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Nijkamp, J.A.

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TARGET VOLUME SHAPE VARIATION DURING IRRADIATION OF RECTAL CANCER PATIENTS IN SUPINE POSITION: COMPARISON WITH PRONE POSITION

Jasper Nijkamp¹, Rianne de Jong¹, Jan-Jakob Sonke¹, Corine van Vliet-Vroegindewej¹ and Corrie A.M. Marijnen²

¹Department of Radiation Oncology, The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands
²Department of Clinical Oncology, Leiden University Medical Center, Leiden, The Netherlands
Chapter 7

Abstract

Purpose
To quantify the inter-fraction shape variation of the mesorectum for rectal cancer patients treated with 5 x 5 Gy in supine position and compare it to variation in prone position.

Material and methods
For 28 patients a planning CT (pCT) and five daily cone-beam-CT (CBCT) scans were acquired in supine position. The mesorectal part of the CTV (MesoRect) was delineated on all scans. The shape variation was quantified by the distance between the pCT- and the CBCT delineations and stored in surface maps after online setup correction. Data were analyzed for male and female patients separately and compared to prone data.

Results
A large range of systematic, 1–8 mm (1SD), and random, 1–5 mm, shape variation was found, comparable to prone patients. Random-shape variation was comparable for male and female patients, while systematic variation was 3 mm larger for female patients.

Conclusions
Shape variation of the MesoRect is substantial, heterogeneous and different between male and female patients. Differences between supine and prone orientation, however, are small. Clinical margins should be differentiated in position along the cranio–caudal axis, in anterior–posterior direction and for gender. Margins should also be increased, even when online setup correction is used. Due to the small margin differences between prone and supine treatments, the setup choice should be determined on dose to the organs at risk.
Introduction
The standard of care for primary resectable rectal cancer has evolved to total mesorectal excision (TME) surgery in combination with pre-operative (chemo-) radiation [1–5].

Besides a low local recurrence rate, the use of pre-operative irradiation also causes an increase in acute and late toxicities. The most important organ at risk (OAR) is the small bowel, in which radiation enteritis, chronic diarrhea, bowel-stricture and perforation, and hemorrhage can be caused [6–8]. Several measures can be taken to reduce the dose to the small bowel. Patients are generally treated in prone position, with or without the use of a belly board, to reduce the amount of small bowel in the high-dose region [9–11]. The patients are also given instructions on drinking to increase the bladder filling, thus pushing the small bowel away from the high-dose region [11]. The downside of treating patients in prone position is that the setup is less reproducible between and during fractions in comparison with treating patients in supine position [12, 13].

Improvements in planning techniques have also contributed in the reduction of dose to the OARs. With the use of intensity modulated RT more conformal treatment plans can be delivered [14]. When delivering these conformal plans it is important to account for all geometrical uncertainties, by using a proper margin from clinical target volume (CTV) to planned target volume (PTV). Uncertainties that should be taken into account are patient setup, target definition uncertainties and organ motion/shape variation.

For patient setup, in-room imaging techniques, such as EPID or MV and kV cone-beam CT (CBCT), can be used to minimize inter-fraction setup errors [15]. A minimization of the inter-fraction set-up errors leaves potential intra-fraction errors as the major source for setup uncertainties.

For target definition uncertainties no intra-observer literature and inter-observer literature are available for rectal cancer patients. Looking at delineation errors for prostate cancer patients, at least errors in the order of 3 mm standard deviation (SD) should be taken into account [16].

For organ motion/shape variation 2 studies are available, for prone setup only [17, 18]. Both studies investigated treatment schedule of 5 weeks for 10 patients each on either repeat CT or MV–CBCT. The majority of the patients in the repeat CT study [17] were treated post-operatively, while in the other study [18] shape variation was only presented averaged over all levels on the cranio-caudal axis and averaged over all patients, which makes it difficult to translate the data into a PTV margin.

