Observational Study

Medicine

OPEN

Dosimetric evaluation of image-guided adaptive radiotherapy for locally advanced cervical cancer

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Abstract

This study evaluates the dosimetric benefits of off-line adaptive radiotherapy (ART) planning during radiotherapy for locally advanced cervical cancer. Forty-four patients in our hospital were included. The patients were monitored by cone-beam CT (CBCT), and the secondary CT scanning was performed timely. The ART2 planning was performed based on tumor regression and compared with the initial radiotherapy planning (ART1). The mean time of the secondary CT scanning was the thirteen fractions, and the mean gross tumor volume (GTV) decreased by 23.3%. The ART2 compared with the ART1 planning, significantly reduced the mean dose of PGTV (defined as the GTV with 5 mm expansion all directions)-$D_{2\%}$, V_{110}, and PTV-V_{110} by 1.9 Gy, 9.2%, and 3.4%, whereas there was no significant difference in tumor target $D_{98\%}$, $D_{50\%}$, and V_{100} between the two groups. The HI of PGTV and planning target volume (PTV) was significantly lower in the ART2 planning. For the comparison of OARs dosimetric parameters, the ART2 planning was significantly decreased the mean dose of rectum-D_{mean} (2 Gy), D_{1cc} (0.6 Gy), V_{30} (7.3%) and V_{40} (5.9%), bladder-D_{1cc} (1.1 Gy), left femoral head-D_{mean} (1.2 Gy), V_{40} (1.3%) and right femoral head-D_{mean} (1.3 Gy), but significantly increased the small intestinal-V_{30} (2.5%). Other OARs dosimetric parameters were similar between two plannings. The Off-line ART planning can adapt for the changes in the target volume, and further decrease the target volume hotspot area/dose and OARs irradiation dose in locally advanced cervical cancer patients. And the clinical benefit of ART still needs to be verified in clinical trials.

Abbreviations: ART = adaptive radiotherapy, CBCT = cone beam CT, GTV = gross tumor volume, HI = homogeneity index, OARs = organs at risk, PGTV = GTV with 5 mm expansion all directions, PTV = planning target volume, VMAT = volumetric modulated arc therapy.

Keywords: adaptive radiotherapy, cone-beam CT, dosimetric, locally advanced cervical cancer, tumor regression

1. Introduction

Cervical cancer is the fourth most prevalent female malignancy and the fourth leading cause of cancer-related death globally.[1] Concurrent chemo-radiotherapy followed by brachytherapy is the standard treatment for the locally advanced cervical cancer patients.[2,3] Traditional external beam irradiation modalities such as the pelvic large field or four-field box irradiation have a wide field coverage, which can fully include tumor target area, paracervical infiltration, and lymph node drainage areas. There was no off-target condition during radiotherapy, but it includes a large amount of surrounding normal tissues, which leads to difficulty in improving the dose to the tumor target area and a low gain ratio.[4] Therefore, the local control rate is poor, and it is easier to experience serious toxic side effects after radiotherapy.

With the development of radiotherapy technology, software systems, and imaging technology, precision radiotherapy techniques such as intensity-modulated radiotherapy, volumetric modulated arc therapy (VMAT), and image-guided radiotherapy are increasingly applied to cervical cancer external irradiation.[5] The patient's positioning accuracy, organs movement, weight change, and other factors during the radiotherapy may lead to target area dose insufficiency and excessive irradiated dose to the organs at risk (OARs).[6] Adaptive radiotherapy (ART) technology has been a research hot topic in recent years, which can be used to adjust the clinical treatment planning according to the feedback information of the imaging detection system on the tumor target area and normal tissue changes in radiotherapy to achieve the purpose of precision radiotherapy.[2] This study aimed to investigate the dosimetric evaluation of tumor target area and OARs in patients treated with external

This study was supported by the Clinical Medical Technology Demonstration Base for Cancer Precision Radiotherapy in Hunan Province (grant no. 2020SK4021); The Science and Technology Innovation Program of Hunan Province (grant no. 2017SK51302).

The authors have no conflicts of interest to disclose.

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

This study was approved by the institutional review board of Changde Hospital, Xiangya School of Medicine, Central South University. The patients/participants provided their written informed consent to participate in this study.

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How to cite this article: Tian W, Du Y, Zhou P, Ren H, Wen Y, Li S, Dong W, Wang H, Wu Z, Wu T, Xiao Z. Dosimetric evaluation of image-guided adaptive radiotherapy for locally advanced cervical cancer. Medicine 2025;104:17(e42280).

