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The Application of Image Guided Radiotherapy on the Precision of Intensity Modulated Radiotherapy in Patients with Locally Advanced Rectal Cancer

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Abstract

Objective: To investigate the effect of onboard image (OBI) system-based image guided radiotherapy (IGRT) on the precision of fractionated intensity modulated radiotherapy (IMRT) for patients with locally advanced rectal cancer. **Methods:** The IGRT validation images of the 12 patients with rectal cancer were obtained after initial setup by the OBI system of Varian Novalis TX linear accelerator, and registered to the planning CT image system. Subsequently, the setup deviations on three translational directions [ventral-dorsal direction (VD), cranial-caudal direction (CD) and lateral direction (LD)] for the three-validation phase including Pre-treatment (Pre-RT1), repositioning (Pre-RT2) and Post-treatment (Post-RT) were obtained and comparatively analyzed. **Results:** The frequency of setup deviation of ≤2.0 mm in the lateral, cephalocaudal and ventral direction was 83.01%, 65.71%, and 68.91%, respectively for Pre-RT1; 100%, 98.72% and 100%, respectively for Pre-RT2; 100%, 97.76%, and 99.68%, respectively for Post-RT. Compared with the Pre-RT1 phase, the ranges of setup deviation on Pre-RT2 and Post-RT phases possessed a significant contraction trend. The absolute values of setup deviations on the three translation directions between the Pre-RT1 and Pre-RT2 or Post-RT were statistically significant ($p < 0.05$). Through positioning adjustment based on IGRT based on the OBI system, the setup deviations on the three translational directions decreased significantly. **Conclusion:** Application of OBI-based daily IGRT may help improve the precise delivery of fractionated IMRT by decreasing the inter- and intra-fractionated setup deviation in the ventral-dorsal direction, cranial-caudal direction and lateral direction for patients with locally advanced rectal cancer.

*Equally contribution.

Keywords

Rectal Cancer, IMRT, IGRT, OBI, Setup Deviation

1. Introduction

According to Globocan 2012, colorectal cancer is the fifth most common cancer in China with approximately 40% of the patients would be diagnosed as rectal cancer, among them 49.9% as Duck B and 33.9% as Duck C diseases [1] [2] [3]. Neoadjuvant chemoradiotherapy (neo-CRT) followed by total mesorectal excision (TME) has been recommended as a standard treatment of choice for patients with locally advanced rectal cancer by National Cancer Center Network (NCCN) guideline since 2006 [4] [5] [6].

Clinical studies have been shown that the application of neo-CRT may help shrink tumor, improve sphincter-preservation, reduce loco-regional tumor recurrence and improve survival and the quality of life; whereas the surgical complications and sequelae associated with neo-CRT would not increase significantly [7] [8]. It has been reported that 18.1% to 30.2% of patients with locally advanced rectal cancer would achieve pathologic complete response (pCR) when they were treated with neo-CRT followed by TME. We have reported that approximately 25% of patients out of 289 patients who achieved pCR demonstrated with better prognosis than those with non-pCR after neo-CRT [9]-[14].

Radiotherapy is a very important component in neo-CRT [15]. As the technology advances, the introduction of intensity modulated radiotherapy (IMRT) has shown the property of higher dose coverage to the plan target volume (PTV) and lower dose irradiation to the adjacent normal critical tissues such as bladder and small intestine; hence the precise delivery of IMRT requires accurate patient positioning during fractionated radiotherapy in patients with rectal cancer. The application of on-board image (OBI) system-based image guided radiotherapy (IGRT) may help improve the precision of fractionated IMRT.

The purpose of the study was designed to investigate the effect of IGRT on the precision of patient set-up in ventral-dorsal direction, cranial-caudal direction and lateral direction for the three-validation phases including pre-treatment (Pre-RT1), repositioning (Pre-RT2) and post-treatment (Post-RT) during inter- and intra-fractionated IMRT for patients with locally advanced rectal cancer.

2. Materials and Methods

1) Patient characteristics

12 patients with clinical stage II-III rectal cancer were recruited to neo-CRT in our facility who had signed agreement for the treatment. All patients who were pathologically diagnosed as rectal cancer were performed clinical stage examinations including physical exam, serum chemical profile including carcinoembryonic antigen (CEA), colonoscopy and two to three image studies, *i.e.*, chest

radiography, chest/abdomen/pelvic computed tomography (CT), pelvic magnetic resonance image (MRI), intraluminal ultrasound (ERUS), positron emission computed tomography (PET/CT) and emission computed tomography (ECT) according to American Joint of Cancer Classification (AJCC) 2010.

