

Original Article

The Effects of Laxative Use on Rectum Volume and Doses During Radiotherapy in Patients With Prostate Cancer

Radyoterapi Uygulanan Prostat Kanseri Hastalarında Tedavi Süresince Laksatif Kullanımının Rektum Hacim ve Dozlarına Etkisi

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ABSTRACT

Objective: Changes in rectum volume can affect dose delivery during prostate radiotherapy. The aim of this study was to evaluate how laxative use affected rectum volumes and doses in patients with prostate cancer treated with Volumetric Modulated Arc Therapy (VMAT).

Material and Methods: Treatment planning computed tomography (simCT) and cone-beam computed tomography (CBCT) images collected from 20 patients with prostate cancer were retrospectively evaluated. These patients were divided into two groups as those who either used or did not use laxatives during radiotherapy. Rectum volumes were re-contoured on 160 CBCT images, and VMAT treatment plans were re-calculated to determine rectum doses.

Results: In all patients, CBCT images showed increased mean rectum volumes and doses relative to simCT images. Furthermore, the percent volume (V_x) of the rectum receiving 40, 50, 60, and 70 Gy doses based on CBCT results were larger than those based on simCT. The D_{mean} values in the treatment plans for the group with laxative use were 39 Gy on simCT images and 43 Gy on CBCT images (p = 0.009). Alternatively, in the group without laxatives, the D_{mean} values in the treatment plans were 40 Gy on simCT images and 44 Gy on CBCT images (p = 0.047).

Conclusion: In patients undergoing prostate radiotherapy, rectum volume and doses increase regardless of laxative use. Although laxatives can limit volume expansion of the rectum, they do not have the expected effect on rectum doses and actually significantly increase all dosimetric parameters.

Key words: Cone-beam computerized tomography, laxatives, prostate cancer, radiotherapy, volumetric-modulated arc therapy.

ÖZET

Amaç: Rektumdaki hacim değişiklikleri prostat radyoterapisi sırasında uygulanan dozu etkilemektedir. Hacimsel Ayarlı Ark Terapi (VMAT) uygulanan prostat kanseri hastalarında tedavi süresince laksatif kullanımının rektum hacim ve dozlarına etkisinin değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Kliniğimizde tedavi edilen 20 hastanın tedavi planlama tomografi (simCT) ve koni ışımlı bilgisayarlı tomografi (CBCT) görüntüleri retrospektif olarak değerlendirildi. Laksatif kullanan (L+)(n:10) ve laksatif kullanmayan (L-)(n:10) hastalar olacak şekilde 2 grup belirlendi. Toplam 160 tane CBCT görüntüsünde rektum hacimleri yeniden konturlandı. Her hastanın kendi VMAT planı kendi CBCT görüntüleri üzerinde tekrar hesaplatılarak rektum dozları elde edildi.

Bulgular: Tüm hastaların rektum hacimleri CBCT görüntülerinde simCT görüntülerine göre artış göstermiştir. Belirli bir dozu alan rektum hacminin % değeri (V_x) için simCT ve CBCT planları karşılaştırıldığında 40Gy, 50Gy, 60Gy ve 70Gy dozlarının hepsi için tüm hastalarda tedavi süresince artış bulunmuştur. Laksatif kullanan hasta grubunun tedavi planlarındaki D_{mean} değerleri simCT görüntülerde 39 Gy ve CBCT görüntülerde 43 Gy bulunmuştur (p = 0.009). Alternatif olarak, laksatifleri

kullanmayan hasta grubunda, tedavi planlarındaki Dmean değerleri simCT görüntülerinde 40 Gy ve CBCT görüntülerinde 44 Gy bulunmuştur ($p = 0.047$).

Sonuç: Prostat radyoterapisi uygulanan hastalarda tedavi sırasında rektum hacmi ve aldığı radyasyon dozu, laksatif kullanımından bağımsız olarak, başlangıç tedavi planına göre artmaktadır.

