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CLINICAL STUDY

Evaluation of interfractional organ motion during neoadjuvant radiotherapy for rectal cancer patients

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ABSTRACT

OBJECTIVE: To investigate interfractional motion of the mesorectum and bladder and to assess dosimetric changes using cone-beam computed tomography (CBCT) during neoadjuvant radiotherapy for locally advanced rectal cancer patients.

METHODS: Twenty-one patients who underwent volumetric arc therapy with CBCT imaging protocol were retrieved. The mesorectum and bladder were delineated on every CBCT image, and treatment plans were recalculated for all CBCTs. The organ motion was analyzed as a mean shift on the X-Y-Z axes. The volume changes were evaluated using the DICE index. Mann–Whitney U test was used in pairwise comparison analysis and ANOVA was used to compare shifts in each direction.

RESULTS: A total of 105 CBCTs were evaluated retrospectively. The movement of the total mesorectum was found to be 1.5 mm, 4 mm, and 5 mm on the X-Y-Z-axes, respectively. In the subgroup analysis, the movement of the 1/3 upper mesorectum on the Y-axis was significantly higher (mean movement 8 mm, p = 0.005). Mean bladder displacements were 2 mm, 4 mm, and 8 mm on the X-Y-Z-axes, respectively. In the D2, D95, and D98 doses, there was no statistically significant change depending on the motion.

CONCLUSION: During radiotherapy planning, the mesorectal movement should not be forgotten and PTV margins should be determined accordingly *(Tab. 6, Ref. 22)*. Text in PDF *www.elis.sk*

KEY WORDS: cone-beam computed tomography, rectal cancer, mesorectum, interfractional organ motion, neoadjuvant radiotherapy.

Introduction

Neoadjuvant chemoradiotherapy (nCRT) is a widely used treatment modality in patients with locally advanced rectal cancer (LARC) all over the world. In randomized controlled studies, it has been shown that better oncologic results are achieved with total mesorectal excision after nCRT (1, 2).

While performing neoadjuvant radiotherapy in rectal cancer patients, the clinical target volume (CTV) should cover the entire mesorectum, which has a high risk of submicroscopic disease due to its richness in blood vessels and lymph nodes, except for the primary tumor and lymph nodes. However, the rectum and mesorectum are structures that constantly move due to bowel peristalsis and bladder filling throughout the treatment. In the past, radiotherapy in rectal cancer was administered with a large 4-field box technique involving the rectum and regional pelvic lymph nodes. Therefore, organ motion was not important during treatment planning. Nowadays, in parallel with the latest developments in radiotherapy devices and treatment techniques, these patients are mostly treated with intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), or helical tomotherapy, which provides a better dose distribution and sharp dose gradient (3–5). Therefore, a margin of safety must be given to the CTV to deliver the planned dose to the target accurately and appropriately, and also a certain treatment margin for setup accuracy. Recently, the implementation of these treatments with the image-guided radiotherapy (IGRT) technique allows for preventing geographical missing, and reduces margins and late toxicity rates (3, 6, 7). In practice, many techniques are used in daily imaging protocols, but megavoltage computed tomography (MVCT) and cone-beam computed tomography (CBCT) are the most commonly preferred methods to see patient positioning (4, 5). To date, the displacement of the rectum during treatment and its effect on target volume has been investigated and shown mostly in prostate and cervical cancer patients (8–15). In recent years, studies on this subject have also increased in patients with rectal cancer, and especially the amount of sufficient safety margin has been tried to be determined. Several publications have suggested the use of CBCT during nCRT to determine the optimal safe margin, monitor changes in size, position,

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and shape of gross tumor volume, and evaluate rectal motion (4, 5, 6, 16). It has also been reported to help improve local control, decrease geographical missing, permit individualized PTV margin, and reduce radiation damage to organs at risk.

As a result, our study aimed to assess the interfractional movement of the total mesorectum and bladder using CBCT images taken during treatment and to determine the dosimetric changes due to movement. The secondary goal is to investigate the movement differences in the upper, middle, and lower thirds of the mesorectum and the effect of bladder volume changes on these motions.

