# Analysis of Volumetric Changes in Rectal Cancer Patients during Preoperative Chemo-Radiation Therapy Using Weekly Cone-Beam Computed Tomography

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**Abstract**: **Objectives:** The purpose of this study was to quantify the rectum & bladder volume changes, as well as assessing the motion of rectum during pre-operative Concurrent Chemo-Radiation Therapy (CRT) in rectal cancer patients, using Simulator Cone Beam Computed Tomography [CBCT] scans. **Patients and Methods:** Between the period of June 2017 and January 2018, 10 consecutive patients with histologically proven, locally advanced rectal adenocarcinoma were enrolled in this study. They received preoperative CRT in Al Kasr Al Ainy Center of Clinical Oncology and Nuclear Medicine (NEMROCK), Cairo University. Weekly CBCTs were acquired by Varian Acuity simulator function (Varian medical systems, Inc. Palo Alto, CA, USA) by re-simulating patients with the same treatment position and isocenter. Variation of rectal and bladder volumes ($cm^3$) for each CBCT image were calculated and compared to the baseline planning CT. Assessment of the inter-fraction movement of the rectum was also studied. **Results:** All patients exhibited a significant linear decrease in the mean rectal volume compared with planning over the treatment course (28.66 vs 61.07 cc; P= 0.0001). An average volume reduction of 53% was found between the start and the end of treatment; almost all reduction was observed in the second half of the treatment course. The mean bladder volume was decreased on CBCTs compared to planning CT (149.85 vs 167.00 cc) but without statistical significant difference (P=0.36). A significant rectal movement was noted more in AP and lateral directions among all patients. The majority of rectal wall displacements were observed in the upper and middle region (P= 0.05) while it was minimal in the lower part (P=0.77). **Conclusion:** Despite the limited number of patients, the availability of weekly simulator CBCT images permitted the careful monitoring of each weekly rectal shape variation during CRT. Individualized asymmetric margins are recommended to adequately overcome the rectal movements.

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**Key words:** Cone Beam CT, Rectal volume, Bladder volume, Rectal movements.

## 1. Introduction

Although surgery is the cornerstone in rectal carcinomas management, yet radiotherapy plays a curial role in the neo-adjuvant setting, especially in locally advanced patients. Neo-adjuvant concurrent chemo-radiotherapy (CRT) reduces local recurrence rate, as well as increases the chance of sphincter preservation **(1)**.

During the radiotherapy course, changes may occur in the bladder and rectal volumes. These changes affect the Clinical target Volume (CTV) and subsequently the Planning Target Volume (PTV) **(2)**. In order to decrease the dose to the organ at risk (OARs), minimizing the PTV margins is a must. However, this cannot be done without accurate estimation and correction of any geometric uncertainties. Image-guided RT (IGRT) can be done using Electronic Portal Imaging Devices (EPID), Cone Beam CT (CBCT), CT scan (Tomotherapy), or MRI **(3)**.

The purpose of this study was to quantify the rectum & bladder volume changes, as well as assessing the motion of rectum during pre-operative Concurrent CRT for rectal cancer patients, using Simulator CBCT scans.

## 2. Methods and Materials

Our institutional scientific and ethical committees' approvals were taken before running this study; as well as written consents were collected from all participants before recruitment, after full explanation of our study design.

Between the period of June 2017 and January 2018, 10 consecutive patients with histologically proven, locally advanced rectal adenocarcinoma were enrolled in this study. They received preoperative CRT using 3 Dimensional Conformal Radiation Therapy (3D-CRT) in Al Kasr Al Ainy Center of Clinical Oncology and Nuclear Medicine (NEMROCK), Cairo University.

**Radiotherapy technique:**

**1. Patients' preparation & positioning**

Patients were instructed to drink 750ml of water within 30-45 minbefore radiotherapy planning CT

scans were taken, and were not regularly given laxatives to empty the intestine.

Patients were positioned in the prone position with hands below the chin, on a flat table, during the initial planning CT imaging, the weekly CBCT acquisition as well as the radiotherapy sessions throughout the study.

**2. Radiotherapy planning CT acquisition**

CT images for treatment planning were acquired using GE Light Speed plus 4 slice model CT scanner (General electric, United Kingdom). A planning non-contrast CT-scan of the pelvis was performed with patient immobilized in prone position with simulation radio opaque markers (two laterals, one central and anal) and alignment lasers. The CT scans were acquired from the top of L5 to 5 cm to below the perineum with a slice thickness of 3 mm. Tattooing was done at each marker site after image acquisition.

