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Scientific Article

Daily Online Adaptive Radiation Therapy of Postoperative Endometrial and Cervical Cancer With PTV Margin Reduction to 5 mm: Dosimetric Outcomes, Acute Toxicity, and First Clinical Experience

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Purpose: This study evaluated the first clinical implementation of daily iterative cone beam computed tomography (iCBCT)-guided online adaptive radiation therapy (oART) in the postoperative treatment of endometrial and cervical cancer.

Methods and Materials: Seventeen consecutive patients treated with daily iCBCT-guided oART were enrolled in this prospective study, with a reduced uniform 3-dimensional PTV margin of 5 mm. Treatment plans were designed to deliver 45 or 50.4 Gy in 1.8 Gy daily fractions to PTV. Pre- and posttreatment ultrasound and iCBCT scans were performed to record intrafractional bladder and rectal volume changes. The accuracy of contouring, oART procedure time, dosimetric outcomes, and acute toxicity were evaluated.

Results: The average time from first iCBCT acquisition to completion of treatment was 22 minutes and 26 seconds. During this period, bladder volume increased by 44 cm^3 using iCBCT contouring, whereas rectal volume remained stable (62.9 cm^3 pretreatment vs 61.9 cm^3 posttreatment). A total of 91.6% of influencers and 88.1% of CTVs required no or minor edits. The adapted plan was selected in all (434) fractions and significantly improved the dosimetry coverage for CTV and PTV, especially the vaginal PTV coverage by nearly 7% ($P < .05$). The adapted bladder D_{mean} was 104.61 cGy, and the rectum D_{mean} was 123.67 cGy, significantly lower than the scheduled plan of 108.24 and 128.19 cGy, respectively. The bone marrow and femur head left and right dosimetry were also improved with adaptation. Grade 2 acute gastrointestinal and genitourinary toxicities were 24% and 0, respectively. There was a grade 3 acute toxicity of decreased white blood cell count in 1 patient.

Conclusions: Daily oART was associated with favorable dosimetry improvement and low acute toxicity, supporting its safety and efficacy for postoperative treatment of endometrial and cervical cancer. These results need to be validated in a larger prospective randomized controlled cohort.

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Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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Introduction

Pelvic radiation therapy plays a crucial role in postoperative endometrial and cervical cancer and has been demonstrated to reduce the local recurrence rate and improve the survival rate.[1-4] However, unpredictable anatomic variations in the pelvis, especially interfractional changes in the bladder and rectum, affect the accuracy of postoperative pelvic radiotherapy.[5,6] Adequate coverage is ensured by a large treatment volume through sufficient expansion of planning target volume (PTV) margins to account for all uncertainties. Intensity modulated radiation therapy (IMRT), with greater conformity and adequate dose coverage of the clinical target volume (CTV), has been widely used in the postoperative treatment of endometrial and cervical cancer.[7,8] A PTV expansion of 7 to 15 mm was recommended for postoperative IMRT in endometrial and cervical cancer if the daily image guidance ensures an accurate setup.[7,9] The severity of irradiation toxicities was related to the treated volume that involved organs at risk (OARs),[10,11] and pelvic radiation therapy may cause severe gastrointestinal (GI) and genitourinary (GU) symptoms with large PTV margins and irradiated volumes, especially in patients with reduced function of the pelvic organs due to surgical resection and treatment with concurrent chemotherapy.[12,13]

Several approaches have been attempted to decrease pelvic OARs doses to reduce irradiation toxicity, including obtaining a dose reduction to the rectum by injecting a hydrogel to establish a stable cervical-rectal space[14,15] and anatomic interventions such as rectal deflation to reduce the impact of OARs deformation.[16] However, these invasive procedures carry certain risks and do not reduce PTV margins. Currently, iterative cone beam computed tomography (iCBCT)-guided online adaptive radiation therapy (oART) could further reduce the CTV-to-PTV margin and irradiated volume compared with IMRT by adapting to the per-fractional anatomic variations and allowing for a full daily replan in a relatively short treatment time.[17,18] In our institute, iCBCT-guided oART was first applied to postoperative treatment of endometrial and cervical cancer, which has not been reported in previous studies.

Our previous prospective study demonstrated a significant reduction in PTV margins to 5 mm,[19] and a cohort of patients was enrolled on the basis of this study on PTV margin. The aim of this study was to evaluate dosimetric outcomes, acute toxicity, and first clinical experience in daily iCBCT-guided oART of postoperative endometrial and cervical cancer with a reduced 5 mm PTV margin.