In our hospital, the lack of knowledge about the different uncertainties has led to an arbitrary uniform 10 mm CTV to PTV margin which is compensated by very generous delineation of the CTV. Parts of the cervix, uterus, bladder and prostate are included in the CTV to account for uncertainties. In the RTOG delineation atlas for anorectal cancer it is advised to include 1 cm of the back of the bladder into the CTV to compensate for day-to-day variation [19]. This incorporation of motion uncertainties into CTV generation, rather than PTV expansion, represents a conceptual break with ICRU 62 conceptual guidelines. This approach also causes large observer variation, because the border of the delineated CTV is not visible as an anatomical border. Furthermore, it is not clear if this approach leads to a sufficient PTV. Till what extent this departmental approach is also used in other hospitals is not known.
Until now, treatment planning studies comparing small bowel exposure for prone and supine position used the same CTV to PTV margin for both types of setup [9–11, 20]. It is, however, not certain that the required margins are the same for both options. In a recent study we investigated the inter-fraction shape variation of the mesorectal part of the CTV in 27 rectal cancer patients treated with hypo-fractionated RT in prone position on a flat table [13] (this study is named “prone study” in the remainder of this paper). In this study large and anisotropic shape variation was observed. Furthermore, a difference in shape variation between male and female patients was found, with variation being larger for female patients.

To make a fair comparison between prone and supine treatments of rectal cancer patients it is important to establish estimates of uncertainties for both types of orientation, using the same methodology.

Therefore, the purpose of this study was to establish the inter-fraction shape variation of the mesorectum in rectal cancer patients treated in supine position. Finally a comparison between the results of this study and the previous prone study has been made.

Material and methods

Patients and treatment

Twenty-eight patients, suitable for either prone or supine orientation treatment with pre-operative 5 x 5 Gy RT, were selected to be treated in supine position in the period between November 2006 and October 2008. The patients with previous pelvic surgery and/or radiotherapy were excluded. Since both prone and supine treatments are generally accepted in the Netherlands, no informed consent was needed.

For each patient a planning CT (pCT) was acquired in a supine position, on a flat table, ranging from the L2–L3 junction to the perineum with 5 mm slice spacing. The clinically delineated CTV generously encompassed the tumor and involved lymph nodes, the mesorectal fat with the anal verge as inferior margin, the pre-sacral lymph nodes, lymph nodes along the internal iliac artery and the superior rectal and internal obturator vessels. A 10 mm margin was added to create the PTV for a 7-field IMRT plan.

All patients received full bladder instructions: they were asked to empty the bladder and drink a fixed amount of water 1 h before pCT and each fraction. The first 7 patients (5 males, 2 females) were treated with a previous protocol where they were asked to drink 250 ml of water, while the latter were asked to drink 350 ml of water.

CBCT acquisition

Daily kV-CBCT scans were acquired just prior to treatment for online setup correction based on bony anatomy. CBCT scans had a diameter of 40 cm in the axial plane and ranged 9 cm cranially and caudally of the iso-center (center of PTV).
Delineation

Three volumes were delineated on each pCT and pre-treatment CBCT scan: the mesorectal part of the CTV, the bladder and the rectum. Due to reduced image quality in CBCT and a low expected day-to-day variation in the nodal regions [17] a sub-part of the CTV (called MesoRect in the remainder of this study) was delineated. The MesoRect encompassed the rectum and mesorectal fat starting at the dentate line up to the last CT-slice where the lateral borders of the mesorectal fascia were still visible (Fig. 7.1). The borders of the MesoRect were defined by the mesorectal fascia. The CBCT delineations were performed after bony anatomy registration to the pCT. During delineation on the
CBCT scans, the MesoRect delineation of the pCT was available to guide the observer when necessary. All delineations were performed by one observer (R. de J.) and evaluated by a radiation oncologist (C.A.M.M.).

For the rectum the outer wall was delineated from the dentate line up to the sigmoid colon.

**Volume variation in bladder, rectum and MesoRect**

For the bladder, rectum and MesoRect delineations the inter-patient volume variation was calculated by taking the mean and standard deviation (SD) over all scans.

Systematic volume differences between the treatment planning and treatment delivery were derived by comparison of the volumes on the pCT and the average volumes on the CBCT scans per patient.

