 (22%) scans, including 11 (11%) in the RB group and 20 (44%) in the group without RB ( $p < 0.0001$ ). On a per-patient basis, 22 (96%) had at least one pv-CT showing the VC outside the CTV (16 [94%] with and 6 [100%] without RB;  $p = 0.4024$ ), and 10 (43%) had at least one scan with the VC outside the PTV (6 [35%] with and 4 [66%] without;  $p = 0.1992$ ). The proportion of pv-CTs with the VC outside the CTV per affected patient was 48% overall (40% with vs. 91% without RB;  $p = 0.0252$ ), and 43% for the PTV (28% with vs. 68% without;  $p = 0.0362$ ). Details are shown in [Table 1](#).

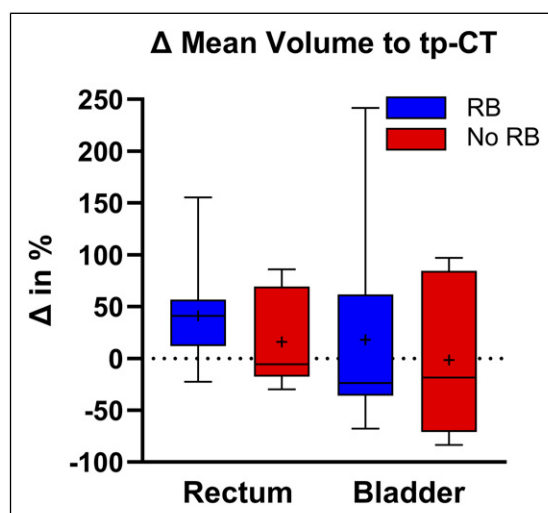
### Organs at Risk

Dose parameters for bladder and rectum from each CT scan were extracted. Volume  $\Delta$  in comparison to the planning CT scan were calculated. Results are displayed in [Table 2](#).

The mean rectal volume over all tp-CT and pv-CT images was 103.5 cm<sup>3</sup>, with 114.8 cm<sup>3</sup> in the RB group and 77.1 cm<sup>3</sup> without RB ( $p = 0.0003$ ). Compared with tp-CT images, rectal volume increased in the pv-CT images by 41.1% in the group with RB and by 15.8% in the group without RB ( $p = 0.2100$ ). The mean rectal dose DMean was 29.35 Gy overall (29.41 Gy

**Table 2.** Mean Rectum and Bladder Volumes, DMean, D95 and D0.03cm<sup>3</sup> including  $\Delta$  to Treatment Planning CT Images (tp-CTs) if applicable.  $p < 0.05^*$ ;  $p < 0.01^{**}$ ;  $p < 0.0001^{****}$

|                                         | All CTs | RB CTs   | No RB CTs | p-value          |
|-----------------------------------------|---------|----------|-----------|------------------|
| Rectum                                  |         |          |           |                  |
| Mean Volume Rectum in cm <sup>3</sup>   | 103.51  | 114.8    | 77.14     | <b>0.0003***</b> |
| Volume $\Delta$ to tp-CTs               |         | +41.1 %  | +15.8 %   | 0.2100           |
| Dmean in Gy                             | 29.35   | 29.41    | 28.42     | 0.6832           |
| Dmean $\Delta$ to tp-CTs                |         | -4.86 %  | -1.60 %   | 0.4997           |
| D95 in Gy                               | 1.80    | 1.113    | 3.090     | 0.0755           |
| D95 $\Delta$ to tp-CTs                  |         | +27.6 %  | +27.5 %   | 0.9996           |
| D0.03cm <sup>3</sup> in Gy              | 52.16   | 51.47    | 52.93     | 0.5058           |
| D0.03cm <sup>3</sup> $\Delta$ to tp-CTs |         | +6.1 %   | +10.4 %   | 0.1852           |
| Bladder                                 |         |          |           |                  |
| Mean Volume Bladder in cm <sup>3</sup>  | 233.55  | 220.7    | 248.8     | 0.4519           |
| Volume $\Delta$ to tp-CTs               |         | + 17.9 % | -1.70 %   | <b>0.0348*</b>   |
| Dmean in Gy                             | 22.74   | 23.44    | 20.83     | 0.3068           |
| Dmean $\Delta$ to tp-CTs                |         | +7.4 %   | -1.44 %   | 0.6016           |
| D95 in Gy                               | 0.2900  | 0.3005   | 0.2868    | 0.9748           |
| D95 $\Delta$ to tp-CTs                  |         | +58.0 %  | +23.9 %   | 0.6093           |
| D0.03cm <sup>3</sup> in Gy              | 53.56   | 53.34    | 53.19     | 0.9300           |
| D0.03cm <sup>3</sup> $\Delta$ to tp-CTs |         | +6.0 %   | +7.4 %    | 0.7367           |