Patients and methods

Patient characteristics

This study included 21 consequent patients with LARC who underwent nCRT between 2019 and 2021. All patients' treatment files, radiotherapy protocols, and daily CBCT images were reviewed retrospectively. Patients had histologically confirmed primary adenocarcinoma. According to the tumor, node, and metastasis (TNM8) staging system, the patients were classified as being in clinical stage II/III using a PET/CT scan and MRI with contrast. The distance between the tumor and internal verge was determined using a combination of colonoscopy and MRI data. Table 1 lists the characteristics of the patients.

CT simulation and contouring

The planning tomography images were obtained from 9 patients in a prone position on a belly board and the remaining 12 patients in the supine position using a thorax board. The simulation scan was taken using the G.E. Lightspeed 16 computed tomography (CT) scanner (General Electric Healthcare, Waukesha, WI) with a slice thickness of 2.5 mm from the third lumbar vertebra to 5 cm below the anal marker. Before the CT simulation and each treatment session, the patients drank 500 ml of water after emptying their bladder and then waited for 30 minutes for optimal bladder volume. Moreover, the bladder volume was checked with ultrasonography for the same fullness by a radiotherapy technician each time. No laxatives were used to empty their rectums. However, a light diet list was applied to the bowel.

Tab. 1. Patient characteristics.

	n	%
Gender		
Male	12	57.1
Female	9	42.9
T stage		
T2	3	14.3
T3	14	66.7
T4	4	19
Tumor location		
Proximal rectum	9	42.9
Distal rectum	12	57.1
Treatment position		
Supine	12	57.1
Prone	9	42.9
Tumor size		
≤5 cm	10	47.6
>5 cm	11	52.4

The diagnostic MRI and PET/CT images were matched with CT simulation scans to achieve an accurate gross target volume (GTV) delineation on the velocity platform. The clinical target volume (CTV) included GTV, the whole mesorectum, rectum, and pelvic regional lymph nodes. The mesorectum was contoured from the sacral promontorium to the insertion of the levator ani muscle into the external sphincter muscles. Then, for internal organ movements and setup uncertainties, a safety margin of 10 mm was added to the CTV from all directions, and PTV was created. The bladder, bowel, and femoral heads were contoured as organs at risk (OAR) by an experienced radiation oncologist.

Treatment

Patients received 45 Gy (1.8 Gy/fx) of pelvic radiotherapy followed by a sequential boost dose of 5.4 Gy to the primary tumor with the VMAT technique. The treatment was delivered using Rapidarc (Varian Medical Systems, Palo Alto, CA, USA) linac device. During the treatment, capecitabine was administered to all patients concomitantly with radiotherapy, at a dose of 825 mg/m^2, twice a day, for a total of 5 days a week.

Imaging

The kV CBCT beam used in this study was Varian on-board imaging (OBI) v.1.6 system integrated into a Clinac iX linear accelerator (Varian Medical Systems, Palo Alto, CA, USA). The Varian OBI CBCT system consists of an X-ray source (kVS) and flat panel detector (kVD). All CBCT scans were performed using an acquisition setting of 125 kV, 80 mA, 13 ms, 2.5 mm slice thickness (standard mode), with 150 cm source to imager distance with the half fan mode. According to our clinic imaging protocol in rectal cancer radiotherapy, CBCT was obtained once a day for the first 3 days, then once a week for the rest of the therapy.

Assessment of organ motion and volumetric/dosimetric changes

To compare the verification, CBCT images were registered with the original planning CT images by using the Eclipse rigid registration tool (version 15.6, Varian Medical Systems). We used hybrid registration (automatic and manual). Firstly, the registration was done using automated matching software. Then the initial registration was adjusted manually based on the bone anatomy. The region of interest included the symphysis pubis anteriorly, the sacrum posteriorly, and laterally included the pelvic bones excluding the femoral head. The mesorectum and bladder were re-contoured on weekly 5 CBCT images for each patient. Then, the VMAT plans made on the simulation CT were applied to the CBCT and dose-volume histograms were calculated.