Received: 31 October 2024 / Received in final form: 1 March 2025 / Accepted: 11 April 2025

http://dx.doi.org/10.1097/MD.0000000000042280

beam radiotherapy for locally advanced cervical cancer using off-line ART, explore its feasibility and provide support for the next application in clinical practice.

2. Materials and methods

In our institution (The first people's hospital of Changde city), forty-four patients with cervical cancer who underwent radical chemoradiotherapy were enrolled from February 2017 to August 2019. All patients were validated for position and monitored for tumor regression by the cone-beam CT (CBCT), which was performed daily for the first five times and every 2 to 3 days thereafter. None of the patients had received any anti-tumor therapy previously.

2.1. Position immobilization and CT scanning

The patients were immobilized in the supine position with foot pads. Their rectums were emptied and their bladders filled (Drink 600 mL of water 1 hour before the scan, and assess urine volume at around 200 mL using bladder volume monitor) before positioning and each radiotherapy fraction. CT scanning was performed using a Siemens large-aperture CT simulator for localization from the 2nd lumbar vertebrae to the lower edge of the ischial tuberosity with a thickness of 4 mm. The CT scanning imaging was transmitted to the Eclipse (Version 13.5; Varian Medical Systems, Palo Alto) treatment planning systems.

2.2. Tumor target and OARs delineation

The tumor target area and OARs were delineated by an experienced radiation oncologist at our hospital according to the Radiation Therapy Oncology Group guideline.[7] The gross tumor volume (GTV) was defined as the primary tumor observed on the CT or MRI imaging (including cervical mass and invaded tissues). The GTVnd was defined as the metastatic lymph node confirmed by imaging or pathology. The PGTV and PGTVnd were defined as the GTV and GTVnd with 5 mm expansion. The clinical target volume was defined as the area containing the GTV, uterus, parametrium, part of the vagina, and pelvic lymphatic drainage area (including common, internal and external iliac, obturator, and presacral area). The planning target volume (PTV) was defined as the expansion of clinical target volume to the ventral side of the bladder by 8 mm and the uniform expansion by 5 mm for the rest.

2.3. Radiotherapy planning

Experienced medical physicists designed 2-arc VMAT planning (181°–179°, 179°–181°) in Eclipse (Version 13.5). The patient was treated with the initial radiotherapy planning (ART1 group). The CBCT was performed during the treatment to validate the position, from which a second CT scanning was performed according to the tumor regression condition (approximately 20%). Subsequently, the same radiation oncologist re-delineated the target area, and the same physicists designed a new plan (ART2 group). The two groups' plans were based on the total prescription for planning design, with the same tumor target area and OARs limitation requirements. The prescription dose was 45 Gy/25 fractions for PTV, 50–57.5 Gy/25 fractions for PGTV, and 62.5 Gy/25 fractions for PGTVnd. All patients were treated on the Varian linear accelerator (Trilogy_6180), the linear accelerator energy was 6 MV, once daily, five times a week. The OARs dose-limitations were as follows: small intestine-D_{mean} (mean dose) ≤ 20 Gy, D_{max} (maximum dose) ≤ 52 Gy, and V_{40} (the percentage of the small intestine volume of receiving dose ≥ 40 Gy) ≤ 40%; rectum-D_{mean} ≤ 35 Gy, D_{1cc} (the maximum dose to 1 mL of the rectum) ≤ 60 Gy; V_{40} ≤ 45%; bladder-D_{mean} ≤ 30 Gy, V_{40} ≤ 40%; (left/right) Femoral Head-D_{mean} ≤ 25 Gy, V_{45} ≤ 5%.

2.4. Planning evaluation

Dose-volume histograms were used to evaluate the planning. The target area dosimetric assessment parameters include: $D_{98\%}$, $D_{2\%}$, and $D_{50\%}$ (represent the dose received by 98%,2% and 50% of the target area volume, respectively). $V_{100\%}$ and $V_{110\%}$ (represent the volume contained in 100% and 110% prescription dose as a percentage of the target area volume, respectively). Homogeneity index (HI) was used to evaluate the uniformity of prescription dose distribution in the tumor target area and was calculated by the following equation[8]:

$$HI = \frac{D2\ \% - D98\ \%}{D50\ \%}$$

The closer the HI to 0, the better the homogeneity of the target area. D_{1cc}, V_{30}, V_{40}, and V_{50} were evaluated for the small intestine, rectum, and bladder. D_{mean}, V_{40}, and V_{45} were assessed for the left/right femoral head. In addition, we also compared the monitor unit difference between the two groups.