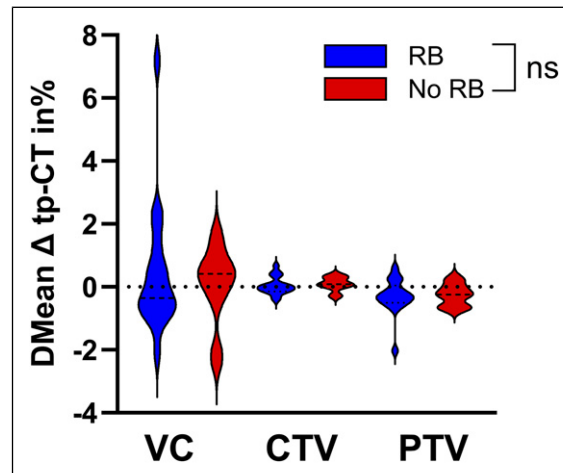


**Figure 1.** Boxplot diagram of the  $\Delta$  (difference) of mean volume compared to treatment planning CT (tp-CT) images of the organs at risk rectum and bladder including median (-), mean (+) and 5 – 95 percentile

with vs. 28.41 Gy without RB;  $p = 0.6832$ ), and the  $\Delta$  to tp-CTs images were  $-4.9\%$  and  $-1.6\%$  ( $p = 0.4997$ ), respectively. The D95 was 1.80 Gy overall (1.11 Gy with vs. 3.09 Gy without RB;  $p = 0.0755$ ), with comparable changes of  $+27.6\%$  with RB and  $+27.5\%$  without RB relative to tp-CTs images ( $p = 0.9996$ ). The D0.03cm<sup>3</sup> was 52.16 Gy overall (51.47 Gy with vs. 52.93 Gy without;  $p = 0.5058$ ), differing by  $+6.1\%$  and  $+10.4\%$  from tp-CTs ( $p = 0.1852$ ).

**Table 3.** Mean CTV, PTV, Vaginal Cuff (VC) and VC Outside CTV (VC-CTV) as well as VC Outside PTV (VC-PTV) Volumes, DMean (Mean Dose) and D95 (Volume 95% Dose in Gy), and Differences ( $\Delta$ ) to Treatment Planning CTs (Tp-CTs) of each ROI if applicable.  $p < 0.05^*$ ;  $p < 0.01^{**}$ ;  $p < 0.0001^{****}$