**3. Contouring of radiotherapy volumes**

CT data sets were revised for proper alignment, completion of cuts and body contour before being imported for treatment planning system (TPS Eclipse version 15.5) for delineation.

**# Gross Tumor Volume (GTV):** The gross tumor volume (GTV) outline included all visible rectal wall macroscopic disease seen on diagnostic CT and/or MRI.

**# Clinical Target Volume (CTV):** The clinical target volume outline included:

a) **High risk CTV (CTV boost)** included the entire rectum from the recto-sigmoid junction to the ano-rectal junction +/- 2 cm margin and expanded to include the mesorectal & presacral spaces.

b) **CTV lymph nodes** included lymph node (LN) regions at risk, namely the common iliac (up to the L5–S1 junction), internal iliac chains, superior rectal and internal obturator.

**# Planning Target Volume (PTV):** 1 cm margin was added to the first CTV LN and boost in three dimensions (according to our institute guidelines) to account for internal organ motion and patient setup errors to obtain planning target volume (PTV1). The PTV for phase 2 included the CTV high risk with a 1-2 cm expansion in three dimensions (PTV2).

**4. Radiotherapy doses prescription**

For phase I, 45 Gy in 25 fractions 1.8 Gy/fraction was prescribed with concurrent 5-fluorouracil (5-FU) and leucovorin in the first and fifth week of radiation course followed by 3 fractions of 1.8 Gy for the phase II.

**5. Cone Beam CT acquisition and assessment**

Cone Beam CTs were acquired by Varian Acuity simulator function (Varian medical systems, Inc. Palo Alto, CA, USA) by re-simulating patients with the same treatment position and isocenter. Radio-opaque markers on treatment isocenter were added weekly to facilitate setup verification. CBCTs were acquired before RT session, once per week for a total of 5 weeks for each patient in prone position. All CBCTs were exported to Eclipse treatment planning workstation (Varian Medical systems version 15.5), for co-registration and re-contouring. For each CBCT image the entire rectum was contoured from the recto-sigmoid junction to the anal verge and the entire urinary bladder was contoured as well. Planning CT and CBCTs volumes were fused and compared using the "offline review" co-registration of ECLIPSE.

Two important parameters were assessed:

1. **Volume variations:**

Variation of rectal and bladder volumes ($cm^3$) for each CBCT image were calculated and compared to the baseline planning CT. Therefore, the shrinkage of the volume over time could be assessed.

2. **Inter-fraction motion**:

Assessment of the inter-fraction movement of the rectum, namely AP, PA, RL and LR, at different rectal locations (upper, mid, and low) was measured by the antero-posterior and lateral distances from the anterior aspect of the sacrum and mid-left femoral head, respectively, as shown in Figure (1). The upper, mid, and low rectum were defined as the average distance taken 0–5 cm, 5.1–10 cm, and >10 cm below the inferior border of L5, respectively. Any extension of the CBCT rectal volume outside of the initial CT rectal wall cut was considered as a shift.

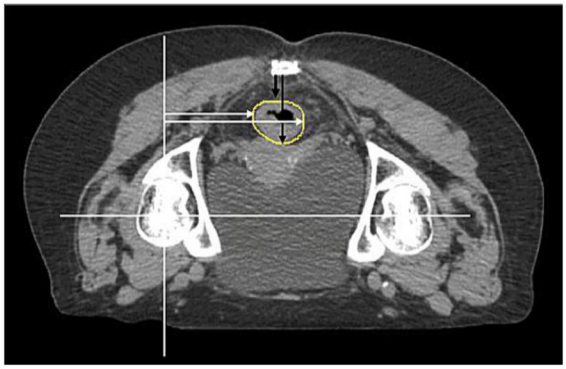

**Figure 1:** Measurement of inter-fraction motion of the rectum. Anterior and posterior rectal movements are taken from anterior aspect of sacrum (black arrows). Lateral rectal movements are taken from mid left femoral head (white arrows).

- **Treatment toxicity profile:**

The Treatment related toxicity was recorded every week during RT treatment course according to Common Terminology Criteria for Adverse Events (CTCAE)v 4.03: June 14, 2010.