Methods

Patients

Between October 2022 and March 2023, 17 patients with postoperative endometrial and cervical cancer treated with daily iCBCT-guided oART were enrolled in this prospective study. Each patient had indications for adjuvant pelvic radiation therapy and received 45 or 50.4 Gy to PTV. The CT-guided high-dose-rate intracavitary brachytherapy was irradiated to a depth of 0.5 cm below the vaginal mucosa according to the prescribed dose of 10 Gy in 2 fractions after oART.

The study was approved by the Institutional Review Board of Peking Union Medical College Hospital.

Reference CT and preimplementation treatment planning study

All patients were instructed to empty their bladder and rectum 1 hour and 40 minutes before the appointment, followed by an intake of 450 to 500 mL water within 10 minutes according to their height and weight before simulation, and the residual urine volume was measured using portable Doppler color ultrasound during positioning. All patients were fixed with a thermoplastic film and simulated in supine position, with their arms above their head or on their chest. The reference CT scans were obtained by a GE Revolution large-bore CT scanner.

According to international standards, the targets in radiation therapy for postoperative treatment of endometrial and cervical cancer include separate nodal CTV (CTV-N) and vaginal CTV (CTV-V) contours.[7] The CTV-N covered pelvic lymph nodes (common, internal and external iliac, obturator, and presacral) and CTV-V covered proximal vagina and any paravaginal or retracted parametrial tissue. The CTV was expanded by a uniform 3-dimensional planning margin of 5 mm to generate PTV, and 9-field IMRT plans were generated in the Ethos treatment planning system (Varian Medical Systems).

Adaptive workflow

One designated physician, 1 physicist, and 2 therapists participated in each treatment fraction. The residual urine volume was measured by ultrasound after setup, and the first iCBCT scan was performed. The Ethos system

automatically generated influencer (defined as organs that are adjacent to the target volume and have a high impact on the deformation of CTVs and OARs) structures of the bladder, rectum, and bowel (individual bowel loops) by artificial intelligence (AI). After adjustment by the physician, the system combined the deformation vector field and the influencer structures to automatically propagate CTVs from the reference planning CT to the iCBCT. Similarly, the propagated CTVs were reviewed and adjusted. The editing degree of the influencers and CTV was based on the method applied by Byrne et al[20] and were classified as either: no edits = no change to the structure; minor edits = no more than 10% of slices need small changes; moderate edits = more than 10% of the slices need small changes, or no more than 10% of the slices need big changes major revisions; major edits = big changes that do not include minor and moderated changes or structural deletions and recontours. A uniform 3-dimensional planning margin of 5 mm was automatically added to the CTV to generate PTV. Finally, an adapted plan (the newly optimized treatment plan on current anatomy) and a scheduled plan (the reference plan recalculated on current anatomy with isocenter optimization based on maximized PTV coverage) were generated, and plan comparison and selection were carried out based on the quality of each plan, such as fulfillment of clinical goals (CTV/PTV coverage and dose to OARs). The second iCBCT scan was obtained to verify the position of the target volume and OARs during adaptation, and treatment was then delivered to the patient. The third iCBCT scan was acquired immediately after treatment completion for verification, and ultrasound was used to record the residual urine volume again. The adaptive workflow time was recorded from the first iCBCT to the end of treatment.

Quality assurance for patients and physicians

Strict quality assurance was carried out for patients and physicians. Patients were informed of their definite treatment time and instructed to intake water and empty their rectum before simulation and each treatment fraction. Physicians conducted bladder volume ultrasound examinations on patients at each fraction, and the first iCBCT scan was performed only when there was a difference of 20% from the simulation to reduce the additional radiation exposure of patients. According to the assumption of the geometric model, the capacity of the bladder was calculated by the following formula:

$$V = (\pi \div 6) \times (H \times W \times D)$$

where V is the bladder volume, H is the height of the longitudinal section of the bladder, W is the width of the transverse section of the bladder, and D is the depth of the longitudinal section of the bladder.

Dosimetric evaluation and follow-up

The volume of CTV and PTV receiving 100% of the prescribed dose ($V_{100\%}$) and the dose to OARs, including the bladder, rectum, bowel, bone marrow, and femur head, were recorded for each fraction and compared between the adapted plan and scheduled plan. The $V_{100\%}$ of CTV required least 99%, and the $V_{100\%}$ of PTV required least 95% were used as clinical goals for per-fractional selection of the best plan. The dose constraint for OARs is presented in Supplementary Tables E1 and E2.