|                                             | All CTs | RB     | No RB   | p-value        |
|---------------------------------------------|---------|--------|---------|----------------|
| <b>CTV</b>                                  |         |        |         |                |
| Mean Volume CTV cm <sup>3</sup>             | 622.91  | 640.0  | 574.6   | 0.0961         |
| DMean in Gy                                 | 47.62   | 47.83  | 47.04   | 0.5364         |
| DMean $\Delta$ to tp-CTs                    |         | 0%     | +0.1%   | 0.6788         |
| D95 in Gy                                   | 45.92   | 46.13  | 45.29   | 0.4950         |
| D95 $\Delta$ to tp-CTs                      |         | -0.54% | -0.83%  | 0.2877         |
| <b>PTV</b>                                  |         |        |         |                |
| Mean Volume PTV cm <sup>3</sup>             | 1065.0  | 1094.0 | 982.7   | 0.0593         |
| DMean in Gy                                 | 47.9    | 47.47  | 46.79   | 0.5954         |
| DMean $\Delta$ to tp-CTs                    |         | -0.3%  | -0.26%  | 0.8764         |
| D95 in Gy                                   | 44.47   | 44.53  | 44.29   | 0.8680         |
| D95 $\Delta$ to tp-CTs                      |         | -1.79% | -2.2%   | 0.7231         |
| <b>Vaginal cuff</b>                         |         |        |         |                |
| Mean Volume vaginal cuff in cm <sup>3</sup> | 20.55   | 18.91  | 22.50   | 0.3184         |
| Volume $\Delta$ to tp-CTs                   |         | +1.7%  | -10.51% | 0.2839         |
| DMean in Gy                                 | 46.97   | 48.01  | 46.61   | 0.2972         |
| DMean $\Delta$ to tp-CTs                    |         | +0.6%  | +0.1%   | 0.5896         |
| D95 in Gy                                   | 42.84   | 44.57  | 41.85   | 0.0755         |
| D95 $\Delta$ to tp-CTs                      |         | -1.93% | -4.17%  | 0.0984         |
| <b>-VC outside CTV</b>                      |         |        |         |                |
| Volume VC-CTV in cm <sup>3</sup>            | 2.50    | 1.711  | 4.462   | <b>0.0189*</b> |
| -DMean in Gy                                | 46.15   | 46.59  | 45.03   | 0.3279         |
| D95 in Gy                                   | 42.34   | 43.56  | 39.27   | 0.1815         |
| <b>VC outside PTV</b>                       |         |        |         |                |
| Volume VC-PTV in cm <sup>3</sup>            | 1.71    | 1.050  | 2.463   | 0.1818         |
| DMean in Gy                                 | 42.30   | 44.13  | 39.53   | 0.1566         |
| D95 in Gy                                   | 37.07   | 40.38  | 32.08   | 0.1717         |



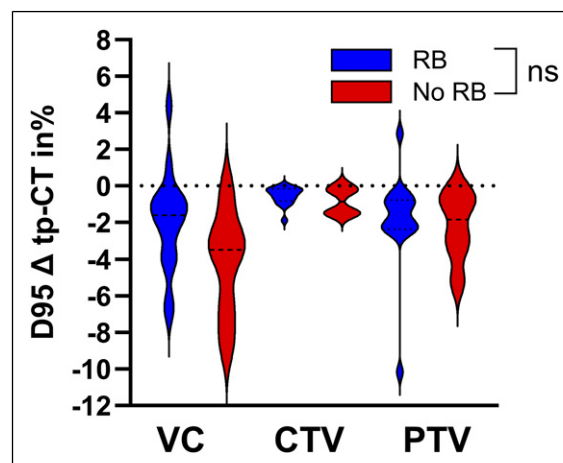
**Figure 2.** Independent t-test on aggregated means of DMean for the target volumes VC, CTV and PTV. Treatment planning CT = tp-CT, VC = vaginal cuff; CTV = clinical target volume; PTV = planning target volume,  $\Delta$  = difference, DMean = mean dose, D95 = 95% dose, ns = non-significant

The mean bladder volume was 233.6 cm<sup>3</sup>, comprising 220.7 cm<sup>3</sup> in the RB group and 248.8 cm<sup>3</sup> without RB ( $p = 0.4519$ ). The volume  $\Delta$  compared with tp-CTs images was +17.9% with RB and -1.7% without RB ( $p = 0.0348$ ). The mean bladder dose DMean was 22.74 Gy overall (23.44 Gy with vs. 20.83 Gy without RB;  $p = 0.3068$ ), corresponding to +7.4% and -1.4% relative to tp-CTs images ( $p = 0.6016$ ). The D95 was 0.29 Gy including all CT images (0.3005 Gy with vs. 0.2868 Gy without RB  $p = 0.9748$ ), with respective tp-CT  $\Delta$  of +58.0% and +23.9% ( $p = 0.6093$ ). The D0.03 cm<sup>3</sup> was 53.56 Gy, 53.34 Gy, and 53.19 Gy for all, RB, and non-RB CT images ( $p = 0.9300$ ), differing by +6.0% and +7.4% from tp-CT images, respectively ( $p = 0.7367$ ).