- **Statistical Analysis:**

All clinical and pathological data were considered for analysis includingpatients

characteristics ( age, gender and performance status) and tumor characteristics (tumor location, distance from anal verge (AV), tumor segment length, Circumferential thickness involved, Tumor pathological type & grade, and T & N stages).

By using IBM SPSS (statistical package for social sciences) version 22 (SPSS Inc., Chicago, IL), numerical data were expressed as mean, and standard deviation or median or range as appropriate. Student's T-test was used as a test of significance for numerical variables. *p* values less than 0.05 was considered statistically significant. Spearman's Rank order correlation test was used to measure the strength and association between sets of data.

## 3. Results

### Patient and tumor characteristics

**Table (1):** Patients and tumor characteristics

| Characteristic | | Numbers | % |
|---|---|---|---|
| Age ( years) | Median | 63 | |
| | Range | 36-74 | |
| Gender | Male | 6 | 60 |
| | Female | 4 | 40 |
| PS | 0 | 5 | 50 |
| | 1 | 5 | 50 |
| Tumor location | UR | 4 | 40 |
| | MR | 5 | 50 |
| | LR | 1 | 10 |
| Distance from Av. (cm) | Median | 7 | |
| | Range | 3-15 | |
| Tumor segment length (cm) | Median | 5.50 | |
| | Range | 3-10 | |
| Circumferential thickness involved | ¼ | 2 | 20 |
| | ½ | 1 | 10 |
| | ¾ | 3 | 30 |
| | Whole | 4 | 40 |
| Rectal volume on planning CT (cc) | Median | 61.07 | |
| | Range | 23-98 | |
| Bladder volume on planning CT (cc) | Median | 167.00 | |
| | Range | 75-301 | |
| Pathological type | Adenocarcinoma | 10 | 100 |
| Pathological grade | 2 | 10 | 100 |
| Pretreatment T-stage | T2 | 1 | 10 |
| | T3 | 9 | 90 |
| Pretreatment N-stage | N0 | 2 | 20 |
| | N1 | 1 | 10 |
| | N2 | 5 | 50 |
| | N3 | 2 | 20 |
| Post-operative T-stage | T1 | 7 | 70 |
| | T2 | 2 | 20 |
| | T3 | 1 | 10 |
| Post-operative N-stage | N0 | 9 | 90 |
| | N1 | 1 | 10 |

From June 2017 to January 2018, we recruited 10 patients diagnosed with locally advanced rectal adenocarcinoma (cT3-4 and/or cN+), whom were treated with long course of preoperative CRT with a weekly CBCT for 5 weeks at NEMROCK. The median age for the whole group of 6 male and 4 female was 63 years (range 36-74 year). ECOG-PS varied between 0-1 with equal percentages. The patients' and tumor's characteristics in the current study are summarized in Table (1).

Radiation therapy was well tolerated among all patients with no grade 3 or 4 acute toxicities, as recorded in Table (2). The median time to surgery after completion of RT was one month (range 4-8

weeks). Nine patients experienced pathological primary T or nodal N down staging, with none achieving complete response.

**Rectal volume changes**

All CBCTs images (N=50) were matched with the planning CT using the bony anatomy as reference. The initial mean rectal volume (± SD) on planning CT for all 10 patients was 61.07 (±3.03) cc (range 23.01-98.0 cc). The mean rectum volume (± SD) was smaller for female patients in comparison to male (46.33 ± 15.94 vs 70.90 ± 26.54) but with no statistically significant difference (P=0.48). Rectal volume varied significantly on a weekly basis CBCTs. All patients exhibited a significant linear decrease in the mean rectal volume compared with planning over the treatment course (28.66 vs 61.07 cc; P= 0.0001) (Figure (2)).

The mean rectal volumes (± SD) on weekly CBCTs (W1, W2, W3, W4 and W5) were 61.31 (±24.00) cc, 48.59 (±21.07) cc, 38.51 (±21.06) cc, 33.79 (±19.22) cc, and 28.66 (±17.82) cc, respectively. An average volume reduction of 53% was found between the start and the end of treatment; almost all reduction was observed in the second half of the treatment course (W3 (p = 0.02), W4 (p = 0.005) and W5 (p = 0.003)).