The bladder and the mesorectum volume changes and organ motion (OM) were calculated by comparing each CBCT with planning CT. In addition, OM examination was performed on both prone and supine position images and evaluated by measuring the displacement of the mesorectum and bladder on X (right-left), Y (cranio-caudal), and Z (anterior-posterior) axes. The volume variability was estimated by the Dice index. The Dice index is a

similarity coefficient that used a statistical validation metric to assess the spatial overlap accuracy of mesorectum and bladder volumes on the CBCTs compared to the planning CT. The Dice value is ranged from 0 to 1. Zero indicated no spatial overlap, and one signified a complete overlap.

The volume of the mesorectum was divided into upper, middle and lower thirds anatomically. Motion analysis was performed for all subgroups. In addition, the changes in D2, D95, and D98 doses of the mesorectum were examined depending on the organ motion.

Statistics

The changes in mesorectal volume from the treatment planning scan to the final CBCT were evaluated using a 2-tailed paired t-test. In the sample of patients with three or more CBCT scans, linear regression analysis was utilized to examine changes in volume. Mann-Whitney U test was used in the pairwise comparison analysis, and analysis of variance (ANOVA) was used for comparison of shifts in the X, Y and Z axes. The computer software SPSS version 21 for Windows (IBM Corp. Armonk, NY) was used for all statistical analyses, and $p < 0.05$ was considered for statistical significance.

The written informed consent form was obtained from each patient participating in the study before treatment, and the research protocol was approved by our university of ethics review board (10.07.2021/ A-34).

Tab. 2. Volumes variability calculations by Dice index.

	DICE index	
45 CBCT (prone)	Mean	Range
Mesorectum	0.80	0.78 to 0.81
Bladder	0.74	0.69 to 0.81
60 CBCT (supine)		
Mesorectum	0.77	0.72 to 0.81
Bladder	0.71	0.66 to 0.81

Tab. 3. Changes in mesorectum volume in CBCT according to planning CT.

	Upper		Middle		Lower	
Mesorectum volume	Mean (cc)	SD	Mean (cc)	SD	Mean (cc)	SD
Planning CT	121.65	39.82	131.87	50.34	79.52	48.64
CBCT1	111.11	23.66	121.71	39.01	81.45	47.90
CBCT2	118.72	38.56	128.25	44.55	89.34	48.64
CBCT3	108.73	38.10	123.64	48.12	76.25	38.95
CBCT4	115.68	52.03	125.00	51.91	74.58	37.86
CBCT5	106.81	24.12	122.27	41.46	75.80	35.63
p	.334		.730		.519	

Tab. 4. Changes in bladder volume in CBCT according to planning CT.

Bladder Volume	Mean (cc)	SD	p
Planning CT	424.13	165.46	
CBCT1	325.24	156.68	
CBCT2	387.61	162.54	
CBCT3	346.44	188.46	
CBCT4	298.12	126.75	
CBCT5	324.70	133.25	
			.075

Results

Twenty-one patients (9 in supine and 12 in prone positions) were analyzed for this study. A total of 105 CBCTs were obtained and reviewed retrospectively. Mean Dice values for total mesorectum and bladder were 0.77 and 0.71 in supine position and 0.80 and 0.74 in prone position, respectively (Tab. 2).

The mean volume of the contoured mesorectum in CBCTs was 323cm^3, and there was no significant difference in volume change in daily imaging ($p = 0.57$). When the upper-middle-lower mesorectum volume changes were examined during the treatment, no significant difference was found ($p = 0.334$; $p = 0.730$; $p = 0.519$) (Tab. 3).

The mean volume of the contoured bladder in CBCTs was 350cm^3, and no significant difference was observed in the volume change in daily imaging ($p = 0.07$) (Tab. 4). No statistical correlation was found between the volume change in the bladder and movement of the mesorectum ($p = 0.075$).