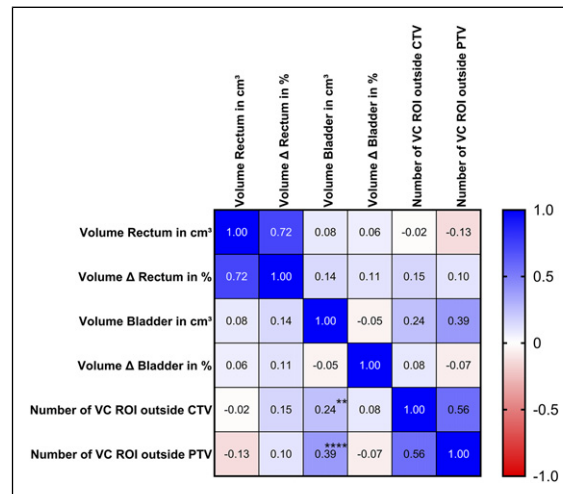
The  $\Delta$  Mean Volume to the tp-CT of the rectum and bladder is visualized in [Figure 1](#).

### Target Volumes

In [Table 3](#), the dosimetric characteristics of the CTV, PTV, and VC are summarized. The mean CTV volume was 622.9 cm<sup>3</sup>, with 640.0 cm<sup>3</sup> in the RB group and 574.6 cm<sup>3</sup> in the group without RB ( $p = 0.0961$ ). The CTV DMean and D95 were 47.62 Gy and 45.92 Gy, respectively, showing no relevant intergroup  $\Delta$ . Deviations from tp-CTs were minimal, with 0.0% vs. +0.1% ( $p = 0.6788$ ) for DMean and -0.5% vs. -0.8% for D95 ( $p = 0.2877$ ).



**Figure 3.** Independent t-test on aggregated means of D95 or the target volumes VC, CTV and PTV. Treatment planning CT = tp-CT, VC = vaginal cuff; CTV = clinical target volume; PTV = planning target volume,  $\Delta$  = difference, DMean = mean dose, D95 = 95% dose, ns = non-significant



**Figure 4.** Results of representative volume and numerical parameters tested with Spearman's correlation.  $p < 0.05^*$ ;  $p < 0.01^{**}$ ;  $p < 0.0001^{****}$ ; VC = vaginal cuff; ROI = region of interest; CTV = clinical target volume; PTV = planning target volume

The mean PTV volume was  $1065.0 \text{ cm}^3$ , measuring  $1094 \text{ cm}^3$  with and  $982.7 \text{ cm}^3$  without RB ( $p = 0.0593$ ). The PTV DMean was 47.29 Gy, and D95 was 44.47 Gy, both comparable between groups ( $p = 0.5954$ ,  $p = 0.8680$ ). Differences to tp-CTs were low with DMean of -0.3% with RB and -0.26% without RB ( $p = 0.8764$ ); D95 of -1.79% with RB and -2.2% without RB ( $p = 0.7231$ ).

For the VC, the mean volume was  $20.55 \text{ cm}^3$ , with  $18.91 \text{ cm}^3$  in the RB group and  $22.50 \text{ cm}^3$  without RB ( $p = 0.3184$ ). The volume  $\Delta$  to tp-CTs increased by +1.7% with RB and decreased by -10.51% without RB, but not significantly ( $p = 0.2839$ ). The DMean for the VC was 46.97 Gy overall, 48.01 Gy with, and 46.61 Gy without RB ( $p = 0.2972$ ). The DMean  $\Delta$  to tp-CTs was +0.6% in the RB group and +0.1% without RB ( $p = 0.5896$ ). The D95 was 42.84 Gy overall, 44.57 Gy with, and 41.85 Gy without RB ( $p = 0.0755$ ), while the D95  $\Delta$  to tp-CTs decreased by -1.93% with RB and -4.17% without RB showing no statistical significance ( $p = 0.0984$ ).

The mean volume of the VC-CTV was  $2.50 \text{ cm}^3$ , with  $1.71 \text{ cm}^3$  in the RB group and  $4.46 \text{ cm}^3$  without RB ( $p = 0.0189$ ). The corresponding DMean was 46.15 Gy, 46.59 Gy, and 45.03 Gy, respectively ( $p = 0.3279$ ). The D95 for VC-CTV was 42.34 Gy overall, 43.56 Gy with, and 39.27 Gy without RB ( $p = 0.1815$ ). Similarly, the volume of the VC-PTV was  $1.71 \text{ cm}^3$  overall,  $1.05 \text{ cm}^3$  with, and  $2.46 \text{ cm}^3$  without RB ( $p = 0.1818$ ). The DMean for VC-PTV was 42.30 Gy overall, 44.13 Gy with, and 39.53 Gy without RB ( $p = 0.1566$ ), while the D95 was 37.07 Gy, with a wider spread between 40.38 Gy with and 32.08 Gy without RB, but the  $\Delta$  not statistically significant ( $p = 0.1717$ ).