To evaluate the intra-patient volume variation, first the relative volumes were calculated. The relative volume was defined as the volume on the delineated scan divided by the average volume of the patient. The intra-patient variation was determined by taking the SD over these relative volumes.

**MesoRect shape variation**

To quantify the shape variation in MesoRect the delineation of the pCT was used as the reference structure for each patient. These reference MesoRect delineations were resliced on the CC axis to 50 slices, and 100 equidistant dots were placed and numbered on each slice, starting at the dorsal side of the patient. From the center of each dot on the reference MesoRect the distance to the five CBCT delineations was calculated perpendicular to the surface.

The mean and SD over the five distances was calculated for each dot and stored in 2D surface maps by virtually cutting and unfolding the delineation at the dorsal side. The horizontal axis of the maps represents the 100 equidistant dots of each slice starting at the dorsal side via left, anterior and right back to dorsal. The vertical axis of the maps represents the 50 slices on the CC axis from the anus up to the cranial border of the MesoRect.

With the mean and the SD map of each patient the systematic- and random-error maps of the total group could be calculated by taking the SD of the mean maps and the root-mean-square of the SD maps, respectively, similar to the prone study.

**Influence of rectum and bladder on changes in the MesoRect shape**

For each CBCT scan the bladder and rectum volume differences with respect to the volume on the pCT were calculated. The Pearson correlation coefficient was then calculated between the changes in the MesoRect shape and bladder/rectum volume for each dot on the reference MesoRect delineations yielding two new 2D surface maps. The $r^2$ value of a pixel in the map represents the portion of the MesoRect shape variance that can be attributed to changes in the volume of bladder or rectum.
**Intra-observer variation**

For a subset of 10 patients, 5 males and 5 females, the MesoRect on the five CBCT scans were re-delineated by the same observer (RdJ) after a time period of at least one month. These re-delineations were used to quantify the intra-observer variation on CBCT scans. The MesoRect of the pCT was available as example during the re-delineation of the CBCT scans, which is comparable to the situation during the initial delineation. The original delineations were taken as the reference and the distance to the surface of the new delineation was calculated for each pair of delineations (comparable to the MesoRect shape variation procedure with 50 slices times 100 dots per slice). The SD over these distances was expressed as intra-observer variation maps. Because delineation errors could have occurred in both the original- and the re-delineation the values in the intra-observer variation maps were divided by $\sqrt{2}$.

**Required margins**

It is not straightforward to combine shape variability with rigid uncertainties into a required PTV margin. Since the MesoRect is a deforming organ only the changes in the shape outside the original delineated volume affect the dose to the target volume. To, nevertheless, get a first order approximation of the required margins the rigid margin recipe of $2.5 \times \Sigma + 0.7 \times \sigma$ was applied [21].

The MesoRect was divided into six regions, the upper- and lower half, divided at the base of the bladder, and anterior, posterior and lateral sides as assigned at the bottom of each map.

The shape variation errors were combined with other uncertainties to obtain a clinically relevant margin. Besides intra-fraction errors from a group of bladder cancer patients treated supine [22], an estimate of the residual inter-fraction setup error (0.5 mm systematic and 1 mm random) and an optimistic estimate of the inter-observer variation (3 mm) were used [16]. Intra-observer variation was not incorporated for margin calculation, as it only served for validation of reproducibility using only one observer.

**Statistical analysis**

Following the prone study, the methods described above were performed for male and female patients separately.

The different systematic- and random-error maps were tested on significant differences. For systematic-errors, a 2-sided $F$-test for each pixel in the map was used to compare the SD over the patient averages in both groups. The random-error maps were compared by using a 2-sided student $T$-test for each pixel to compare the average over the patient SDs as a surrogate for the root-mean-square over the patient SDs. The level of significance for all comparisons was chosen at $p < 0.05$.  

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Results

Patient characteristics
The male and female patient groups were very much comparable on age, tumor location and TNM stage, and very much comparable to the patients of the prone study (not shown).