Anahtar Kelimeler: Hacimsel Ayarlı Ark Terapi, Laksatif, Prostat kanseri, Prostat radyoterapisi, koni ışınli bilgisayarlı tomografi

Introduction

Radiotherapy is a well-established treatment modality for managing clinically localized prostate cancer [1]. To be effective, the radiotherapy treatment volume should encompass the prostate gland and any extension of the primary tumour [2]. Importantly, both the localization of the prostate gland and seminal vesicle and the volumes of normal tissues can vary during daily radiotherapy [3]. Changes in prostate gland and seminal vesicle localization are more affected by changes in rectum volume and length than changes in bladder volume [4,5]. The excess of rectal filling on treatment planning tomography (simCT) reduces the probability of biochemical and local control [6]. Several methods such as evacuation techniques, dietary interventions, laxatives, and enemas have been applied to limit changes in rectum volume during treatment planning tomography and daily treatment; however, which of these methods is optimal is unknown [7].

Furthermore, radiotherapy in prostate cancer patients can produce side effects that persist for up to 10 years after diagnosis. In particular, bowel-related side effects lower the patient's quality of life [8]. Relative to conformal radiotherapy, intensity-modulated radiotherapy (IMRT) reduces acute and late rectal toxicity by limiting the radiation dose delivered to surrounding organs, including the rectum, while increasing biochemical control by applying high radiation doses to the prostate gland [9,10,11]. Volumetric modulated arc therapy (VMAT) provides a more homogeneous dose distribution for shorter treatment times with gantry rotation when compared to IMRT [12]. These daily radiotherapy treatments can be evaluated with cone-beam computed tomography (CBCT) to

assess internal organ movements and reduce daily setup uncertainties [13,14]. Specifically, during daily treatment, the dose given to the target and surrounding critical organs can be calculated from CBCT images [15,16].

Patient positioning errors and changes in rectum filling create uncertainty in radiotherapy applications [17]. However, in the daily CBCT images used to minimize this uncertainty, rectum filling and the received rectum dose do not appear as planned in the simCT [18]. The percent change in rectal volume during prostate radiotherapy can also affect the calculated rectum dose [19]. Indeed, the actual dose received by the rectum is higher than the planned dose as calculated by simCT images [20].

The aim of this study was to assess the effects of laxative use on rectal volume changes to estimate potential effects on rectal dose changes using weekly CBCT images, which were collected during VMAT in patients with prostate cancer.

Material and methods

Patient selection

In our clinic, retrospective assessment of treatment files between November 2015 and October 2017 showed that laxatives (magnesium hydroxide) were prescribed before treatment in 10 patients with prostate cancer, and were used during treatment. We randomly selected another 10 patients with prostate cancer who were treated with radiotherapy in our clinic, but did not use any laxatives during treatment. SimCT images, treatment plans, and CBCT images were obtained for these 20 patients, who were subdivided into 2 groups based on whether or not they used laxatives.

We used the following inclusion criteria: patients who completed definitive or adjuvant

radiotherapy with VMAT; laxative use began at least four days prior to simCT imaging; and laxatives were used without interruption during treatment. Patients that received hybrid treatment with 3D-CRT or laxative use that was interrupted during treatment, were excluded.

The study was approved by the local ethics committee on 08/02/2018 with decision number of 3/7.

Simulation and treatment

Patients were immobilized with a knee support and footrest while in the supine position. SimCT images (Aquilion-LB, Toshiba, Japan) were obtained with a 2-mm cross-sectional thickness that covered the entire pelvis. All patients were recommended to drink 500 mL of water after emptying their bladder and wait for about 1 hour before simCT imaging. The same procedure was repeated before each radiotherapy treatment fraction. Our clinic did not routinely use a specific protocol to achieve an empty rectum. Low gas and well-balanced diet with plenty of fiber was advised to all patients. For patients with excessive rectum filling, simCT imaging was repeated after defecation. Laxatives were prescribed to patients whose excessive rectum filling had not changed between repeated simCT images. In patients with laxative use, magnesium hydroxide (30-60 mL/day peroral at bedtime) was initiated at least four days prior to simCT imaging and was recommended for use during treatment.