DMean and D95  $\Delta$  of the pv-CT images compared to the treatment tp-CT images of the target volumes VC, CTV and PTV in both cohorts are visualized in Figures 2 and 3.

Spearman's correlation test was performed to identify possible effects of rectum and bladder filling during radiation treatment onto VC coverage. Especially the bladder volume presented correlation with a significant positive Spearman coefficient of 0.24 ( $p = 0.002$ ) for the ROI VC outside CTV and 0.39 ( $p < 0.0001$ ) for the ROI VC outside the PTV. On the other hand, the mean rectum volumes and the volume  $\Delta$  were not correlating significantly. Details including significant p-values and Spearman coefficients are displayed in Figure 4. We additionally tested the correlations for the RB and no RB groups without a change in the stated results.

## Discussion

Technical progress and new developments in the field of external beam radiotherapy have improved treatment for patients with gynaecological malignancies. The implementation of IMRT in clinical routine has led to significantly reduced toxicity without compromising oncological outcome compared to the 3D-era.<sup>17,32</sup> The increasing availability of proton beam therapy offers new options with further potential in reducing toxicity. Few retrospective studies and the prospective APROVE trial have shown the feasibility and safety combined with low toxicity rates of postoperative radiotherapy for patients with gynaecological cancers using IMPT.<sup>10,33</sup> Song et al demonstrated that proton therapy achieved superior sparing of pelvic bone marrow and other organs at risk compared with IMRT in cervical cancer patients, highlighting the dosimetric advantages of protons in lowering low-dose exposure while maintaining target coverage.<sup>20</sup> Similarly, Marnitz et al confirmed

in an intraindividual comparison that intensity-modulated proton therapy provides excellent target conformity and homogeneity with significantly reduced doses to the bowel, bladder, and rectum compared with advanced photon techniques, suggesting a potential reduction of acute and late toxicity.<sup>19</sup>

However, the management of intra- and interfraction organ movement still remains challenging. Different target volume concepts exist to address this issue, either applying wide PTV margins or creating ITVs.<sup>25,34</sup> This leads to increased doses in the adjacent organs at risk. Daily on-line position verification with either cone beam computed tomography (CBCT) or even MRI and current developments in daily online plan adaptation (both CBCT or MRI-guided) are approaches for keeping these margins at a minimum while ensuring adequate target coverage of IMRT. There are current clinical trials evaluating these concepts also for e.g. uterine cervical cancer patients (AIM-C1-Trial)<sup>24</sup>. Especially in patients treated with protons, not only the movement of organs but also the density of the tissue in the beam path is relevant for dosimetry.<sup>21</sup> Changes in the consistency of rectal filling may lead to under- or overdosage in distinct regions, especially if air is trapped in the rectal volume.<sup>22</sup> These arguments are the basis for using rectal balloons for IMPT to minimize changes in rectal filling and organ movement. This is all the more important when conditions for daily positioning control are sub-optimal, e.g., only on-line orthogonal x-ray-imaging is available. On the other hand, the use of rectal balloons is costly and uncomfortable for the patients and has been mainly studied in patients undergoing prostate cancer radiotherapy.<sup>35</sup> The assessment of patient-reported outcomes regarding the tolerability and discomfort related to the use of a RB was not part of our retrospective analysis but is an important issue for future evaluation in gynaecologic cancer patients.

To our knowledge, this is the first trial evaluating the benefits of rectal balloons in gynaecological cancer patients treated with postoperative IMPT and assessing interfractional variations in pelvic anatomy as well as their dosimetric consequences during postoperative IMPT.