Intra-observer variation
Intra-observer variation was on average 1 mm SD with a maximum of 3 mm for male and 2 mm for female patients. The maximum values were located in small areas in the upper half at the transition from anterior to the lateral sides (not shown).
**Volume variation of bladder, rectum and MesoRect**

Over all the patients, the bladder volume was comparable between male (210 ± 153 cc) and female (226 ± 154 cc) patients, while the rectum (108 ± 31 cc vs. 92 ± 38 cc) and MesoRect (226 ± 39 cc vs. 199 ± 76 cc) volume were significantly smaller for female patients (p < 0.01, 2-sided t-test).

The intra-patient variation was large for the bladder (range 25–338% of the patient average volume). The relative bladder volumes had a SD of 0.41 for male and 0.54 for female patients. The intra-patient variation for males and females in rectum volumes was 0.17 and 0.21 and in MesoRect volumes was 0.06 and 0.07, respectively.

For 7 patients with the 250 cc drinking protocol the average bladder volume was 184 ± 128 cc (1 SD), while for the 350 cc protocol the average was 229 ± 159 cc (p = 0.05, 1-sided t-test). No significant time trends in any of the volumes were found during the 5 day course of radiotherapy.

**MesoRect shape variation**

The average delineated CC length of the MesoRect was 10.4 ± 1.2 cm (1SD) for male patients and 9.3 ± 1.4 cm for female patients. On the 2D error maps (Fig. 7.2), the average CC level of the tip of the os coccyx (OsC), the bottom of the bladder (Bl) and the top of the prostate without seminal vesicles (Pr), has been indicated with horizontal lines (1SD ± 0.9 cm).

The systematic-errors were 2–3 mm larger for female patients compared to male patients (Fig. 7.2). The random errors in supine are similar for male and female patients with maximum values of 5 mm.

**Required margins**

An overview of the systematic and random-shape variation values in the six regions is shown in Table 7.1. The required margins in the lower half are approximately 16 mm in all directions for both male and female. For the upper anterior region in female patients a 24 mm margin was required, while for male patients in the same region a 5 mm smaller margin was required.

**Influence of rectum and bladder on changes in the MesoRect shape**

Changes in the MesoRect shape were mainly caused by changes in rectal volume (Fig. 7.3). For both male and female patients the highest correlation of 50% was found at the anterior side of the MesoRect cranial of the tip of the os coccyx.

Hardly any correlation between changes in bladder volume and MesoRect shape was observed in female patients (Fig. 7.3a). For male patients the maximum bladder correlation was 30%, which is still a minor influence.
In the current study slightly larger systematic changes in the MesoRect shape were found (Fig. 7.2 a & c), while for female patients the random changes in shape were smaller compared to those in prone position (Fig. 7.2b). The maximum systematic error in male patients was 5 mm at the upper anterior side, which is comparable between prone and supine (Fig. 7.2c), but the region is larger and also extends inferiorly to the level of the prostate for supine setup.

The first order approximation of required margins shows slightly larger margins for supine position compared to prone position. For both types of setup the required margin at the upper anterior side of the MesoRect is approximately 5 mm larger for female patient compared to male patients.

Since patients in this study were suitable for both prone and supine orientation treatments, a comparison of data from this study with those of the prone study can be made. In Fig. 7.4 the systematic changes in shape in the current study and the prone
study are combined to validate if differences in position and gender are significant. The systematic error map for all prone patients together (Fig. 7.4a) is tested on significant differences (Fig. 7.4c, 2-sided f-test) with the systematic error map for all supine patients together (Fig. 7.4b). The same comparison has been made comparing all male patients with all female patients (Fig. 7.4d–f). Although differences due to patient orientation are similar to the differences in gender, being in the order of 2–3 mm, the difference in the upper anterior region is mainly significant when stratifying for gender. For patient position the differences are mainly significant at the posterior side at the level of the os coccyx and at the lower-anterior region, where the magnitude of shape variation is smaller, and clinically less relevant.

The correlation between changes in rectal volume and MesoRect shape is also different between prone and supine positions in male patients. Where in prone position a change in rectal volume primarily influenced the MesoRect shape to anterior and lateral cranially of the prostate, in supine position a clear influence only towards anterior is found which also extents to the level of the prostate. For female patients the opposite is found with the highest correlation more cranially for supine orientation compared to prone orientation.