Data were collected prospectively for toxicity and outcomes. Patients received a hematological examination weekly, were assessed for toxicity from receiving oART by a physician weekly to study completion, and were re-evaluated by thoracic and abdominal CT and pelvic magnetic resonance (MR) examination at 1 and 3 months after completion of treatment. Physician-reported acute toxicities (up to 90 days after the start of treatment) were graded using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

Statistical analysis

The statistical analysis was performed using SPSS (version 27.0; IBM Corp). Data conforming to a normal distribution are described by the mean ± SD, and data with a nonnormal distribution are expressed by median (first quartile, third quartile) (M (Q1, Q3)). Data with a normal distribution were analyzed by the *t* test, and data with a nonnormal distribution or heterogeneous variance were analyzed by a nonparametric test. *P* values <.05 denoted a significant difference.

Results

Patient characteristics

The clinical characteristics of the 17 patients enrolled in this study are shown in Table 1. The median age of all patients was 49 years (range, 31-69 years), and most primary tumors were postoperative cervical cancer (65%, 11/17). The median initiation of postoperative oART was 48 days (range, 32-99 days).

Timing data

The timing data are shown in Table 2. All patients complied well with the online adaptive procedure, including first iCBCT acquirement, influencer generation, influencer edits, target and OARs generation, target and OARs edits, plan generation and selection, which took an

Table 1 Clinicopathologic characteristics

Characteristics	Patients (%)
Age (year)	17 (100)
<50	9 (53)
≥50	8 (47)
Primary tumor	17 (100)
Endometrial	6 (35)
Cervical	11 (65)
FIGO staging	17 (100)
I	12 (71)
III	5 (29)
Prescribed dose and fractions	17 (100)
45 Gy/25f	14 (82)
50.4 Gy/28f	3 (18)
Concurrent chemotherapy	17 (100)
Yes	7 (41)
No	10 (59)
Previous chemotherapy	17 (100)
Yes	2 (12)
No	15 (88)

Abbreviation: FIGO = International Federation of Gynecology and Obstetrics.

average of 16 minutes and 25 seconds. Followed by a second iCBCT scan and treatment, the average total time consumed was 22 minutes and 26 seconds.

Target and OARs contouring accuracy

A total of 434 fractions for 17 patients received daily oART, and each fraction included 3 editors for the influencer structures (bladder, rectum, and bowel) and 2 editors for CTV (CTV-N and CTV-V). Figure 1 shows the frequency of CTV and influencers editing needed. Overall, 91.6% (1192/1302 times) of the influencers required no or minor edits, and 88.1% (765/868 times) of CTV-N and CTN-V required no or minor edits.

Intrafraction organ changes

By delineating bladder contours on the first and third iCBCT images, the bladder volume was 353.9 ± 130.2 cm^3 and 397.9 ± 138.7 cm^3 before and after treatment, respectively, and the bladder volume increased by 44.0 ± 40.3 cm^3. The bladder volume measured by ultrasound was 225.7 ± 90.6 cm^3 and 292.4 ± 110.3 cm^3 before and after treatment, respectively, and the increase was 66.7 ± 42.1 cm^3. By delineating rectum contours on the first and third iCBCT images, the rectum volume was 62.9 ± 33.5 cm^3 and 61.9 ± 25.9 cm^3 before and after treatment, respectively.

Dosimetric outcomes

The adapted plan was selected for all fractions. For 10 out of 868 times in 434 fractions, $V_{100\%}$ of PTV (included PTV-N and PTV-V) was less than the required 95% for the adapted plan, but all $V_{100\%}$ values were more than 90%. The $V_{100\%}$ of PTV less than the required 95% was the case 542 times for the scheduled plan. The $V_{100\%}$ of CTV and PTV are shown in Fig. 2. The adapted plan achieved superior dosimetric coverage for the target volume compared with the scheduled plan, and the median $V_{100\%}$ of CTV-N, CTV-V, PTV-N, and PTV-V were 99.8% versus 99.1%, 99.8% versus 97.5%, 97.2% versus 94.3%, and 97.0% versus 90.4%, respectively ($P < .05$).