It should be noted that this study is a retrospective analysis with inherent limitations. The number of available CT image sets varied among patients. While the clinical protocol recommended at least one position verification CT per week, some patients underwent additional scans, potentially introducing bias in the reported mean and median dose parameters. Furthermore, the group sizes were imbalanced, with a higher number of patients in the rectal balloon (RB) group. The application of the RB was not standardized but left to the discretion of the treating physician. The small sample size of the non-RB group (n=6) may have contributed to the absence of statistically significant  $\Delta$  between groups. Additionally, the cohort was heterogenous regarding tumour entity and tumour stage (cervical and uterine cancer patients included). The majority were endometrial cancer patients, with a smaller number of cervical cancer patients – and even within these, stages varied. But due to the comparable treatment of both subgroups including mainly total abdominal hysterectomy with bilateral lymphadenectomy and postoperative pelvic radiotherapy with the same dose and target volume concept we do not expect a relevant difference in VC motion depending on tumour entity.

Use of an RB resulted in improved positional stability of the VC, reflected by significantly smaller VC displacements and reduced VC volumes located outside the CTV and PTV. Patients treated without an RB showed larger interfractional motion, with the VC extending beyond the CTV and PTV boundaries in a higher proportion of pv-CTs. All in all, the volumes of the vaginal cuff outside the PTV were quite small in both groups (1.05ccm vs 2.463ccm) and D95 of the vaginal cuff didn't differ significantly between groups (44.57 vs 41.85 Gy,  $p=0.0755$ ). Despite the lack of statistical significance which might be due to the small sample size of patients without RB (n=6), these findings highlight the RB's role in minimizing rectal and vaginal cuff motion, thereby enhancing geometric reproducibility during the treatment course. The vaginal cuff volume itself exhibited minor fluctuations. The observed reduction in vaginal cuff volume with the RB in place is attributable to mechanical effects of the balloon. The rectal balloon lies just posterior to the vaginal cuff and, when inflated, it gently presses against the posterior vaginal wall. This flattens and stabilizes the vaginal cuff, likely reducing its apparent volume on imaging. The magnitude of change of VC volume did not significantly affect dose coverage. The observed decrease in the VC volume and the less frequent VC outside the target regions in the RB group implies that rectal immobilization effectively limits pelvic soft-tissue shifts. The absolute dose values to the VC and adjacent structures were comparable between groups; but the smaller positional deviations achieved with RB could not show a significant  $\Delta$  in the reproducibility of dose distribution over the course of treatment. The PTVs margins were a uniform 5 mm expansion and 7 mm in the beam direction and probably provided sufficient robustness against interfractional anatomical variations. As a result, dose coverage of the CTV and PTV remained stable across all verification CT images, demonstrating that these margins effectively compensated for changes in bladder and rectal filling throughout the treatment course. At this point it is worth mentioning that we observed no recurrences of the VC in our cohort which supports the safety of treatment application even without a RB in this setting.

One weakness of this study is the lack of markers to better localize the vaginal cuff and to be able to measure the displacement metrically. Other trials using vault markers reported median vaginal displacement of 1.2 mm (mediolateral), 4 mm (super inferior) and 2.8 mm (anteroposterior) in an analysis from Chopra et al.<sup>17</sup> or median maximum movement of the markers of 5.9 mm (mediolateral), 12 mm (super inferior) and 14.6 mm (anteroposterior) in the trial from Jhingram et al.<sup>12</sup> Big variations between observations in different studies are obvious. In which extent the displacement of the markers correlated

with volume of the vaginal cuff outside the PTV and thus underdosage often remains unclear. In our trial, the volume of the vaginal cuff in relation to the CTV and PTV was used to assess vaginal displacement and consequently dose coverage of this important structure in postoperative pelvic radiotherapy after hysterectomy, which is the clinically relevant aspect. We intentionally employed rigid registration instead of deformable registration aligning the bony anatomy on each pv-CT image to the planning CT in order to optimally mimic the clinical workflow using orthogonal x-ray-imaging. To capture any internal deformation of the cuff or surrounding tissues, these structures were re-contoured on each CT image. But we mapped the initial CTV and PTV without adaptation, to assess the “real” dose coverage of the VC.