<table>
<thead>
<tr>
<th>Table 7.1: Margin calculation table, with the base of the bladder as divider for upper and lower MesoRect</th>
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<tbody>
<tr>
<td><strong>Millimeters</strong></td>
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<td><strong>Deformation Upper half</strong></td>
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<td><strong>Deformation Lower half</strong></td>
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<td><strong>Setup, inter-fraction</strong></td>
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<td><strong>Setup, intra-fraction [22]</strong></td>
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<tr>
<td><strong>Inter-observer delineation</strong></td>
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<tr>
<td><strong>Margin Upper half</strong></td>
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<td><strong>Margin Lower half</strong></td>
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</table>
**Fig. 7.4:** Systematic error maps for prone (top left), supine (middle left), male (top right) and female (middle right) patients. Statistically significant different areas (white: $p < 0.05$, grey: $p < 0.10$, 2-sided f-test) between prone and supine are shown in bottom left and between male and female bottom right. Horizontal axis runs from posterior via left, anterior and right back to posterior. Vertical axis runs from anus up to the end of the mesorectal fascia.
Discussion
This is the first study to evaluate the changes in the mesorectum shape, the most variable part of the CTV, in rectal cancer patients treated in supine position. In addition changes in the target volume shape between prone and supine positioning were compared, which is the main source of errors when online setup correction is used. Large systematic and random-shape variation up to 7 and 5 mm was observed. To account for different systematic- and random-shape variability in different areas of the MesoRect anisotropic margins are needed, similar to the prone study. Differences between prone and supine positions were: smaller random errors for changes in MesoRect shape in female patients treated in supine position (≤5 mm vs. ≤7 mm), and the MesoRect was also clearly more movable at the border with the prostate in male patients treated in supine position.

Volume variation of bladder, rectum and MesoRect
In this study 2 different bladder filling instructions were used. The influence of drinking 250 or 350 cc of water one hour before treatment led to a significant increase in the average bladder volume from 184 to 229 cc. However, the day-to-day variation remained large, independent of the bladder filling instructions. This is in agreement with the publication of O’Doherty [23] who demonstrated that the use of standardized bladder instructions does not lead to a stable bladder filling. We continued to use the 350 cc instructions, because the higher the average volume of the bladder, the more small bowel is kept out of the high-dose region [11].

Shape variation of the MesoRect
The MesoRect mostly deforms at the anterior side cranially from the tip of the os coccyx and, to a lesser extent, at the posterior part caudal of the os coccyx. In other regions the border of the MesoRect is adjacent to bony anatomy which prevents deformation. The upper anterior region of the MesoRect is the most clinically important region. Since in this region the difference was only significant between male and female and not between prone and supine setups (Fig. 7.4), PTV margins should be differentiated in gender, and not in orientation of the patient.

For male patients the change from prone to supine resulted in a larger area with the maximum systematic error of 5 mm. This area was located cranial of the prostate in prone position [13], while in supine position it is also located at the level of the prostate (Fig. 7.2c) suggesting that in prone setup the prostate is blocking the MesoRect from deforming because its movement is restricted by the os pubis.

Intra-observer delineation variation
In the study the 5 CBCT scans were re-delineated for 10 patients, 5 males and 5 females. With at least 1 month between the initial and the re-delineation no memory based choices were expected to influence the outcome. The intra-observer variation was largest at the transition edges from anterior to the lateral sides. With relative small maximum values of 3 and 2 mm SD for male and female, intra-observer variation has hardly influenced the found systematic and random-shape variability.
Bladder/rectum volume correlation with changes in the MesoRect shape

Similar to patients in prone position, changes in rectum filling was found to be the major cause of changes in the shape of the MesoRect. However, the location with the highest correlation was different between prone and supine orientations. For female patients the high rectum correlation region changed from widespread anterior and lateral at the level of the tip of the os coccyx in prone setup, to anterior-right entirely above the tip of the os coccyx in supine setup. For male patients in prone setup the rectum correlations were high at the anterior and lateral areas cranial of the prostate and to a lesser extent to lateral at the level of the prostate. In supine setup a change in rectal filling correlates best with a change in the MesoRect shape at the borderwith, and above the prostate (Fig. 7.3). These differences support the theory that the prostate is less affected by rectal filling in prone setup due to gravity and anatomy.