For the total mesorectum, the average motion was 1.5 mm on the X-axis, 4 mm on the Y-axis, and 5 mm on the Z-axis directions (Tab. 5). For the bladder, the median shift was 2 mm, 4 mm, and 8 mm in the directions of X, Y, and Z axes, respectively. The largest movements in both the total mesorectum and bladder during treatment were in the anterior-posterior (Z-axis) direction. When organ movements are evaluated according to the treatment position (supine vs prone), the median shifts of the total mesorectum and bladder for the supine position are –0.09 mm and 0.00 mm on the X-axis, 0.09 mm and 0.03 mm on the Y-axis, and –0.10 mm and –0.51 mm on the Z-axis, respectively. For the prone position, the median shifts of the total mesorectum and bladder were measured as –0.02 mm and 0.09 mm on the X-axis, 0.12 mm and 0.01 mm on the Y-axis, and –0.28 mm and –0.11 mm on the Z-axis directions. There was no statistically significant difference between them. In addition, there was no significant relationship between both total mesorectum and bladder movements and gender, tumor size, and location.

On the other hand, in the upper-middle-lower mesorectum subgroup analysis, it was observed that the upper mesorectum moved significantly more in the cranio-caudal direction (Y-axis) (mean motion 8 mm; $p = 0.005$).

When the changes in the D2, D95, and D98 doses taken due to the movement of the total mesorectum were analyzed, there were variations up to 2 % in the median dose values. However, no statistical significance was found ($p = 0.563$; $p = 0.301$; $p = 0.313$) (Tab. 6.).

Discussion

Nowadays, neoadjuvant long-course radiotherapy and fluoropyrimidine/capecitabine chemotherapy are the standard treatment in patients with LARC (1, 2). High conformal radiation treatments such as IMRT and VMAT have provided a better dose distribution and reduced long-term toxicity rates, thus allowing

Tab. 5. Maximum movement of mesorectum in X,Y and Z axis.

Mesorectum movement	X		Y		Z	
	Median	Range	Median	Range	Median	Range
Planning CT	0	–1.13 to 0.35	0.11	–0.81 to 0.98	–0.22	–1.31 to 0.65
CBCT1	–0.12	–1.01 to 0.19	–0.03	–0.97 to 1.05	–0.18	–1.59 to 1.25
CBCT2	–0.01	–1.26 to 0.31	0.18	–0.70 to 1.24	–0.10	–1.21 to 0.56
CBCT3	–0.10	–0.73 to 0.82	0.18	–1.86 to 0.79	–0.32	–1.70 to 2.42
CBCT4	–0.50	–0.87 to 0.23	0.26	–0.68 to 1.15	–0.39	–1.60 to 0.62
CBCT5	–0.02	–0.79 to 0.48	0.29	–1.03 to 1.24	–0.34	–1.23 to 1.00

Tab. 6. Changes in the mesorectum mean doses estimated using VMAT planning calculated using CBCT.

Mesorectum volume	D2		D95		D98	
	Mean (Gy)	SD	Mean (Gy)	SD	Mean (Gy)	SD
Planning CT	48.46	2.05	46.36	2.07	45.92	2.43
CBCT1	49.01	2.49	46.99	2.50	46.61	2.72
CBCT2	48.99	2.41	46.99	2.47	46.28	3.03
CBCT3	48.98	2.41	47.07	2.53	46.79	2.59
CBCT4	48.98	2.43	46.99	2.42	46.65	2.73
CBCT5	48.85	2.48	47.00	2.39	46.81	2.67
p	.563		.301		.313	

more comfortable treatment planning in rectum tumors (3, 6, 7). However, during radiation, the rectum and mesorectum mobility must be evaluated to reduce the target dose missing. Failures in target coverage can play an important role in local control as they can cause dose reductions of up to 20 % in the target volume, especially in hypo-fractionated treatments such as the 5x5 Gy protocol (17). Furthermore, if surgery is not carried out, the danger of a geographical miss in a rectal tumor may be even greater (6, 17).