The target coverage remained stable across groups, with changes in dose parameters (DMean and D95) for both CTV and PTV differing non-significantly. Differences to tp-CT images were negligible, indicating that robust optimization sufficiently compensated for anatomical variations. The stability of CTV and PTV doses suggests that the use of an RB primarily improves geometric consistency rather than requiring additional dosimetric correction. Nevertheless, in selected cases, the use of a rectal balloon may be particularly beneficial, especially when pronounced variations in rectal filling are observed. Significant interfractional changes in rectal volume or the presence of rectal air may alter the proton beam range and thereby affect dose distribution within the target. Yao et al could show that the air volume in the large and small bowel as well as the rectum has an important effect on target coverage, especially in gynaecologic cases and when the air is in the pathway of multiple beams.<sup>22</sup> Under such conditions, rectal stabilization with a rectal balloon could help to minimize anatomical variability and maintain consistent beam geometry throughout the treatment course.

For the OARs, the mean rectal and bladder doses remained within clinically acceptable limits, and no statistically significant  $\Delta$  were observed between RB and non-RB groups. Mean and near-maximum doses to both organs were stable relative to tp-CT images, confirming that rectal stabilization does not compromise OAR sparing. The larger rectal volumes observed in the RB group reflect the expected anatomical expansion due to balloon inflation but did not translate into increased rectal dose exposure. Similarly, bladder dose parameters remained consistent despite variations in bladder filling between fractions. Other trials also reported a wide variation in bladder filling during the course of postoperative pelvic IMRT after hysterectomy. Despite instructing patients to have a full bladder, a median  $\Delta$  in bladder filling of 247 cm<sup>3</sup> (range 95–585 cm<sup>3</sup>) has been reported with less pronounced variations in rectal volume.<sup>12</sup>

The observed link between variable bladder filling and VC displacement emphasizes the necessity of reproducible and sufficiently large bladder volumes to ensure stable target positioning. In our cohort, patients were instructed to have a comfortably full bladder at simulation and before each treatment. Typically, this meant voiding 1 hour prior to treatment and then drinking a specific amount of water (e.g., 300–500 mL) about 30–45 minutes, aiming for a reproducible bladder volume. Nevertheless, we observed relevant variations in bladder filling. The mean bladder volume was 233.6 cm<sup>3</sup>, with 220.7 cm<sup>3</sup> in patients treated with a RB and 269.7 cm<sup>3</sup> in those without. Despite similar mean values, the bladder volume  $\Delta$  compared with the planning CT was significantly larger in the RB group (+17.9 % vs. −1.7 %,  $p = 0.0348$ ), reflecting a greater variability in bladder filling across fractions. Concurrently, patients with smaller or less consistent bladder volumes demonstrated a higher proportion of VC displacements outside the clinical and planning target volumes. Specifically, the percentage of pv-CTs with the VC outside the CTV was 40% in the RB group compared with 91% without ( $p = 0.0252$ ), and 28% versus 68% for the PTV ( $p = 0.0362$ ). These findings suggest that inconsistent bladder filling contributes indirectly to target motion by altering the relative organ position. Therefore, implementing a strict and consistent bladder-filling protocol is advisable for postoperative pelvic proton therapy. The time period between drinking and radiation treatment application should not be too short to achieve a consistent bladder volume. The use of image guidance (e.g., daily CBCT), bladder scanners or real-time ultrasound may be helpful to ensure a minimum volume before treatment, or having an adaptive plan library for different bladder sizes.

A larger consistently filled bladder stabilizes the vaginal cuff and reduces its anterior–posterior variability. Conversely, insufficient or variable bladder filling allows increased pelvic organ mobility, which may lead to displacement of the VC outside the intended target volumes. Therefore, maintaining a reproducible bladder-filling protocol with sufficiently large volumes is essential to minimize interfractional target shifts and ensure accurate dose delivery, particularly in postoperative pelvic proton therapy where small geometric deviations can significantly affect proton beam range and target coverage. This makes improved pre-treatment imaging crucial in the application of IMPT, as daily variations in bladder and rectal filling can affect proton range.<sup>36</sup> Furthermore, the implementation of online adaptive particle therapy, allowing treatment adaptation based on daily imaging, has been highlighted as a promising approach to address such anatomical changes on a daily basis and to maintain plan quality.<sup>30,37–39</sup>

## Conclusion

RB application provided effective anatomical stabilization in postoperative pelvic proton therapy, reducing interfractional VC motion without negatively impacting target coverage or organ-at-risk doses, even though there was no significant  $\Delta$  in target coverage or organs at risk doses. The  $\Delta$  of bladder volumes had a large impact on organ positioning inside the pelvis,

which emphasizes the importance of reproducible and sufficiently large bladder volumes to maintain target stability and minimize VC displacement.