2.5. Statistical analysis

All were described as mean ± variance, and the paired *t* test was conducted between two groups. Statistical analysis was performed with SPSS 25.0 (IBM SPSS Statistics, IBM Corp., Armonk), and $P < .05$ was considered statistically significant.

3. Results

In total, 44 patients enrolled in this study. The median age is 56 years. Almost all patients were pathologically confirmed to be squamous cell carcinoma (42/44). According to FIGO stage (2009 version), 20 had II stage, 9 had III stage, and 11 had IV stage (Table 1).

According to the CBCT monitoring tumor regression results, all included patients performed the second CT scanning from the ninth to the seventeenth fraction treatments, with a mean CT scanning time of the thirteenth. The mean reduction of the

Table 1

Detailed information of included patients.

Characteristics	No. (N = 44)	Percentage
Age		
Median	56.0 (range, 40–83)	
<65	32	72.7
≥65	12	27.3
Histology		
Squamous Cell carcinoma	42	95.5
No Squamous Cell carcinoma	2	4.5
FIGO stage (2009)		
IB	4	9.1
IIA	6	13.6
IIB	14	31.8
IIIA	1	2.3
IIIB	1	2.3
IIIC	7	15.9
IVA	11	25.0
KPS score		
< 80	2	4.5
≥ 80	42	95.5
Mean GTV (range, cm^3)	90.2 (13.7–255.0)	

FIGO = International Federation of Gynecology and Obstetrics, GTV = gross tumor volume, KPS = Karnofsky Performance Status.

GTV volume in the ART2 group compared with the ART1 group was 23.3%, and the difference was statistically significant (69.2 ± 45.0cc vs 90.2 ± 54.3cc, $P < .001$).

For the comparison of the ART1 and ART2 radiotherapy planning groups, there were no significant differences in the $D_{98\%}$, $D_{50\%}$, and V_{100} of PGTV, PGTVnd, and PTV between the two groups ($P > .05$). Whereas, the ART2 group planning had statistically significantly lower dose of $D_{2\%}$ (54.9 ± 2.7Gy vs 56.8 ± 1.8Gy), V_{110} (2.6 ± 6.6% vs 11.8 ± 11.1%) for PGTV, and V_{110} (21.9 ± 10.8% vs 25.3 ± 11.7%) for PTV ($P < .05$). This represented that both groups met the radiotherapy planning requirements while having fewer hotspot area/dose. At the same time, the HI of PGTV and PTV was significantly lower in the ART2 group, which represented better homogeneity of the ART2 planning ($P < .05$). The dosimetric parameters of the tumor target area are presented in Table 2.

For the comparison of OARs dosimetric parameters of two groups. The ART2 planning significantly decreased the mean dose of rectum-D_{mean}, D_{1cc}, V_{30} and V_{40} by 2 Gy, 0.6 Gy, 6.3% and 5.9%, respectively ($P < .05$). It significantly decreased the mean dose of bladder-D_{1cc} by 1.1 Gy ($P < .05$), while there was no significant difference in D_{mean}, V_{30}, V_{40}, and V_{50} ($P > .05$). It also significantly decreased the mean dose of left femoral head-D_{mean}, V_{40}, and right femoral head-D_{mean} by 1.2 Gy, 1.3%, and 0.1 Gy, respectively ($P < .05$). In contrast, the mean irradiation dose of small intestinal-V_{30} (24.3 ± 10.8% vs 21.8 ± 8.8%, $P < .05$) significantly increased in the ART2 group planning compared with the ART1 group planning. The number of monitor units was similar between the two groups, and the difference was not statistically significant (691.3 ± 122.6 vs 697.6 ± 129.8, $P = .730$). All the dosimetric parameters of OARs are listed in Table 3. The example of planning and dose–volume histograms are shown in Figure 1.

Table 2

Dosimetric parameter comparison of target area in ART1 and ART2 planning.