Patients received one of three different treatment volumes defined as follows. The first was radical radiotherapy, in which the prostate gland and seminal vesicle were contoured as the clinical target volume (CTV). A 5-mm posterior margin and 8-mm margins in all other directions were used to create a planning target volume (PTV). The second treatment volume was pelvic treatment, which was delivered to the prostate gland, seminal vesicle, and pelvic lymph nodes, followed by a prostate gland and seminal vesicle boost. The CTV of this treatment included the obturator, external iliac, internal iliac, and S1-2 sacral lymph nodes. For pelvic treatment, 5-mm margins in

all directions were used to define the PTV. The final treatment volume was given to patients treated with salvage radiotherapy to control biochemical failure after radical prostatectomy. This CTV included the clips of the prostate gland and seminal vesicle bed. The Radiation Therapy Oncology Group (RTOG) contouring atlas [21] was used as the reference to create the surgical bed, with the same PTV margins that were used for radical radiotherapy. Finally, the bladder, the rectum from the anal canal to the sigmoid curve, bilateral femoral heads, and small intestine were contoured as the organs at risk (OARs). All patients were treated with fraction doses of 1.8-2 Gy in 38-41 fractions, and CBCT imaging was performed with the Elekta XVI pelvis M20 protocol every day in the absence of fiducial markers. In our clinic, placement of gold seed markers into the prostate was not performed routinely during VMAT preparation. Radiotherapy schedules of each group of patients were summarized at Table 1. VMAT treatment plans were created with double arc on the CMS Monaco 5.1 treatment planning system using 6 MV photon energy. In all treatment plans, 95% of the prescribed dose was positioned to cover 98% of the target volume. OAR doses were kept below the tolerance dose limits of the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) [22].

Cone-beam computed tomography

To evaluate the original treatment plans on the CBCT images, we first matched patient CBCT and simCT images using bone tissue matching. The original treatment plans were re-calculated in the same isocentre after CBCT electron density information was specified in the treatment planning system for Elekta XVI Pelvis M20 imaging.

CBCT images were obtained daily during treatment and assessed by bone tissue matching. CBCT imaging was repeated before treatment in the following three cases: 1) after defecation of patients with excess rectum filling, 2) after prolonged waiting in patients with an empty bladder, and 3) after appropriate corrections for the PTV.

Table 1: Treatment characteristics of 20 patients with prostate cancer whose separated into two groups as those who either used (L+) or did not use (L-) laxatives during radiotherapy (RT).

| Treatment | Dose (Gy) | L (+) (n:10) | L (-) (n:10) |
|------------|-----------|-----------------|-----------------|
| Radical RT | 76- 78 | 6 | 4 |
| Pelvic RT | 74 | 0 | 2 |
| Salvage RT | 70.2- 72 | 4 | 4 |

The CBCT image obtained on the first day of treatment was accepted as the first week image, and eight CBCT images for each patient were included in the study. Dosimetric calculations were performed on a total of 160

images. The rectum was contoured in every CBCT image. The VMAT treatment plan of each patient was re-calculated at the same treatment centre on corresponding CBCT images. The rectum volumes and doses were evaluated on CBCT images. The rectum mean dose (D_{mean}) and percent rectum volume (V_x) receiving 40, 50, 60, 70, and 75 Gy were evaluated in the dose volume histogram (DVH).

Statistical analysis

IBM SPSS Statistics version 21 (www.spss.com) was used for the statistical analysis. The Wilcoxon test was used to analyse the rectum variations of each group of patients and to evaluate the planned and delivered dose parameters. A p-value < 0.05 was considered statistically significant.