Table 3 shows the dosimetric outcomes of oARs for all 434 fractions of treatment of 17 patients. In the adapted plan group, the mean bladder dose was 104.61 ± 8.02 cGy, and the mean rectum dose was 123.67 ± 13.09 cGy,

Table 2 Timing data of online adaptive workflow

Times (minutes and seconds) consuming	AVG	Min	Max
First iCBCT acquirement	36 s	32 s	40 s
Influencer generation	29 s	22 s	33 s
Influencer edits	3 min 21 s	45 s	7 min 28 s
Target and OARs generation	59 s	24 s	2 min 6 s
Target and OARs edits	6 min 55 s	54 s	14 min 18 s
Plan generation and selection	4 min 5 s	2 min 50 s	7 min 55 s
Treatment	3 min 43s	2 min 55 s	5 min 0 s
Online adaptive time	16 min 25 s	11 min 45 s	25 min 35 s
Total time	22 min 26 s	17 min 5 s	32 min 3 s

Abbreviations: iCBCT = iterative cone beam computed tomography; OARs = organs at risk.

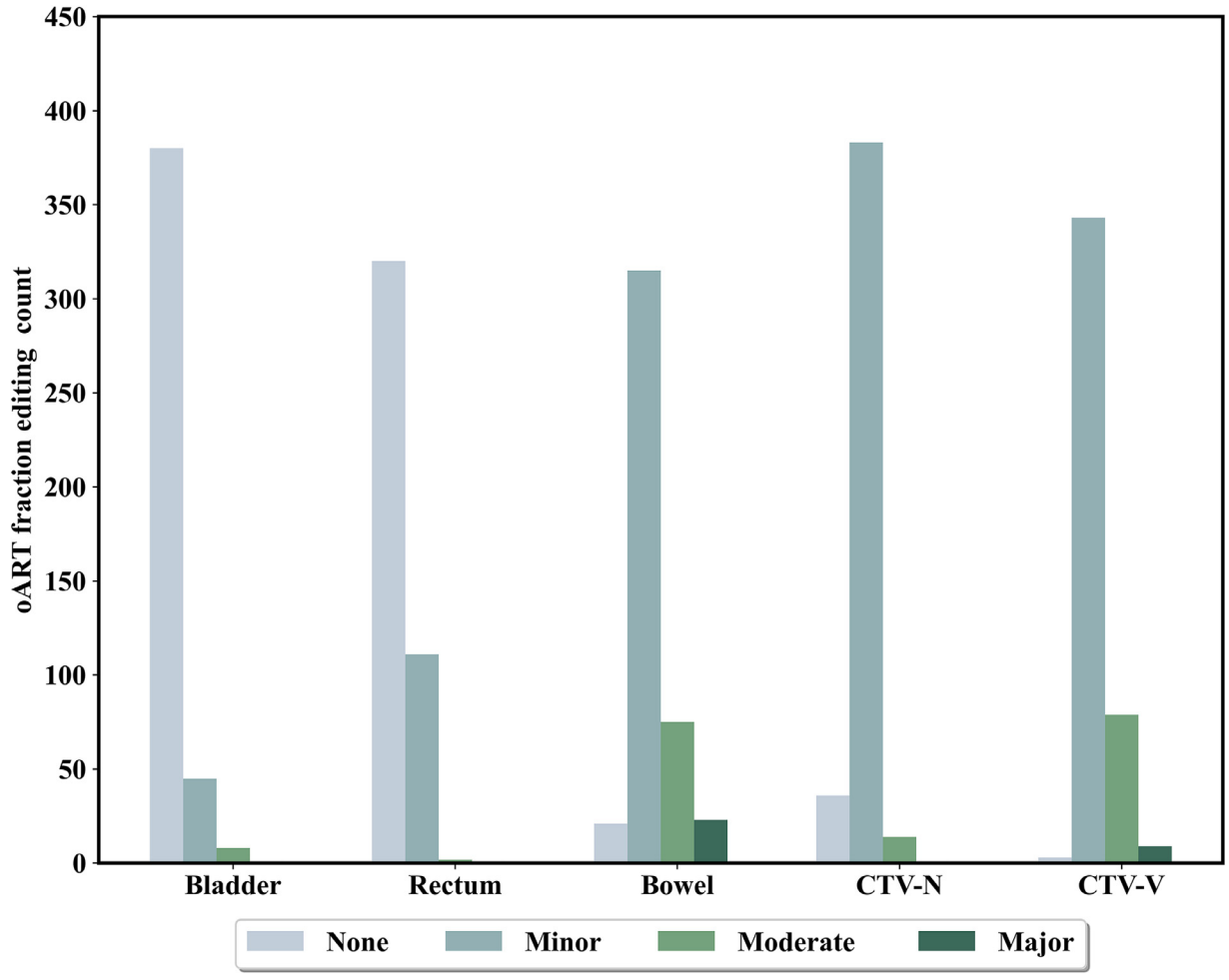

Figure 1 Frequency of edits required for influencer structures (bladder, rectum, and bowel) and CTV (CTV-N and CTV-V).