	ART1	ART2	*t*	*P* value
PGTV				
$D_{98\%}$ (Gy)	50.9 ± 1.7	50.9 ± 1.6	−1.133	.263
$D_{2\%}$ (Gy)	56.8 ± 1.8	54.9 ± 2.7	5.410	<.001*
$D_{50\%}$ (Gy)	53.1 ± 1.8	53.0 ± 1.9	1.854	.071
V_{100} (%)	97.8 ± 1.2	98.0 ± 1.4	−1.214	.232
V_{110} (%)	11.8 ± 11.1	2.6 ± 6.6	6.080	<.001*
HI	0.112 ± 0.038	0.075 ± 0.042	5.542	<.001*
PGTVnd				
$D_{98\%}$ (Gy)	62.3 ± 0.7	62.3 ± 0.5	0.708	.486
$D_{2\%}$ (Gy)	65.6 ± 0.8	65.4 ± 0.6	1.630	.117
$D_{50\%}$ (Gy)	64.3 ± 0.7	64.2 ± 0.6	0.914	.371
V_{100} (%)	97.5 ± 1.6	96.9 ± 1.8	0.899	.379
V_{110} (%)	0.0 ± 0.0	0.0 ± 0.0	1.000	.328
HI	0.052 ± 0.009	0.050 ± 0.007	0.973	.341
PTV				
$D_{98\%}$ (Gy)	44.8 ± 0.3	44.9 ± 0.3	−1.470	.149
$D_{2\%}$ (Gy)	57.4 ± 4.3	57.5 ± 4.7	−0.093	.927
$D_{50\%}$ (Gy)	47.7 ± 0.8	47.5 ± 0.7	1.937	.059
V_{100} (%)	97.3 ± 1.0	97.6 ± 1.0	−1.763	.085
V_{110} (%)	25.3 ± 11.7	21.9 ± 10.8	3.573	.001*
HI	0.222 ± 0.066	0.202 ± 0.076	3.821	<.001*

Values are represented as mean ± variance.

ART = adaptive radiotherapy, ART1 = initial radiotherapy planning, ART2 = based on tumor regression performed new planning, $D_{98\%}/D_{50\%}/D_{2\%}$ = the dose received by 98%/50%/2% of the target volume, HI = homogeneity index, PGTV/PGTVnd/PTV = the area formed by the gross tumor target/metastatic lymph node/clinical target volume with expansion, V_{100}/V_{110} = the volume contained in 100%/110% prescription dose as a percentage of the target volume.

*Statistically significantly.

4. Discussion

Traditionally, locally advanced cervical cancer patients received radiotherapy only by utilizing localized CT images obtained before treatment for target area delineation and radiotherapy planning design, and the same planning was implemented throughout the entire treatment period. Failure to consider and assess the regression of the gross tumor target dynamically during the treatment may lead to the actual dose distribution of patients not matching the initial planning.[9] This results in insufficient dose to the tumor target area and excessive dose to the OARs, ultimately affects the patients' local control rate and the incidence of adverse reactions. Therefore, precise radiotherapy should be as individualized as possible and requires timely planning modification based on new imaging information during the treatment. In this study, we used CBCT to validate the position and monitor the tumor regression of the patients and timely performed a second CT scanning for re-planning.

The results showed that the volume of the GTV was reduced by an average of 23.3% when secondary CT scanning (with a mean time of 13th fractions) was performed through CBCT monitoring, and the difference was statistically significant ($P < .05$). Chen et al.[10] used CBCT to monitor the trends of tumors in cervical cancer radiotherapy patients and showed that tumor regression and positional changes were most apparent at ten to fifteen fraction treatments, which is similar to our results. Van et al[11] showed that the mean volume of the GTV was significantly reduced by 46% after external irradiation doses up to 30 Gy. The more significant tumor regression in their study might be associated with a longer number of external irradiations, a smaller sample size, and the heterogeneity of two groups of patients. The secondary CT scanning in fixed radiotherapy fractions makes it difficult to assess changes of tumor target area and to reduce the impact of radiation on OARs timely. Pang et al[12] showed that

Table 3

Dosimetric parameter comparison of OARs in ART1 and ART2 planning.