Table 2: Comparison of mean rectum doses (\pm standart deviations) between the treatment plans using treatment planning tomography (simCT) and cone-beam computed tomography (CBCT)

| | L (+) | | | L (-) | | |
|-----------------|-----------------|-----------------|---------|-----------------|-----------------|---------|
| | simCT | CBCT | p-value | simCT | CBCT | p-value |
| D_{mean} (Gy) | 39 (\pm 5.1) | 43 (\pm 5.6) | 0.009 | 40 (\pm 4.9) | 44 (\pm 5.8) | 0.047 |
| V_{40} (%) | 50 (\pm 8) | 58 (\pm 9) | 0.013 | 54 (\pm 11) | 57 (\pm 10) | 0.44 |
| V_{50} (%) | 35 (\pm 7) | 43 (\pm 9) | 0.013 | 35 (\pm 8) | 41 (\pm 15) | 0.16 |
| V_{60} (%) | 23 (\pm 6) | 31 (\pm 9) | 0.013 | 21 (\pm 6) | 30 (\pm 14) | 0.028 |
| V_{70} (%) | 9 (\pm 5) | 17 (\pm 8) | 0.005 | 9 (\pm 6) | 20 (\pm 13) | 0.013 |

Abbreviations: D_{mean} : Mean rectum dose, L (+): Group with laxative use, L (-): Group without laxative use, V_x : % volumes of the rectum receiving 40, 50, 60, and 70 Gy.

Table 3: Comparison of mean rectum doses (\pm standart deviations) between the patient groups with and without laxative use.

| | | simCT | | CBCT | |
|-----------------|-------|-----------------|---------|-----------------|---------|
| | | | p-value | | p-value |
| D_{mean} (Gy) | L (+) | 39 (\pm 5.1) | 0.50 | 43 (\pm 5.6) | 0.87 |
| | L (-) | 40 (\pm 4.9) | | 44 (\pm 5.8) | |
| V_{40} (%) | L (+) | 50 (\pm 8) | 0.38 | 58 (\pm 9) | 0.72 |
| | L (-) | 54 (\pm 11) | | 57 (\pm 10) | |
| V_{50} (%) | L (+) | 35 (\pm 7) | 0.87 | 43 (\pm 9) | 0.95 |
| | L (-) | 35 (\pm 8) | | 41 (\pm 15) | |
| V_{60} (%) | L (+) | 23 (\pm 6) | 0.64 | 31 (\pm 9) | 0.87 |
| | L (-) | 21 (\pm 6) | | 30 (\pm 14) | |
| V_{70} (%) | L (+) | 9 (\pm 5) | 0.64 | 17 (\pm 8) | 0.87 |
| | L (-) | 9 (\pm 6) | | 20 (\pm 13) | |

Abbreviations: CBCT: Cone-beam computed tomography, D_{mean} : Mean rectum dose, L (+): Group with laxative use, L (-): Group without laxative use, simCT: Treatment planning tomography, V_x : % volumes of the rectum receiving 40, 50, 60, and 70 Gy.

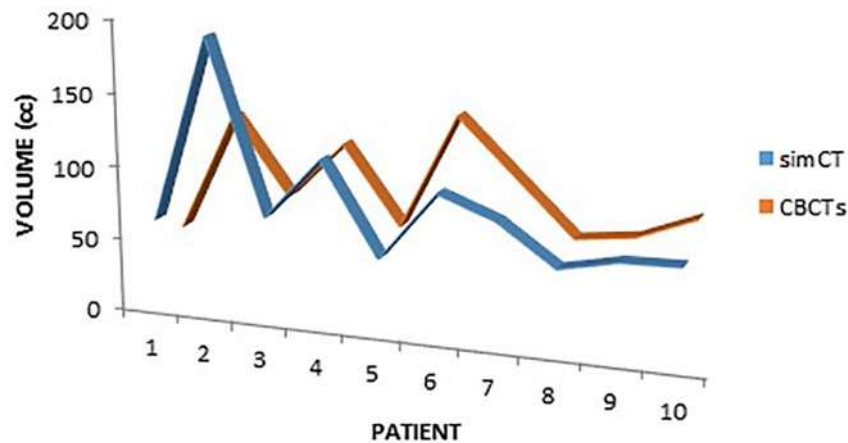


Figure 1: Comparison diagram of rectum volume changes in patients with laxative use, based on treatment planning-tomography (simCT) and mean cone-beam tomography (CBCTs) evaluations of 10 patients.