**Table (2):** Concurrent chemo-radiotherapy treatment related toxicity

| Systems/organ | Toxicity | Grade | N | % |
|---|---|---|---|---|
| GIT | Nausea ± vomiting | 2 | 1 | 10 |
| | Proctitis | 1 | 6 | 60 |
| | | 2 | 2 | 20 |
| | Enteritis | 1 | 1 | 10 |
| Skin | Dermatitis | 1 | 9 | 90 |
| | | 2 | 1 | 10 |
| U. bladder | Cystitis | 1 | 8 | 80 |
| | | 2 | 2 | 20 |

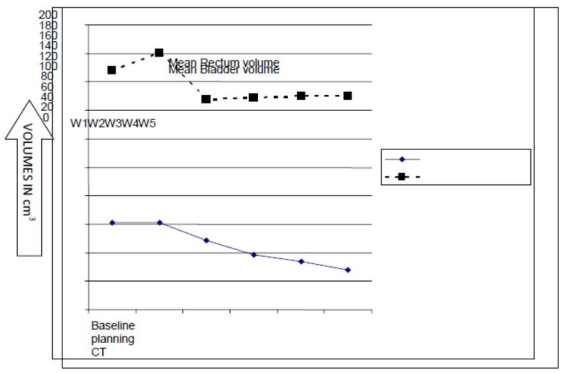


**Figure 2:** Mean rectal and bladder volumes changes throughout 5 weeks RT for all patients.

**Bladder volume changes**

The initial bladder volume varied from 75.10 to 301.22 cc on planning CT for all 10 patients with the mean of 167.00 ±19.76 cc. The mean bladder volume was comparable between male (188.58± 92 cc) and female (136.71 ± 82 cc) patients, (P=0.39). In addition, the mean bladder volume was decreased on CBCTs compared to planning CT (149.85 vs 167.00 cc) but without statistical significant difference (P=0.36).

The mean bladder volumes on weekly CBCTs (W1, W2, W3, W4 and W5) were 180.13 (±18.83) cc, 147.64 (±18.06) cc, 148.92 (±14.40), 150.42 (±16.83) cc, and 149.85 (±16.36) cc, respectively. There was no statistical significant volumetric variations of the bladder throughout the treatment period with W1 (p = 0.35), W2 (P=0.31), W3 (P=0.41), W4 (P=0.41) and W5 (P=0.44).

**Inter-fraction rectal motion**

In the current study, the overall mean of rectal inter-fraction motion was 2.28 (±1.34) mm, 1.54 (±1.66) mm, 1.12 (±1.34) mm and 2.70 (±2.25) mm in AP, PA, RL, LR directions, respectively.

The comparison between planning CT and CBCTs revealed a statistically significant AP rectal shift on W2 (P=0.011), W4 (P=0.0001) and W5 (P=0.008) respectively while PA rectal shift was significant on W2 (P=0.01). In addition, RL rectal shift was significant throughout the treatment period starting from W2 (P=0.002), W3. (P=0.03), W4 (P=0.04) and W5 (P=0.032) while LR direction shift was significant on W2 (P=0.04), W3 (P=0.024) and W5 (P=0.048). A significant rectal movement was noted more in AP and lateral directions among all patients.

It is worth noting that there was a significant association between the rectal shift and location of the tumor, the majority of rectal wall displacements were observed in the upper and middle region (P= 0.05) while it was minimal in the lower part (P=0.77). Nevertheless, no correlation could be found between bladder volume variations and rectal movements in all the directions: AP spearman's rho (-0.169) and (p=0.651), PA spearman's rho (-0.142) and (p=0.695),

RL spearman's rho (-0.562) and (p=0.091) then LR spearman's rho (-0.37) and (p=0.293) respectively.

**PTV2 coverage**

When considering the phase II of treatment, margins of 20 mmin all directions was adequate for rectal coverage in all patients.

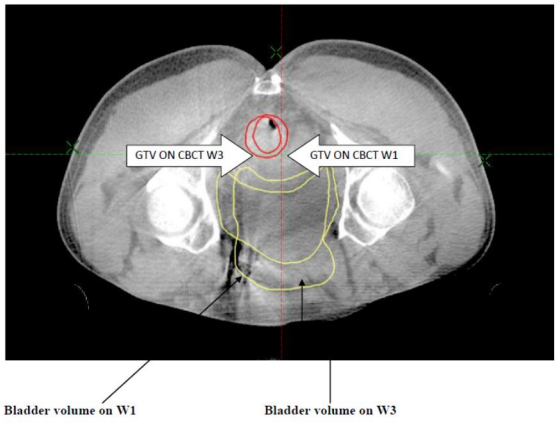


**Figure 3:** Example of the rectal tumor shrinkage & urinary bladder filling variations on CBCT cuts of one of our patients.