which were significantly lower than those in the scheduled plan (108.24 ± 9.48 and 128.19 ± 17.73, respectively). Compared with the scheduled plan over all sessions, the adapted plan could significantly improve the bladder dosimetry in the $V_{4000\ cGy}$, $V_{3000\ cGy}$, $V_{2000\ cGy}$, and $V_{1000\ cGy}$ groups ($P < .05$), and similar results were achieved in the rectum and bowel dosimetry. However, there was no significant difference for $V_{4000\ cGy}$ ($P = .378$ and $P = .071$, respectively) and $D_{2\ cm3}$ of the bowel (190.27 ± 1.44 cGy adapted plan vs 190.20 ± 2.65 cGy scheduled plan, $P = .15$). The bone marrow and femur head left and right dosimetry were also improved with adaptation.

Irradiation toxicity

All patients completed treatment per protocol, and no local recurrence or distant metastasis occurred 3 months after the completion of treatment. Grade 2 acute gastrointestinal and genitourinary toxicities were 24% and 0, respectively. One grade 3 acute toxicity, which was a hematologic disorder, consisted of decreased white blood cells in 1 patient (Table 4). The most common GI toxicity was diarrhea, and 1 patient had GU toxicity of mild vaginal discharge. However, no patient had a urinary-related disorder.

Discussion

oART is a revolutionary radiation therapy technology after IMRT that can redelineate the target volume and OARs and reoptimize the treatment plan within a short time frame, and the patient does not need to leave the treatment couch. Currently available oART equipment mainly includes MR imaging guidance. MR-guided oART has the advantage of superior soft-tissue contrast, but the total adaptive workflow time could last up to 1 hour,[21,22] especially with recontouring of OARs and target, which inevitably increases intrafractional errors with bladder volume changes. Compared with the above linac, iCBCT-based oART, benefiting from the fast scanning of images, iterative CBCT reconstruction algorithm, and the use of AI, significantly shortened the total time for patients to