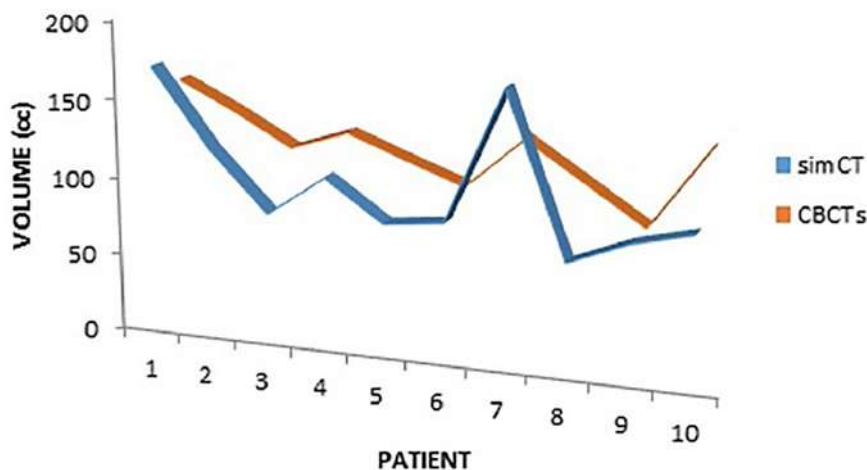


Figure 2: Comparison diagram of rectum volume changes in patients without laxative use, based on treatment planning-tomography (simCT) and mean cone-beam tomography (CBCTs) evaluations of 10 patients.

Results

This study included 820 daily CBCT images obtained from a total of 20 patients. In the group of patients with laxative use, a mean of 39 (38-43) CBCT images were collected during a mean of 39 (39-43) treatment fractions. In the group without laxative use, a mean of 42 (39-46) CBCT images were collected during a mean of 40 (39-43)

treatment fractions. The total number of repeated CBCT images due to changes in treatment position or rectum and bladder filling were 34 and 40 in the groups with and without laxative use, respectively. When the CBCT images were examined individually, the number of daily repeated CBCT images after defecation due to excess rectum filling was five in three patients from both groups.

We then evaluated changes in rectum volume during treatment on a total of 160 weekly CBCT images. This revealed that in the group with laxative use, the mean rectum volumes were 85.69 cc (\pm 41.57) in simCT images and 89.17 cc (\pm 31.16) in CBCT images (Figure 1). Thus, the mean rectum volume increase during treatment was 4%. Alternatively, in the group without laxative use, the mean rectal volumes were 106.87 cc (\pm 36.93) in simCT images and 120.96 cc (\pm 20.58) in CBCT images (Figure 2). In this group, the mean rectum volume increase during treatment was 13%. Overall, CBCT images showed higher mean rectal volumes than simCT images in the groups with and without laxative use ($p = 0.24$ and $p = 0.13$, respectively). Furthermore, analysing these results based on laxative use revealed that the group without laxative use had a higher mean rectal volume compared with the group with laxative use in both simCT and CBCT images ($p = 0.11$ and $p = 0.028$, respectively).

We next evaluated the resulting changes in rectum doses on weekly CBCT images. The Dmean values in the treatment plans for the group with laxative use were 39 Gy on simCT images and 43 Gy on CBCT images ($p = 0.009$). Thus, the 4% increase in mean rectal volume resulted in a 10% increase in Dmean during treatment. In the group without laxative use, the Dmean values in the treatment plans were 40 Gy on simCT images and 44 Gy on CBCT images ($p = 0.047$). In this group, a 13% increase in mean rectal volume resulted in a 10% increase in mean rectum dose during treatment.