## 4. Discussion

Neo-adjuvant long course of CRT followed by surgical excision of the mesorectum is considered the standard of care for the treatment of locally advanced rectal adeniocarcinomas. Variation in the CTV is expected to occur throughout the 5 weeks of RT due to changes in bladder and rectal volume and shape. In the current clinical practice, the CTV and the PTV are delineated on a planning CT scan (pCT). The PTV margin is put to cover the geometric uncertainties which are due to systematic and random errors. The random errors are those due to daily variations, while the systematic ones are due to expected differences between the planned volume and the actually treated volume **(2)**.

Adaptive radiotherapy (ART) is a terminology of continuously monitoring and modifying the radiation planning throughout the treatment course to reflect the expected anatomic changes that may occur. Modifying the plans to account for anatomical changes and differences in the tumor volume is the cornerstone of adaptive radiotherapy **(4)**. Adaptive RT (ART) is required for adjustment of the CTV shape changes and minimizing the PTV margin; thus reducing the dose to the OARs **(2)**.

To the best of our knowledge, this is the first study in Egypt using simulator CBCT images to evaluate the rectal volume change and its motion for irradiation of locally advanced rectal cancer during 5 weeks of CRT in order to obtain better tumor coverage. The simulator CBCT images were unique in obtaining verification scans, allowing detailed study of patient positioning and organ motion over the entire radiotherapy course.

In the current study we recorded significant inter-fractional motion of the rectum in all directions throughout the treatment period. It was greatest in the lateral and antero-posterior directions. While most of the rectal wall displacements were observed in the upper and middle regions rather than the lower third as recorded in other studies. Lee and his colleagues had noticed that motion maximally seen in the mid-rectum lesions, whereas it was reported in the upper rectum in another studies **(5)**.

We recorded a significant trend decrease of rectal volumes over the course of treatment and 53% volume reduction (28.66 vs 61.07 cc; P= 0.0001). Our results are consistent with a recent trial, where the authors reported 27% decrease in the rectal volume by the 5$^{th}$ week in the CBCT when compared to planning CT (56.5 vs 77.3 cc; P=0.001) **(6)**.

In this study 32 rectal cancer patients were treated with preoperative CRT in the supine position. Planning CTs and weekly CBCTs (day 1, 7, 13, 19, 25) were analyzed for the 32 patients. The rectums and bladders were contoured on the planning CTs and CBCTs. The rectal volume was found to decrease week after week. They noticed that there was no correlation between changes in the bladder volume and inter-fraction motion of the rectum. They concluded that 10-15 mm margin is enough for the rectum during Simultaneous Integrated Boost Intensity Modulated Radiation Therapy (SIB-IMRT) **(6)**.

Maggiulli E et al. used daily Mega Voltage Computed Tomography (MVCT) to study rectal shape changes in neoadjuvant treatment of 10 rectal cancer patients. They noticed 57% average volume reduction throughout the treatment course, most of the reduction was found in the first half of the treatment **(7)**.

In our analysis there was reduction of the mean bladder volume on CBCTsbut without statistical significant difference (P=0.36). The reductioncould be due to patients becoming less attentive to the bladder filling instructions during radiotherapy treatment or due to increased frequency of diarrhea which makes it difficult for patients to control micturation. Our finding was consistent with arecent study by S. Sithamparam and his colleagues; they reported reduced bladder volume by the 4$^{th}$ and 5$^{th}$ week of radiotherapy treatment (10% and 18%, respectively). This mean bladder volume reduction did not reach a significant value (P =0.104). **(8)**.

## 4. Conclusion

With the increasing trend towards conformal radiotherapy the assessment of internal motion will become more important to avoid geographical miss

and sequel of tumor recurrence. We believe that optimal IGRT strategy in terms of imaging modality and frequency must be determined.

Despite the limited number of patients, the availability of weekly simulator CBCT images permitted the careful monitoring of each weekly rectal shape variation during CRT. The anterior and lateral rectal wall shifts were the most in the upper and mid rectum thirds. Individualized asymmetric margins are recommended to adequately overcome the rectal movements.

**Acknowledgments:**

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**Disclosure:**

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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