2) Radiotherapy

Radiotherapy (RT) was administered with intensity modulated radiation therapy (IMRT) in all patients with 6 MV X-ray. The patients were prone positioned at the home-made vacuum with specific foam board of high density which mimicked Orfit fixation to push small bowel out from the pelvis. The patient was encouraged to have bowel movement and drink 500ml water with 20ml Iopromide Injection solution (Ultravist®, Bayer) to make proper filling of bladder 30 minutes before CT simulation.

Plain and contrast CT images (140 kV/250 mAs, 120/300 mAs) were captured with big-bore helical CT simulator (Brilliance™ Big Bore, Philips, USA), reconstructed with slice of 1 mm thickness and then transferred to ARIA workstation (Varian, USA). The definition of target volume was followed by the recommendations of International Commission of Radiation Units reports 50 & 83. The delineation of clinical target volume (CTV) included primary rectal cancer, both ends of the affected rectum, the surrounding tissues of the affected rectum, the mesorectal region, the presacral lymph nodes, the obturator lymph nodes, and the internal iliac lymph nodes. For patients with stage T4 rectal carcinoma with bladder or prostate involvement, the delineation of CTV also included external iliac lymph nodes.

The planned target volume (PTV) was designated as 5 mm margin from the CTV. The dose prescription was as follows: 100% of the prescription dose covered at least 95% volume of the PTV; 95% of the prescription dose covered 100% volume of the PTV. The reference point was set as the intersection of the central axes of the five beams for IMRT. The radiation dose to the PTV was 50.0 Gy, 2 Gy per fraction, 5 fractions per week. The dose to the organs at risk (OARs) was aimed to be as low as possible and must at least comply with the following constraints: bladder of 50 Gy in <50% volume; the mean dose (Dmean) of small bowel < 45 Gy, small bowel of 50 Gy in <5% volume.

For every individualized fractionated IMRT, the patient was encouraged to have bowel movement and drink 500 ml water to make proper filling of bladder 30 minutes prior to radiotherapy, which was the same procedure as for CT simulation. The IGRT validation images were captured after initial setup by the OBI system of Varian Novalis TX linear accelerator (Varian, Palo Alto), and registered to the planning CT images. Cone beam CT images (120 kV/1.04 mAs) were captured once a week and orthogonal images (70 kV/10 mAs, 105 kV/80 mAs) 4 times a week. Subsequently, the setup deviations on three translational directions including ventral-dorsal direction (VD), cranial-caudal direction (CD) and lateral direction (LD) for the three-validation phase, *i.e.*, pre-treatment (Pre-RT1), repositioning (Pre-RT2) and post-treatment (Post-RT) were acquired and comparatively analyzed. For the Pre-RT1, any deviation ≥ 5 mm in any di-

rection would lead to patient reposition and capture Pre-RT2 image. The deviation ranging from 2 to 5 mm would move the couch per the registration between IGRT and CT simulation images and capture the Pre-RT2 image. The patient would be delivered with radiotherapy if the deviation was <2 mm. Post-RT image set would be captured post fractionated IMRT.

3) Chemotherapy

All patients were treated chemotherapeutic regimens of XELOX with 2 cycles during radiotherapy (Capecitabine, 1000.0 mg/m^2, on d1 - 14; Oxaliplatin, 100.0 mg/m^2, IV on day 1; two cycles at an interval of 3 weeks) [9] [10].

4) Surgery

Total mesorectal excision was performed approximately 6 - 8 weeks (range: 4 - 20 weeks) after the completion of neo-CRT. The surgical procedure was either low anterior resection/double stapling method or abdominoperineal resection.

5) Adjuvant chemotherapy

Patients would receive post-operative adjuvant chemotherapy with either XELOX or FOLFOX according to the pathological TNM staging.

6) Data statistics

All statistical analyses were performed using SPSS v17.0 software. ANOVA test was utilized to analyze setup deviations between Pre-RT1 and Pre-RT2 or Post-RT images, and a p value < 0.05 was considered to be significant. The setup deviations were represented as mean ± standard error.

3. Results

There were 9 males and 3 females with median age of 51.0 ranging from 32 to 67 years old. Among them 9 patients were treated with neo-CRT followed by total mesorectal resection and the other 3 treated with concurrent chemoradiotherapy and adjuvant chemotherapy.