While IMPT achieved excellent target coverage even without additional rectal spacers, rectal balloon use may be particularly beneficial in patients with pronounced gastrointestinal variability or recurrent rectal air, where range uncertainties are more likely to affect dose delivery. Together, these results may support the integration of rectal stabilization and standardized bladder-filling protocols into postoperative pelvic proton therapy to enhance reproducibility and ensure robust, high-quality treatment delivery.

## Acknowledgments

Language learning models like Chat GPT were used to improve the language and readability.

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## Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Heidelberg University (S-808/2019) on December 12, 2019, with the need for written informed consent waived.

## Consent for Publication

Informed consent for patient information to be published in this article was not specifically obtained due to the retrospective nature of the study and in accordance with ethics approval.

## Author Contributions

Lars Wessel: Conceptualization, methodology, formal analysis, data curation, investigation, writing – original draft, writing – review & editing, visualization. Friderike K. Longarino: Investigation, writing – review & editing. Natalia Sycheva: Investigation, writing – review & editing. Jan-Hendrik Bolten: Writing – review & editing. Hanna Waldsperger: Writing – review & editing. Katharina Kozyra: Writing – review & editing. Philipp Schroeter: Writing – review & editing. Julia Bauer: Conceptualization, Writing – review & editing. Fabian Weykamp: Writing – review & editing. Eva Meixner Lang: Writing – review & editing. Laila König: Writing – review & editing. Jürgen Debus: Project administration, investigation, resources. Nathalie Arians: Conceptualization, methodology, investigation, writing – review & editing, resources, supervision, validation.

## Funding

The authors received no financial support for the research or authorship. For the publication fee we acknowledge financial support by Heidelberg University

## Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: FW reports speaker fees from AstraZeneca, Varian Medical Systems, Siemens Healthineers, Chulabhorn Royal Academy and Merck Sharp & Dohme and travel support for attending meetings from AstraZeneca, Varian Medical Systems, Novocure GmbH, German Center for Lung Research (DZL), Fraunhofer MEVIS, Chulabhorn Royal Academy and Micropos Medical as well as compensation for advisory boards from Novocure GmbH and Merck Sharp & Dohme. JD received grants or has contracts with RaySearch Laboratories AB, Vision RT Limited, Merck Serono GmbH, Siemens Healthcare GmbH, PTW-Freiburg Dr. Pychlau GmbH, and Accuray Incorporated outside the submitted work. JD is CEO of the Heidelberg Ion Therapy Center (HIT) and member of the board of directors of Heidelberg University Hospital. JD holds an experimental accelerator from IntraOP. NAR reports speaking honoraria from IF-Kongress Management GmbH and travel grants from the German Society for Senology outside the submitted work. All other authors declare that none of them has any conflicts of interest in relation to the present publication.

## Data Availability Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author on request.

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## Appendix

### Abbreviations

|          |                                         |
|----------|-----------------------------------------|
| $\Delta$ | Difference                              |
| AP       | Anterior-posterior                      |
| CBCT     | Cone beam computed tomography           |
| CTV      | Clinical target volume                  |
| DMean    | Mean dose                               |
| D95      | Dose in 95% volume                      |
| IG       | Image guided                            |
| IMPT     | Intensity modulated proton beam therapy |

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|        |                                                 |
|--------|-------------------------------------------------|
| IMRT   | Intensity-modulated radiation therapy           |
| ITV    | Internal target volume                          |
| MRI    | Magnetic resonance image                        |
| NaCl   | Sodium chloride                                 |
| OAR    | Organs-at-risk                                  |
| PTV    | Planning target volume                          |
| pv,-CT | Position verification computed tomography       |
| RT     | Radiotherapy                                    |
| RBE    | Relative biological effectiveness               |
| ROI    | Region of interest                              |
| tp-CT  | Treatment planning computed tomography          |
| VC     | Vaginal cuff                                    |
| VC-CTV | Vaginal cuff outside of clinical target volume  |
| VC-PTV | Vaginal cuff outside of planning target volume. |