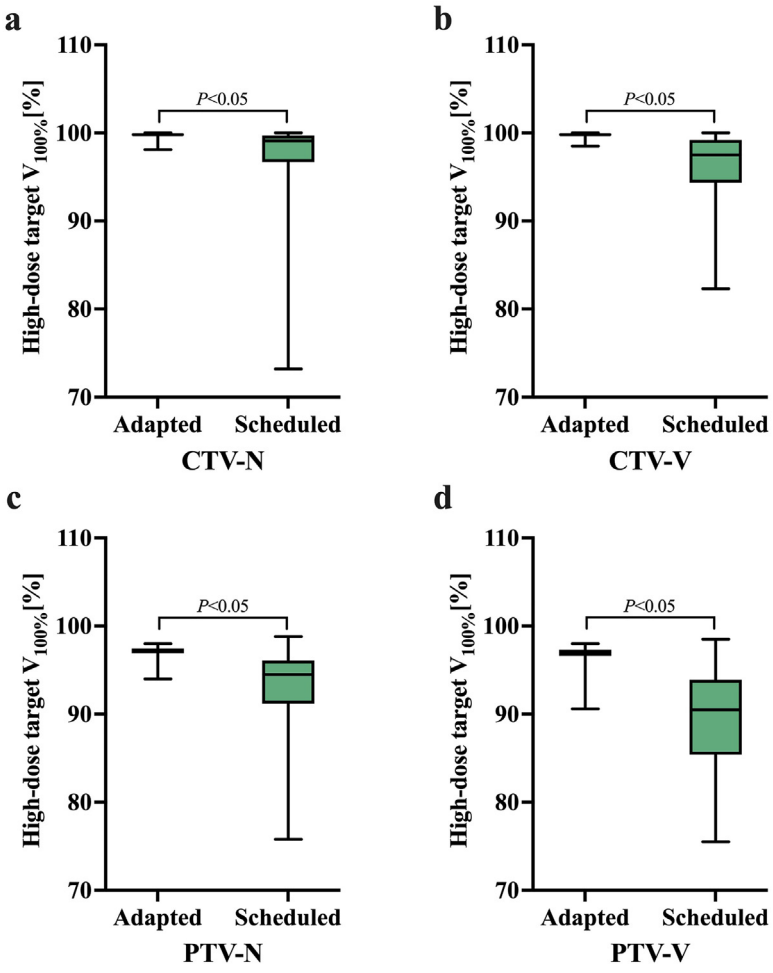

Figure 2 Boxplot showing $V_{100\%}$ of the adapted and scheduled plan. In the adapted plan, the M (Q1, Q3) of $V_{100\%}$ of CTV-N (a), CTV-V (b), PTV-N (c), and PTV-V (d) were 99.8% (99.7%, 99.9%), 99.8% (99.7%, 99.9%), 97.2% (96.9%, 97.4%), and 97.0% (96.6%, 97.3%), respectively. In the scheduled plan, the M (Q1, Q3) of $V_{100\%}$ of CTV-N (a), CTV-V (b), PTV-N (c), and PTV-V (d) were 99.1% (96.6%, 99.7%), 97.5% (94.4%, 99.2%), 94.3% (90.4%, 96.0%), and 90.4% (85.2%, 93.8%), respectively.

maintain a fixed position with good pelvic soft tissue display resolution, which could reduce intrafractional motion of pelvic organs. Currently, iCBCT-guided oART is implemented mainly in the bladder, prostate, and rectal cancer in the pelvic region. de Jong et al[23] reported that the average adaptive procedure before delivery (CBCT2-CBCT1) time was 20 minutes and that the complete online adaptive workflow time was 26 minutes in CBCT-based oART for neoadjuvant treatment of rectal cancer. Sibolt et al[24] showed that 5 patients with pelvic malignancies treated on a CBCT-based oART system complied well with the median adaptive procedure duration of 17.6 minutes (from CBCT acceptance to treatment delivery start). In this study, it took approximately 16 minutes for the online adaptive procedure and 23 minutes for the total treatment time, which was less than previously reported. In addition, the results of this study showed that 91.6% of the influencers and 88.1% of the target required no or minor edits, which were broadly in agreement with Byrne et al,[20] who reported that the frequency of minor or no edits to the influencer and target contours were 92% and 91%, respectively. This demonstrated that an efficient AI-based procedure was feasible in the postoperative treatment of gynecologic tumors and laid the foundation for rapid adaptive processes.

The main concern of oART is stability throughout the treatment process, ensuring low bladder inflow rates and reducing movement during irradiation. Referring to the previous experience sharing of bladder preparation by various centers in the online adaptive treatment of pelvic malignancies,[20,23] the patients in our study had an intake of 450 to 500 mL water within 10 minutes 1 hour and 40 minutes before daily treatment to reduce intrafractional variation. Li et al[25] delineated the bladder in the pre- and posttreatment MR scans, and the results showed that the bladder volume increased on average by 86.37 ± 70.63 mL with a drink of 500 mL of water each treatment session, which is larger than what we reported in our

Table 3 Dosimetric outcomes of oARs for all 434 daily fractions of treatment of 17 patients are compared between the adapted plan and the scheduled plan

Target and OAR	Goal	Adapted plan	Scheduled plan	*P*
Bladder	$V_{4000\ cGy}$ (%)	24.22 ± 5.50	25.60 ± 5.79*	.001
	$V_{3000\ cGy}$ (%)	37.89 ± 6.03	40.03 ± 7.00*	<.05
	$V_{2000\ cGy}$ (%)	59.17 ± 7.24	62.67 ± 9.06*	<.05
	$V_{1000\ cGy}$ (%)	92.07 ± 4.41	94.01 ± 3.91*	<.05
	D_{mean} (cGy)	104.61 ± 8.02	108.24 ± 9.48*	<.05
Rectum	$V_{4000\ cGy}$ (%)	38.07 ± 12.69	39.00 ± 16.41	.378
	$V_{3000\ cGy}$ (%)	55.98 ± 10.56	59.22 ± 14.45*	<.05
	$V_{2000\ cGy}$ (%)	74.85 ± 9.87	78.77 ± 10.74*	<.05
	$V_{1000\ cGy}$ (%)	94.00 ± 4.94	95.22 ± 6.32*	.03
	D_{mean} (cGy)	123.67 ± 13.09	128.19 ± 17.73*	<.05
Bone marrow	$V_{4000\ cGy}$ (%)	14.02 ± 4.39	15.10 ± 5.88*	.004
	$V_{1000\ cGy}$ (%)	80.22 ± 4.33	82.24 ± 4.46*	<.05
	$D_{90\%}$ (cGy)	25.78 ± 6.22	28.25 ± 6.96*	<.05
Femur head left	$V_{3000\ cGy}$ (%)	1.02 ± 1.14	1.38 ± 1.36*	<.05
	D_{mean} (cGy)	49.06 ± 6.38	50.37 ± 6.22*	.004
	$D_{5\%}$ (cGy)	81.50 ± 23.82	90.91 ± 10.58*	<.05
Femur head right	$V_{3000\ cGy}$ (%)	0.97 ± 1.02	1.49 ± 1.44*	<.05
	D_{mean} (cGy)	48.45 ± 5.99	50.82 ± 6.31*	<.05
	$D_{5\%}$ (cGy)	88.63 ± 9.43	92.37 ± 11.49*	<.05
Bowel	$V_{4000\ cGy}$ (%)	14.53 ± 4.26	15.19 ± 5.41	.071
	$V_{3000\ cGy}$ (%)	27.90 ± 6.01	29.67 ± 7.30*	.01
	$V_{2000\ cGy}$ (%)	47.87 ± 5.62	53.82 ± 7.48*	<.05
	$V_{1000\ cGy}$ (%)	69.31 ± 5.81	78.35 ± 9.14*	<.05
	$D_{2\ cm3}$ (cGy)	190.27 ± 1.44	190.20 ± 2.65	.622