OARs	ART1	ART2	*t*	*P* value
Rectum				
D_{mean} (Gy)	38.0 ± 4.2	36.0 ± 4.23	2.976	.005*
D_{1cc} (Gy)	53.0 ± 2.1	52.4 ± 1.9	2.235	.031*
V_{30} (%)	75.0 ± 15.1	67.7 ± 14.1	2.919	.006*
V_{40} (%)	51.5 ± 17.2	45.6 ± 15.4	2.459	.018*
V_{50} (%)	13.0 ± 8.9	12.2 ± 7.7	0.528	.600
Bladder				
D_{mean} (Gy)	36.8 ± 5.3	35.8 ± 3.4	1.180	.245
D_{1cc} (Gy)	54.1 ± 3.0	53.0 ± 2.5	3.160	.003*
V_{30} (%)	66.5 ± 12.7	64.9 ± 12.7	1.027	.310
V_{40} (%)	44.5 ± 9.9	44.3 ± 12.0	0.151	.881
V_{50} (%)	6.7 ± 5.4	5.6 ± 5.1	0.936	.355
Small intestine				
D_{1cc} (Gy)	53.5 ± 5.4	52.3 ± 6.9	1.233	.224
V_{30} (%)	21.8 ± 8.8	24.3 ± 10.8	-2.086	.043*
V_{40} (%)	10.8 ± 5.3	12.2 ± 7.2	-1.783	.082
V_{50} (%)	0.6 ± 0.9	0.6 ± 1.1	0.138	.891
(L) Femoral Head				
D_{mean} (Gy)	26.5 ± 4.0	25. 3 ± 3.6	2.170	.036*
V_{40} (%)	4.4 ± 6.2	3.1 ± 4.4	2.380	.022*
V_{45} (%)	0.3 ± 0.8	0.2 ± 0.4	1.047	.301
(R) Femoral Head				
D_{mean} (Gy)	26.1 ± 3.8	24.8 ± 4.0	2.657	.011*
V_{40} (%)	4.4 ± 7.3	3.1 ± 5.9	1.864	.069
V_{45} (%)	0. 3 ± 0.5	0.2 ± 0.5	1.636	.109

Values are represented as mean ± variance.

ART = adaptive radiotherapy, ART1 = initial radiotherapy planning, ART2 = based on tumor regression performed new planning, OARs = organs at risk, D_{mean} = mean dose, D_{1cc} = the maximum dose to 1 mL of the OARs, Vx = the percentage of the OARs volume of receiving dose ≥ x Gy, L/R = left/right.

*Statistically significantly.