To date, many studies have evaluated the mesorectum and its internal movement to determine an appropriate PTV margin in the treatment of rectal cancer. Tournel et al. explored intrafractional internal organ mobility usage of daily MV-CT images of 10 patients with LARC in a phase II study. They reported minimal lateral motion and major movements in anterior-posterior and craniocaudal directions. As a result, they suggested that in rectal cancer patients who got RT with helical tomotherapy, set-up margins might be reduced by measuring intrafractional internal organ motions using daily MV-CT scanning (16). Similarly, both Brierly et al. and Ippolito et al. found the largest movement in anterior-posterior and craniocaudal directions and they suggested a CTV-PTV margin of 8 mm for left, right, and anterior directions and 9 mm for the posterior one (18, 19). Similar to these findings, we observed that the movement of the mesorectum in the lateral direction was smaller (1.5 mm), and its movement in the Y and Z axis was bigger (4 mm and 5 mm).

Furthermore, when the difference between the movements of the upper, middle, and lower thirds of the mesorectum is investigated in the literature, it has been reported that the superior third of the mesorectum exhibited larger variations than the inferior ones (9). In a systematic study, inter- and, intra-fractional OM were examined. Similar to our findings, they observed substantial movement, particularly in the superior mesorectum, which might have been mitigated by rectal filling (5). Some clinicians recommend bowel prep to reduce organ motility. Enema is mostly used to empty the rectum in prostate and cervical cancer radiotherapy. However, it is not routinely used in patients with rectal cancer because of their low tolerance due to tumor-related symptoms.

In the literature, organ movement variations in supine and prone positions and between genders have also been compared. Nijkamp and colleagues reported intra and interfractional setup errors smaller in the supine position (20). In the same way, Rosa et al. retrospectively evaluated 32 patients for organ motion on CBCTs. They showed a minimal difference between the two positions with smaller variations in the supine position (21). However, in our study, no significant difference was found between the treatment positions in terms of organ movements.

Likewise, Nijkamp et al compared setup errors in male and female patients. They reported that the difference was greater in the upper region, especially in female patients, and they recommended different PTV margins in female patients for this (20). In this study, there was no difference between the genders in terms of organ movement. However, it should be considered that the number of patients is small for evaluation (12 males vs 9 females).

Some researchers suggest that tumor size or stage may also be related to mesorectal movement. In the study of Alickikus et al., in which they examined interfractional mesorectum movement and dosimetric changes in 14 locally advanced rectal cancer patients who underwent neoadjuvant chemo-radiotherapy, it was reported that mesorectal movement was smaller in T2 stage tumor. They interpreted this as a more limited internal organ movement in patients with intact mesorectum. On the other hand, they emphasized that a larger sample size is needed for a reliable interpretation (22). In our study, T stage did not significantly affect the mesorectum and bladder movements. We also examined the correlation between tumor size and mesorectal movement. Ten patients had tumors smaller than 5 cm, and eleven patients had tumors bigger than 5 cm. Patients' distribution was homogeneous, yet there was no statistically significant difference regarding mesorectal movement between the two groups.

We also investigated the bladder filling impact on mesorectal motion and dose change. Because of its excessive filling in some cases, the mean bladder motions were measured at 2 mm in the horizontal, at 4 mm in the cranial-caudal, and 8 mm in the anterior-posterior directions. This issue, however, did not appear to affect mesorectal motility. We think that the most important reason for this is that the preparation protocol has been performed before the simulation and treatment and the measurement of bladder fullness by ultrasonography before each session.

When evaluating our study, it should be taken into account that there are some limitations. Most importantly, the number of patients is small and the study is of retrospective nature. However, it is valuable for us to have our own single-center experience so as to know that the PTV margin (1cm) we give is sufficient and we do not see significant dosimetric changes due to organ movement.

Conclusion

The mesorectum has internal movement depending on its position and amount of filling of the rectum and bladder over time. Target volume changes due to mesorectal movement during radiotherapy may enhance side effects by giving higher doses than expected to the surrounding healthy tissues, as well as a bring about loss of local control due to delivering lower doses to CTV and PTV than planned. In our study, we observed that mesorectal movement was limited to 8 mm in the craniocaudal direction at most in the upper third of mesorectum, and there were variations of up to 2 % in the median dose values of D2, D95, and D98. Our results were found to be consistent with previously published studies in the literature. As a consequence of our research, we suggest that each clinic should set its own PTV margin.

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