As described in Materials and Methods, each single patient presented with 3 sets of OBI-based IGRT images including Pre-RT1, Pre-RT2 and Post-RT for every fractionated IMRT. There were total 313 sets of IGRT images for 12 patients. Detailed information for set-up deviation between CT simulation and IGRT images in the directions of lateral deviation (LD), cephalocaudal deviation (CD) and ventral deviation was shown in **Figure 1** at positioning (Pre-RT1) or adjusting position (Pre-RT2) or completion of fractionated IMRT (Post-RT).

As summarized in **Table 1** and **Figure 2**, the average and standard deviation for setup deviation between CT simulation and IGRT images for Pre-RT1 was −0.50 ± 1.79 mm ranging from −13.0 mm to 5.0 mm laterally, −0.39 ± 2.53 mm ranging from −8.0 mm to 5.0 mm cephalocaudally and 0.29 ± 2.76 mm ranging from −6.0 mm to 9.0 mm ventrally. It was −0.19 ± 0.87 mm (−2 mm - 2 mm), −0.12 ± 1.09 mm (−3.0 mm - 3.0 mm) and 0.08 ± 1.02 mm (−2.0 mm - 2.0 mm), respectively for Pre-RT2; −0.18 ± 0.92 mm (−2.0 mm - 4.0 mm), −0.09 ± 1.10 mm (−4.0 mm - 3.0 mm) and 0.21 ± 0.97 mm (−2.0 mm - 3.0 mm), respectively for post-RT.