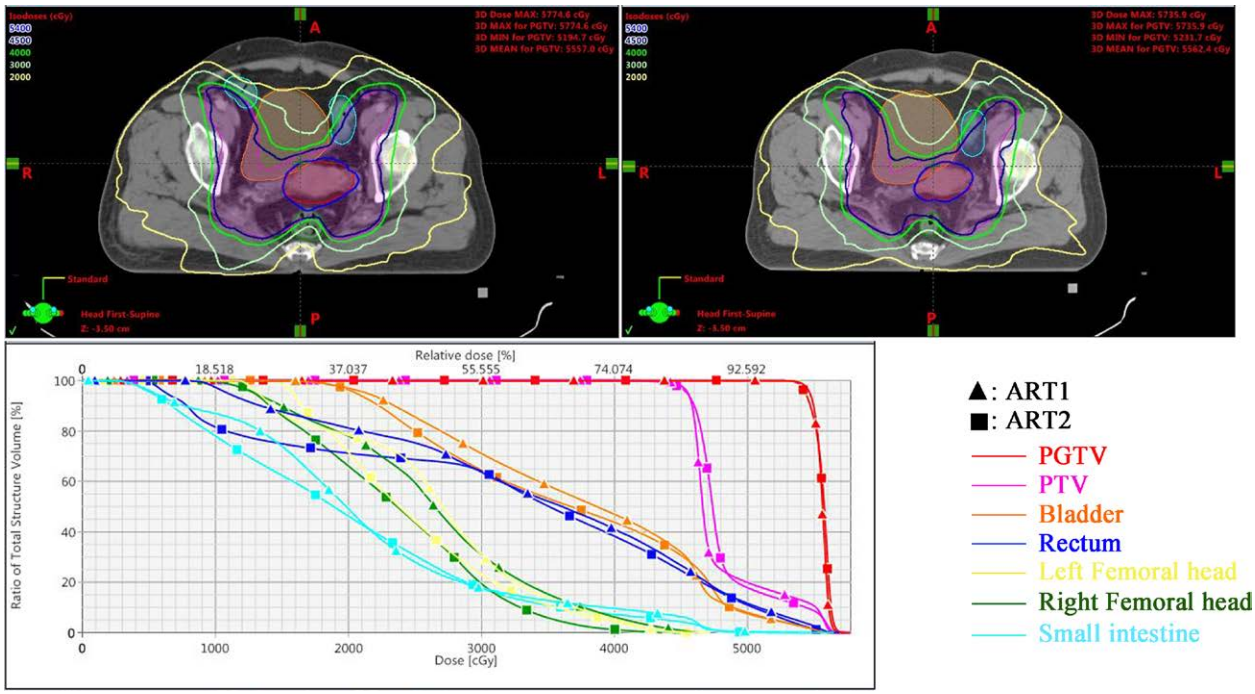

Figure 1. The example of planning and dose–volume histograms. Upper left: ART1 (pretreatment) planning; Upper Right: ART2 (during treatment) planning. ART = adaptive radiotherapy.

GTV decreased by an average of 48.2% at the end of radiotherapy in patients with cervical cancer, and re-planning was recommended for those with significant tumor regression.

Secondary CT scanning images-based re-planning (ART2) showed no significant difference in the $D_{98\%}$, $D_{50\%}$, and V_{100} of PGTV, PGTVnd, and PTV between the two groups compared with the ART1 planning. In contrast, the ART2 planning had a significantly lower dose of $D_{2\%}$, V_{110} for PGTV and V_{110} for PTV. And the HI of PGTV and PTV was significantly lower in the ART2 planning. Meanwhile, The ART2 planning also significantly decreased the mean dose of rectum-D_{mean}, D_{1cc}, V_{30} and V_{40}, bladder-D_{1cc}, left femoral head-D_{mean}, V_{40}, and right femoral head-D_{mean}, but significantly increased the small intestinal-V_{30}. It might be associated with spatial location (affected by the GTV or bladder volume changes) and volume changes of the small intestine.[13] But the results showed that both plans met the planning requirements, and the ART2 planning significantly reduced the target hotspot area/dose and improved the target homogeneity while reducing the irradiated dose to the rectum, bladder, and femoral head. Previous studies showed that the higher the V_{30}, V_{40}, V_{50}, and D_{1cc} of OARs, the higher the incidence of radiation-related toxicities, so we compared this dosimetric parameters.[14] Van et al[11] demonstrated that the re-planning significantly reduced the rectum dose, with no significant difference in the small intestine and bladder dose, which was associated with the significant reduction in GTV volume. The anatomical location of normal organs, such as the bladder and rectum are adjacent to the tumor target area, and as cavity organs, their filling degree has greater variable factors. Therefore, GTV regression during treatment can significantly impact on the positional distribution of surrounding OARs, which may increase the occurrence of radiation-related side effects such as radiation proctitis and cystitis. Kerkhof et al[15] performed weekly MRI scans with four plans in patients and showed that after modification of the plans, there was a significant reduction in V_{10} to V_{45} in all OARs, except for V_{10} in the bladder and sigmoid colon, which was similar to our results. Other studies have demonstrated that VMAT significantly decreased rectal and bladder high-dose volumetric parameters compared with intensity-modulated radiotherapy, and this study is based on the VMAT planning.[14,16]

In this study, we observed that radiotherapy for patients with locally advanced cervical cancer can better protect the OARs by timely adjusting the planning according to the changes in the volume of the target area during treatment, especially for the rectum, and can reserve dose space for brachytherapy. There were several limitations in this study. Firstly, only off-line ART planning modification was used for the external irradiation dosimetric evaluation, and the value of ART in the treatment of cervical cancer still needs to be verified in large-sample multi-center clinical trials. In contrast, although the online ART planning can be based on daily target volumes and OARs anatomical variations, it is still very challenging as it needs to be fast enough to create a deliverable plan including segmentation and quality assurance in minutes, and it may become more widespread in the future.[2,5] Secondly, volume changes of the OAR were not monitored, and the relationship between target area regression and changes in the OAR could be assessed in the future.

5. Conclusion

Locally advanced cervical cancer radiotherapy patients can be validated for position and monitored for target volume changes by CBCT, and adaptive planning at the thirteenth fraction of radiotherapy might be appropriate. Off-line ART planning can adapt for the changes in the target volume and further decrease the target volume hotspot area/dose and OARs irradiation dose. Especially beneficial for rectal and allowing reserving dose space for brachytherapy. Therefore, our study provides a reference to support the adaptive radiotherapy plan for cervical cancer, which is helpful to reduce radiation-related toxicities.

Acknowledgments

The authors thank all the people who had participated in this study.

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