In the group with laxative use, CBCT images showed significantly elevated V40, V50, V60, and V70 values relative to the simCT images ($p = 0.013$, $p = 0.013$, $p = 0.013$, and $p = 0.005$, respectively) (Table 2). Thus, a 4% increase in rectal volume during treatment resulted in an 8% increase in V40, V50, V60, and V70 values. In 6 of these patients, the total doses prescribed were 76-78 Gy, CBCT images showed higher V75 values relative to simCT. Specifically, the mean V75 values estimated from the simCT and CBCT images were 4% (0.3%-9%) and 10% (5%-13%), respectively.

In the group without laxative use, CBCT images showed significantly elevated V40, V50, V60, and V70 values relative to the simCT images ($p = 0.44$, $p = 0.16$, $p = 0.028$, and $p = 0.013$, respectively) (Table 2). Thus, a 13% increase in rectal volume during treatment resulted in 3%, 6%, 9%, and 11% increases in V40, V50, V60, and V70, respectively. In 4 of these patients, the total doses prescribed were 76-78 Gy, CBCT images showed higher V75 values relative to simCT. Specifically, the mean V75 values estimated from the simCT and CBCT images were 8% (4%-10%) and 20% (5%-39%), respectively.

Finally, individual evaluation of DVH parameters in both simCT and CBCT images revealed that there were no significant differences between the groups with and without laxative use (Table 3).

Discussion

Treatments such as evacuation techniques, dietary interventions, laxatives, and enemas have been applied to limit changes in rectum volume during daily radiotherapy treatment. Of these methods, one of the most common is the use of laxatives. However, reports on the efficacy of laxative use differ [7]. Indeed, Smitsmons et al. [23] showed that laxative use and adherence to dietary plans significantly lower faeces and gas percentages observed on 576 CBCT images ($p < 0.001$). Alternatively, Oates et al. [24] analysed 435 CBCT images and reported that laxative use does not significantly affect general rectum filling ($p = 0.13$). Here, our results revealed that patients with laxative use had smaller rectal volumes than patients without in both simCT and CBCT images. During treatment, patients with laxative use had smaller changes in rectal volume than in those without. Furthermore, in the group with laxative use, all DVH parameters were significantly affected. Alternatively, in the patients without laxative use, significant changes were found only in the V60 and V70 values despite having larger rectal volumes.

Previously, Collery et al. [25] evaluated a total of 360 CBCT images from 9 prostate cancer

patients who were treated with 7-field-IMRT. This revealed that the treatment significantly increased all DVH parameters relative to the initial treatment plan ($p < 0.05$). Furthermore, rectum V50 and V60 fell below the tolerance limits despite the increase in treatment, while the rectum V70 and V75 increased above the tolerance limits. Here, we observed an increase in all DVH parameters on the CBCT images, which were evaluated in both patient groups. Importantly, in prostate radiotherapy applications with VMAT, the actual mean values did not exceed the QUANTEC tolerance limits for any of the significantly altered DVH parameters. We did not statistically evaluate the V75 values in both groups due to the small number of patients. Ariyaratne H. et al. [14] reported that in prostate cancer patients treated with 7-field-IMRT, daily rather than weekly CBCT imaging decreases the rectum dose and increases the coverage dose of the CTV. In that study, a total number of 844 CBCT images were collected from 20 patients. The current study included 820 CBCT images taken from 20 prostate cancer patients who received VMAT. Importantly, fewer CBCT images were collected from the group with

laxative use relative to the group without because this group received fewer treatment fractions. Although the total number of daily repeated CBCT images was lower in the group with laxative use, the number of daily repeated CBCT images due to rectum fullness was the same in both groups.

This study had several limitations, including the retrospective design, inhomogeneous distribution of treatment variables between groups and the absence of clinical side effect assessment. Thus, future prospective studies should evaluate daily CBCT images in combination with a clinical side effect assessment to provide more information on the actual doses of the OARs.

In conclusion, in patients undergoing prostate radiotherapy, rectum volumes and radiation doses increase regardless of laxative use. However, laxative use during treatment decreases the likelihood of having an increased rectal volume. Furthermore, contrary to the expected outcomes, laxative use significantly increases all DVH parameters. Thus, dose constraints should be kept as low as possible during treatment planning to anticipate that rectal DVH parameters can increase during treatment.

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