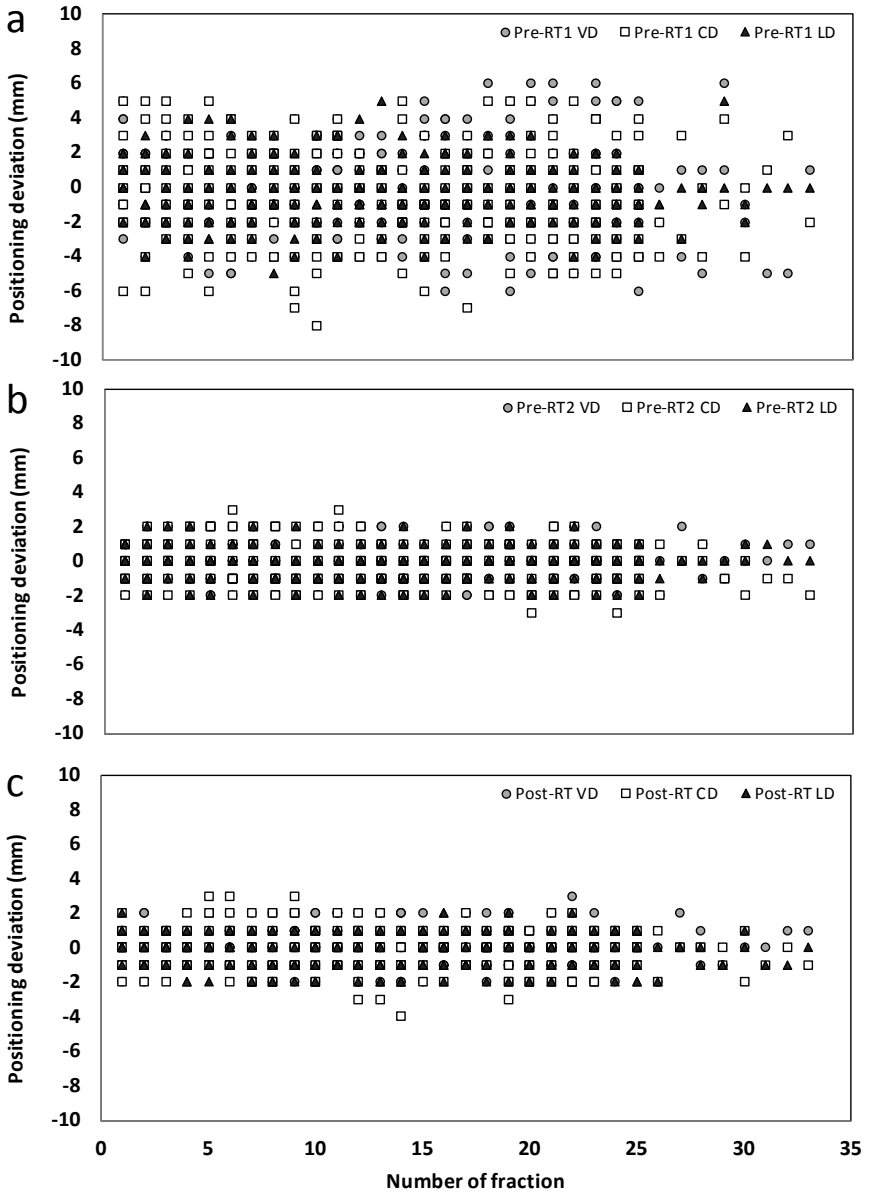

Figure 1. Plot for set-up deviation between CT simulation and IGRT images which were acquired at positioning (Pre-RT1) or adjusting position (Pre-RT2) or completion of radiotherapy (Post-RT) in the direction of lateral deviation (LD), cephalocaudal deviation (CD) and ventral deviation.

Table 1. Set-up deviation between IGRT Image and CT-Simulation image (Mean ± SD, range, mm).

	Pre-RT1	Pre-RT2	Post-RT
Lateral deviation	−0.50 ± 1.79 (−13 - 5)	−0.19 ± 0.87 (−2 - 2)[a]	−0.18 ± 0.92 (−2 - 4)[b]
Cephalocaudal deviation	−0.39 ± 2.53 (−8 - 5)	−0.12 ± 1.09 (−3 - 3)[a]	−0.09 ± 1.10 (−4 - 3)[c]
Ventral deviation	0.29 ± 2.76 (−6 - 9)	0.08 ± 1.02 (−2 - 2)[a]	0.21 ± 0.97 (−2 - 3)[d]

Note: When compared to the deviation acquired at Pre-RT1, the analysis of difference in lateral deviation, cephalocaudal deviation or ventral deviation between Pre-RT1 and Pre-RT2 or Post-RT was made using ANOVA, SPSS v17.0 software. (a) p = 0.000; (b) p = 0.344; (c) p = 0.008; and (d) p = 0.002.

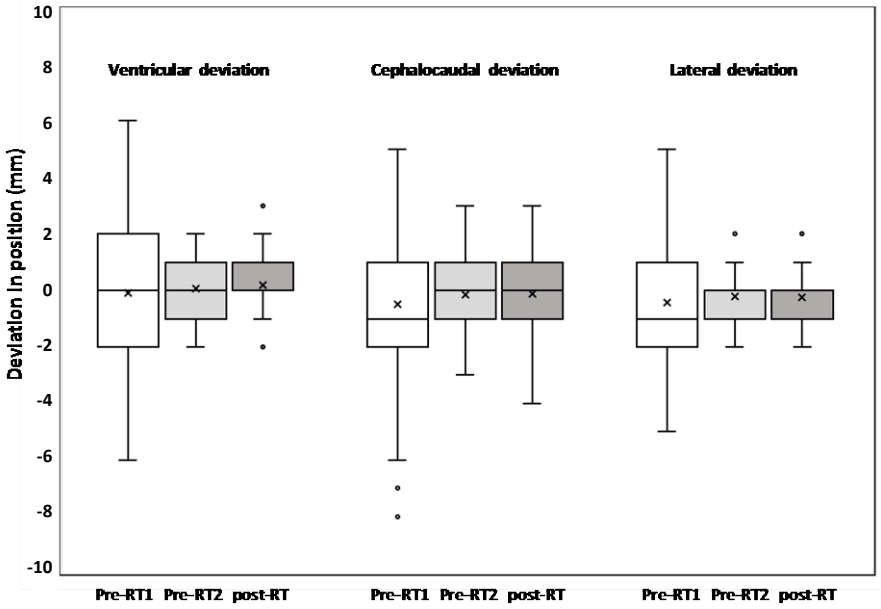

Figure 2. Box plot of set-up deviation between CT simulation and IGRT images which were acquired at positioning (Pre-RT1) or adjusting position (Pre-RT2) or completion of radiotherapy (Post-RT) in the direction of lateral deviation (LV), cephalocaudal deviation (CD) and ventral deviation.

Compared with the Pre-RT1 phase, the ranges of setup deviation on Pre-RT2 and Post-RT phases possessed a significant contraction trend. The absolute values of setup deviations on the three translation directions between the Pre-RT1 and Pre-RT2 or Post-RT were statistically significant ($p < 0.01$) except the difference on lateral deviation between Pre-RT1 and Post-RT ($p = 0.344$).