Abbreviations: OARs, organs at risk.
Note: Results are presented as the average value together with one standard deviation. *P* value represents the outcome of *t* test.
*Adapted plan compared with scheduled plan, $P < .05$

study. These discrepancies could be due to the time span, given that the average time between the pre- and post-fraction MR scans was 27.82 minutes (range, 10-55 minutes), and the Li and colleagues study had patients drink water 1 hour before each session. In our study, this time span was near 23 minutes (range, 17-32 minutes), and the time interval for patients avoiding the consumption of fluid was as long as 1.5 hours before treatment in our study. Ultrasound monitoring of the bladder volume was recommended during positioning due to the reduction in additional radiation exposure.[25,26] However, the results of our study using ultrasound to estimate changes in pre- and posttreatment bladder volume showed that it was consistent with the volume trends by iCBCT and was not much different under the strict bladder preparation mentioned above. Thus, the effect of ultrasound was actually attenuated in the setting of daily oART treatment with strict bladder preparation. In addition, there was almost no change in the rectal volume before and after treatment, which correlated with preparation to empty the rectum and was also consistent with a previous finding that rectal gas may remain stable for 20 to 25 minutes.[27]

The reference plan for conventional IMRT did not truly show the dose for OARs and target volumes due to daily variation in pelvic organs. The scheduled plan, the reference plan recalculated on current anatomy, is theoretically achieved with superior dose coverage than image guided irradiation therapy (IGRT), which only allows image registration without intervention and could represent the per fractional dose of IMRT to a certain extent. The worse dose converges for the scheduled plan with greater deformation, but in our study, the median $V_{100\%}$ of PTV-V from the scheduled plan was 90.4%, indicating

Table 4 Acute treatment-related toxicities

Acute toxicities	Grade 1	Grade 2	Grade 3	Grade 4
During treatment				
Hematologic	1 (6%)	7 (41%)	1 (6%)	0
GI	4 (24%)	4 (24%)	0	0
GU	1 (6%)	0	0	0
Dermatitis	0	0	0	0
Laboratory test for hepatobiliary disorders	1 (6%)	0	0	0
Malaise	3 (18%)	1 (6%)	0	0
End of treatment to 1 month				
GI	1 (6%)	0	0	0
End of treatment to 3 months				
Disorders	0	0	0	0

Abbreviations: GI = gastrointestinal; GU = genitourinary.
Note: Grading is reported as the maximum symptoms at the trial time points.

that the bladder-rectal preparation of patients was fully feasible. Compared with the scheduled plan, the chosen adapted plan significantly improved the target volume dosimetry coverage for CTV and PTV, especially PTV-V coverage by nearly 7% ($P < .05$), indicating the advantages of oART over IMRT in the postoperative treatment of endometrial and cervical cancer. This was in line with expectations; the scheduled plan was the recalculated reference plan without changing the relevant dose parameters, whereas the adapted plan was reoptimized based on the current anatomic position. The relatively poor dosimetry coverage of the PTV-V of the scheduled plan further illustrated that the operative bed changed daily based on the pushing boundaries of the adjacent bladder and rectum and the necessity of oART implementation. In addition, PTV was generated by uniform expansion of CTV by 5 mm, and the scheduled plan was isocenter optimization based on maximized PTV coverage, which explained why the difference between the scheduled plan and adapted plan was larger in the PTV group than in the CTV group.