Margins

As expected, the small differences in systematic error between prone and supine resulted in small differences in the required margin, but this was hardly relevant. It is more important to separate required margins between male and female instead of prone and supine.

The required margins up to 19 mm and 24 mm for male and female patients are much larger than the clinically used uniform margin of 10 mm. This increase in required PTV margin, however, does not necessarily increase the PTV. The current clinical margin is applied on top of a generously delineated CTV implicitly accounting for anisotropic rectum shape variability, while in the prone and supine study the anatomical borders of the CTV were used for delineation of the MesoRect. This is illustrated in Fig. 7.5 with an example of a male patient in prone position and a female patient in supine position with the CTV and PTV (white) and the CTV (MesoRect + pre-sacral region) and PTV according to this study (black), which are in the case of the female patient very close to each other, while for the male patient the new approach led to a smaller PTV at the whole anterior border.
Limitations of the study
This study was conducted on a dataset of 28 patients divided into two groups of 14 patients. Determination of systematic and random errors on a group of 14 patients gives a reasonable, but not definite estimate of the errors. The results of this study were compared to those of a similar limited study on 27 patients in prone position. Larger studies, but also studies from other hospitals, are required to confirm the results and improve the statistical power of the analyzed variations. Current study does, however, give a good estimate of the order of magnitude and especially the heterogeneity of systematic and random errors for shape variation in supine position.

Intra-fraction setup errors were taken from a supine pre- and post-fraction CBCT dataset of 18 bladder cancer patients [22]. The fact that no intra-fraction setup data on rectal cancer patients were available demands for more research in this area for a fairer comparison.

The defined MesoRect in this study does not extend as far cranially as the real CTV for patient treatment. The more cranial part of the CTV is defined by the pre-sacral- and iliac-lymph node areas. Variation in the position of the iliac vessels is usually limited [17] and the pre-sacral lymph nodes are located adjacent to the bony anatomy, thus corrected by online setup corrections. Therefore, variation in the CTV beyond the MesoRect can be expected to be smaller than the measured deformations.

In the margin comparison the systematic and random-error maps were simplified by dividing into six regions. Because of the small influence of random shape variation on the required margins and comparable maximum values for systematic Mesorect shape variation, required margins for prone and supine positions were comparable. Only when surface location specific margins become applicable differences between prone and supine shape variations will affect the planned target volumes. Until then, first a margin recipe on a combination of shape variation and rigid setup errors should be derived.

In this study intra-observer delineation was quantified. It is however not clear if this observer variation is the same for patients treated in prone position. A difference is that CBCT scans in prone position suffer from breathing artifacts. Further investigation is needed to quantify if there is a difference.

Inter-observer variation potentially has a larger impact on margins needed. This is however never investigated for rectal cancer patients. Inter-observer variation studies are generally performed on planning CT scans. Since image quality differences of CT scans in prone and supine are small, inter-observer variation is expected to be similar for both types of setup. Therefore, the influence of inter-observer might be different than the assumed variation of 3 mm, but also comparable for prone and supine.
Conclusions
In conclusion, inter-fraction shape variation of the mesorectum was found to be substantial, heterogeneous and anisotropic. As a result, the PTV margin should be differentiated in position on the cranio-caudal axis, in anterior–posterior direction. Differences in shape variation are smaller for prone versus supine compared to male versus female. Therefore, margins should be differentiated for gender. The CTV to PTV margin should be increased above the standard 10 mm in combination with a strict delineation of the CTV. Since required treatment margins are similar for prone and supine when using online setup correction, decision making on patient setup can be based on dose to the organs at risk.
References


Target volume shape variation during 5x5 Gy RT of rectal cancer patients (supine)
Chapter 7