The frequency of absolute setup deviation of ≤1.0 mm, 1.0 - 2.0 mm, 2.0 - 5.0 mm and >5.0 mm between CT simulation and IGRT images was 48.72%, 23.82%, 25.75% and 1.71%, respectively for Pre-RT1; 83.12%, 16.45%, 0.43% and 0%, respectively for Pre-RT2; 86.65%, 12.5%, 0.85% and 0%, respectively. Detailed information was shown in Table 2.

We investigated the impact of directions of patient position on the set-up deviation between CT simulation and IGRT images. As shown in Figure 3, the frequency of setup deviation of ≤2.0 mm in ventral direction for Pre-RT1, Pre-RT2 and Post-RT was 69.01%, 100% and 99.68%, respectively; it was 65.81%, 98.72% and 97.76%, respectively in the cephalocaudal direction; 83.01%, 100% and 100%, respectively in the lateral direction.

4. Discussion

Our study has demonstrated that OBI-based IGRT is associated with improvement in the precise delivery of fractionated IMRT and reduction of intra- or inter-fractionated setup deviation by approximately 27% for patients with locally advanced rectal cancer, which may be proven to increase tumor control in terms of pathologic complete response, decrease bladder and intestinal toxicities associated with radiotherapy and further improve the quality of life.

Table 2. Frequency of position deviation between IGRT Image and CT-Simulation image (%).

	Pre-RT1	Pre-RT2	Post-RT
$\|x\| \le 1$	48.88	83.17	86.58
$1 < \|x\| \le 2$	23.75	16.40	12.57
$2 < \|x\| \le 5$	25.67	0.43	0.85
$\|x\| > 5$	1.70	0.00	0.00

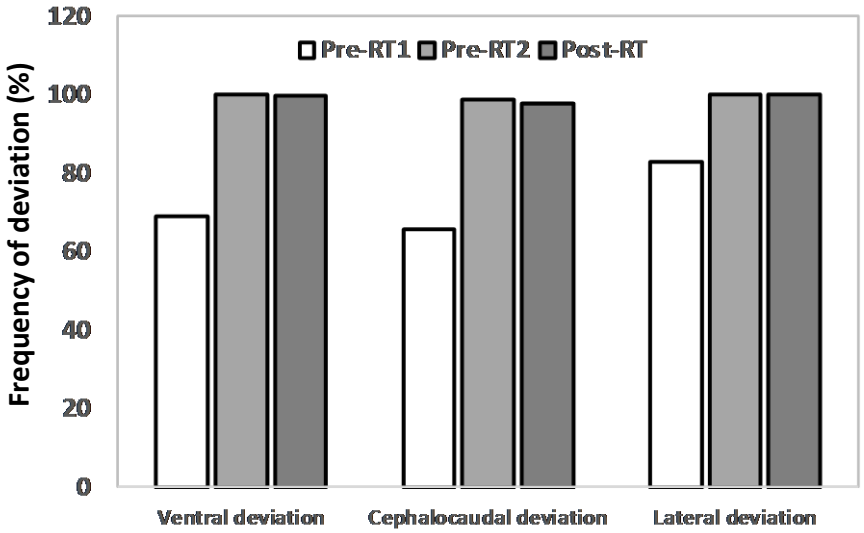

Figure 3. Frequency of set-up deviation between CT simulation and IGRT images ≤ 2 mm which were acquired at positioning (Pre-RT1) or adjusting position (Pre-RT2) or completion of radiotherapy (Post-RT) in the direction of lateral deviation (LV), cephalocaudal deviation (CD) and ventral deviation.

Rectal cancer is the fourth to fifth most frequently diagnosed cancer and the second to third leading cancer death when combined with colon cancer [16]. Allemani C *et al.* [17] have reported in their meta analysis of CONCORD-2 that in the developed countries the 5-year survival has improved steadily over the period from 1995 to 2005 and reached 60% or higher especially for those diagnosed from 2005 to 2009. The improvement in treatment outcomes has been postulated to the advancement in 1) diagnostic modalities, *i.e.*, CT, MRI; 2) surgical procedure, especially the introduction of total mesorectal excision; 3) neo- or adjuvant chemotherapy; 4) pre- or post-operative radiotherapy.

Radiation therapy has been evolved over the past 3 decades in the management of patients with locally advanced rectal cancer. It has been reported that the addition of postoperative radiotherapy has decreased the local regional recurrence by 10% - 20%. Further studies [18]-[23] have demonstrated that preoperative chemoradiotherapy has been shown to increase local tumor control, reduce treatment-related toxicity, and improve sphincter preservation when compared to postoperative chemoradiotherapy.