In this study, the dosimetric outcomes for OARs from all 434 fractions of treatment were evaluated, demonstrating significant improvements in the bladder, rectum, and bowel dosimetry with relative reductions. We did not accumulate the dose from the adapted or scheduled plans. We tracked the dose from each fraction independently to accurately assess daily targets and OAR metrics, avoiding compounding errors from an inaccurate dose deformation algorithm. This approach is common in current adaptive studies.[28,29] Of note, the high-dose $V_{40\ Gy}$ of the rectum and bowel was decreased but not significantly in the adapted plan. This may be explained by the volumes receiving 40 Gy or the higher dose being close to the prescribed dose of 45/50.4 Gy for PTV, and these 2 organs tended to be adjacent to or overlapping part of the target volume. This was also verified on $D_{2\ cm3}$ of the bowel representing the high-dose area with no difference (190.27 ± 1.44 adapted plan vs 190.2 ± 2.65 scheduled plan, $P = .622$). In addition, oART also improved the dosimetry for OARs such as the bone marrow and femur head and that were less prone to deformation.

In the clinical treatments, oART was safe and acceptable, and we prospectively reported irradiation toxicities for 17 patients using reduced 5 mm margins. Klopp et al[9] demonstrated that pelvic IMRT significantly reduced GI and urinary toxicity compared with standard 4-field radiation therapy, but 33.7% of patients who received IMRT reported frequent or almost constant diarrhea at the end of IMRT. An earlier study prospectively evaluating toxicity in cervical and endometrial cancer patients treated with postoperative radiation therapy using intensity modulated arc therapy showed that grade 2 acute GI, GU, and hematologic toxicity were observed in 63%, 18%, and 21%, respectively, and grade 3 were 0, 1%, and 12%, respectively.[30] Hasselle[31] reported a group of 22 cervical cancer patients treated with postoperative IMRT, and the results showed that 19 (86%) had grade 1 to 2 acute GI toxicity, 1 (5%) had grade 3 to 4 acute GI toxicity, and 7 (32%) had grade 1 to 2 acute GU toxicity. Compared with these previous studies concerning IMRT, the acute complication rates observed in our patients were more satisfactory, with no grade 3 to 4 adverse GI complications and no urinary complications, which is consistent with the dosimetry improvement for the bladder, rectum, and bowel. The low acute toxicity may be related to the reduced irradiated volumes. A PTV expansion of 7 to 15 mm was recommended for postoperative IMRT in endometrial and cervical cancer if the daily image guidance ensures an accurate setup.[7,9] The CTV was expanded by a uniform 3-dimensional planning margin of 5 mm to generate PTV in this study, which significantly reduced the irradiated volume of OARs.

Different from previous studies concerning oART, which were mainly intermittent weekly,[18,32] designated physicians, physicists, and technicians participated to ensure a safe, efficient, and high-quality delivery of daily oART in our study. But committing huge resources may be a limitation to some extent that may make this harder to replicate. In addition, given that the interventional study model was a single group assignment, these findings concerning irradiation toxicity could only be compared with data from previous studies. The results of this prospective study showed that oART achieved dosimetric and clinical benefits, but the clinical data presented were based on a cohort of 434 fractions for 17 patients. This was sufficient for evaluating fractional dosimetric outcomes but may underestimate or overestimate the clinical effect of oART. And this study was a preliminary prospective clinical study lacking patient-reported outcomes for GI and GU toxicity. But all patients received daily oART, and each fractional treatment required the presence of physicians to participate adaption, so physician-reported toxicity could be evaluated in detail, which may make up for this shortcoming to a certain extent. We find the results of this study promising, and we look forward to testing these benefits in future large-scale prospective randomized controlled studies.

Conclusion

This study is the first to describe the implementation of daily iCBCT-based oART for postoperative endometrial and cervical cancer, with PTV margin reduction to 5 mm and excellent dosimetric coverage. Margin reductions enabled by strict patient and physician quality assurance resulted in significant dosimetry improvement of critical OARs and acute toxicity reductions with shorter online adaptive times and fewer OARs and target volume edits. Our findings provide a novel strategy for postoperative adjuvant radiation therapy aimed at mitigating irradiation toxicity, especially in cases of significant variations in the pelvic region.

Disclosures

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.

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Supplementary materials

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