The putative advantages of preoperative radiotherapy are associated with 1)

shrinking tumor volume which may facilitate resection rate and increase the probability of a sphincter-sparing procedure; 2) irradiating tumor tissue which is surgery naive and better oxygenated may lead to increased sensitivity to radiotherapy; 3) avoidance of the occurrence of radiotherapy-induced injury to small bowel that is trapped in the pelvis by postoperative adhesions; and 4) resection of irradiated tissue which may make assurance of anastomosis with healthy colon. The disadvantage of preoperative radiotherapy may lead to over-treat patients with early stage tumor who do not require adjuvant radiotherapy [24] [25].

Technical advances in radiotherapy, particularly the development of intensity modulated radiation therapy (IMRT) and image guided radiation therapy (IGRT), have improved our abilities to place the radiation dose precisely in three-dimensional space, ensuring adequate coverage of the gross tumor and clinical target volumes while simultaneously sparing normal tissues [26] [27] [28]. As the anatomic location of the rectum is near the critical organs at risk, appropriate beam shaping, and precise placement had been challenges for the radiation oncologists.

Although the implementation of IMRT allows significant improvement in the survival, local recurrence remains challenging for patients with locally advanced rectal cancer. The utilization of IMRT in the treatment of rectal cancer requires a different mindset when compared with conventional radiotherapy. One of the most important differences is the target volumes need to be accurately determined and delineated before the planning of IMRT can be initiated. The other important one is to keep patient positioned repeatedly and deliver IMRT precisely to maximally minimize the setup deviation during inter- and intra-fractionated radiotherapy. It is of clinical importance to improve precise delivery of IMRT. The application of IGRT based on on-board image (OBI) system may help improve the precision of fractionated IMRT [29] [30].

According to American Association of Physicist in Medicine (AAPM) Task Report #142 [31] the deviation in patient position between CT simulation and fractionated IMRT should be limited within a margin of 2.0 mm. Our research has shown that the frequency of setup deviation ≤ 2 mm was 68.91% ventrally, 65.71% cephalocaudally and 83.01% laterally for the Pre-RT1 IGRT which meant approximately every 1 out of 4 fractionated IMRT would be delivered outside the margin of 2.0 mm without the guidance of OBI-based IGRT. Whereas it reached approximately 100% within the margin of 2.0 mm when the patient was repositioned or adjusted per Pre-RT1 IGRT image. It remained to approximately 100% at the completion of fractionated IGRT.

In comparison with the Pre-RT1 phase, the ranges of setup deviation on Pre-RT2 and Post-RT phases showed a significant contraction trend. The absolute values of setup deviations on the three translation directions between the Pre-RT1 and Pre-RT2 or Post-RT were statistically significant except the difference on lateral deviation between Pre-RT1 and Post-RT ($p = 0.344$). Through the couch positioning adjustment per IGRT based on the OBI system, the setup

deviations on the three translational directions is decreased significantly.

5. Conclusion

In summary, our research has demonstrated that the application of OBI-based IGRT help improve the precise delivery of fractionated IMRT by decreasing the inter- and intra-fractionated setup deviation in the ventral-dorsal direction, cranial-caudal direction and lateral direction for patients with locally advanced rectal cancer. Adjusting patient position per the OBI system-based IGRT image may guarantee the precise delivery of fractionated IMRT.

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Conflicts of Interest

The authors declare that there is no conflict of interest with respect to the research, authorship, and/or publication of this article.

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Abbreviations

OBI, onboard image; IGRT, image guided radiotherapy; IMRT, intensity modulated radiotherapy; VD, ventral-dorsal direction; CD, cranial-caudal direction; LD, lateral direction; Pre-RT1, Pre-treatment; Pre-RT2, repositioning; Post-RT, Post-treatment; neo-CRT, Neoadjuvant chemoradiotherapy; TME, total mesorectal excision; NCCN, National Cancer Center Network; pCR, pathologic complete response; PTV, plan target volume; CEA, carcinoembryonic antigen; CT, computed tomography; MRI, magnetic resonance image; ERUS, intraluminal ultrasound; PET/CT, positron emission computed tomography; ECT, emission computed tomography; AJCC, American Joint of Cancer Classification; RT, Radiotherapy; CTV, clinical target volume; OAR, organs at risk; AAPM, American Association of Physicist in Medicine.