(Un-)certainties in radiotherapy of rectal cancer
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Citation for published version (APA):
TARGET VOLUME SHAPE VARIATION DURING HYPO-FRACTIONATED PRE-OPERATIVE IRRADIATION OF RECTAL CANCER PATIENTS

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Abstract

Purpose
To quantify the day-to-day target volume shape variation in rectal cancer patients treated with preoperative 5 x 5 Gy radiotherapy.

Material and methods
For 27 patients a prone position plan-CT (pCT) and five daily pre-treatment cone-beam-CT (CBCT) scans were acquired. A sub-region of the CTV (MesoRect, anus up to the cranial end of the mesorectal-fascia) was delineated on all scans. The MesoRect deformation was quantified by the distance between pCT- and CBCT-delineations and was stored in surface-maps. Finally, the influence of bladder and rectum filling on MesoRect deformation was evaluated. Data were analyzed for male and female patients separately.

Results
A large range of systematic and random deformations, 1–7 mm (1SD), on different areas of the MesoRect were found. The maximum deformations were located at the upper-anterior-side of the MesoRect. For females the errors were up to 3 mm larger than for males. Small correlations, \( r^2 \leq 0.4 \), were found with changes in bladder volume. Larger correlations, \( r^2 \leq 0.7 \), were found for rectal volume in a distinctive area in the upper-half of the MesoRect.

Conclusions
Substantial and heterogeneous deformations of the MesoRect were found. Therefore different PTV margins in positions along the cranio-caudal axis, in the anterior–posterior direction. Margins should also be larger for female patients compared to male patients.
Target volume shape variation during 5x5 Gy RT of rectal cancer patients (prone)

Introduction

For primary resectable rectal cancer, total mesorectal excision (TME) is the standard treatment in many countries [1–3]. When a TME is performed using a standardized technique by a highly experienced group of surgeons, local recurrence (LR) rates as low as 8% can be achieved [3, 4]. The LR rates can be further reduced by adding pre-operative (chemo-) radiation [5–8].

During pre-operative radiotherapy the small bowel is the most important organ at risk. Several studies have shown a clear relationship between dose to the small bowel and acute radiation enteritis, as well as late toxicity, such as chronic diarrhea, bowel stricture, perforation and hemorrhage [9–11]. With the use of intensity-modulated radiotherapy (IMRT), it is possible to create a more conformal treatment plan that has similar target coverage and a large reduction in dose to the organs at risk [12] compared to conventional techniques. As a consequence of this conformality, it has become more critical to correctly estimate and account for all geometrical uncertainties. This is especially true for hypo-fractionated treatments like the 5 x 5 Gy scheme used in the Dutch and Swedish national trials [3, 5]. In such cases, a single geographical miss can lead to a local under-dosage in a part of the target volume of maximum 20%. Geometrical uncertainties that need to be taken into account are inter- and intra-fraction setup errors, delineation uncertainties and inter- and intra-fraction target volume variation.

Patients are treated in prone or supine position, with the argument that inter- and intra-fraction setup errors are smaller in supine position compared to prone position, while with treatment in prone position the small bowel is pushed away from the high dose region, reducing the dose to the small bowel compared to that in supine position. Offline and online setup correction protocols are used to reduce inter-fraction setup errors. However, there are hardly any data on delineation variation and the day-to-day variation of the target volume in rectal cancer patients. Inter-observer variations in prostate cancer patients, which are assumed to be easier to delineate, are in the order of 2–3 mm standard deviation [13]. A number of studies published guidelines to define the CTV in rectal cancer [14–16], and two studies [17, 18] described the displacement of the CTV border on repeat-CT and mega-voltage cone-beam CT (CBCT) data in a treatment schedule of 5 weeks for 10 patients each. With 10 patients only, no subgroup analysis was possible, and they also did not describe the causes of variation.

In clinical practice the lack of knowledge about uncertainties is “compensated” by generously delineating the CTV up to 10 mm outside the anatomical definition, including a part of the bladder, prostate, cervix and uterus into the CTV and adding a PTV margin on top of that.

The purpose of this study was to quantify the day-to-day shape variation of the mesorectal fat in rectal cancer patients treated in prone position with hypo-fractionated pre-operative radiotherapy based on delineations on CBCT-scans. The influence of changes in rectum and bladder volume on the shape of the CTV was also quantified as well as the intra-fraction setup errors.
Chapter 6

Material and methods
Patients and treatment
A total of 27 patients treated with pre-operative 5x5 Gy radiotherapy were selected. Patients with anatomical abnormalities, such as myomas, or previous abdominal surgery were excluded. The RT fractions were given on five consecutive days, and the TME was planned within 5 days after RT.

For each patient a planning CT (pCT) was acquired in a prone 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. For patients receiving an abdominoperineal resection the anus was also taken into the CTV. A 10 mm margin was added to create the PTV.

All patients received full bladder instructions: they were asked to empty their bladder and drink 250 ml of water 1 h before pCT and each fraction.

Daily CBCT-scans
Daily CBCT-scans were acquired just prior to treatment for online setup correction based on bony anatomy to minimize inter-fraction setup errors. CBCT-scans were made using Synergy 3.5 (Elekta Synergy™, Elekta Oncology Systems Ltd., Crawley, West Sussex, United Kingdom) over an arc of 360 in 2 min. This yielded a scan of 40 cm in diameter in the axial plane, which ranged 12.5 cm above and below the isocentre on the cranial-caudal (CC) axis. The isocentre was placed at the centre of the PTV.

Intra-fraction setup errors
Because inter-fraction errors were minimized with online corrections, it was important to quantify intra-fraction setup errors as the remaining source of setup uncertainty. For all but one patient, a post-treatment CBCT-scan was acquired after each fraction to assess the intra-fraction stability of the patients. Intra-fraction setup errors were determined as the bony anatomy displacement on the post-treatment CBCT-scan with respect to the pCT after adjustment for the fact that pre-treatment errors were only corrected by translations.

Delineation
In this study three volumes were delineated on each pCT and pre-treatment CBCT-scan: a part of the CTV, the bladder and the rectum. Due to CBCT image quality and a low expectancy of 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 anus 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. 6.1). The borders of the mesorectal fat were defined by the mesorectal fascia. The caudal border was chosen because for abdominoperineal resections the anus is part of the CTV for RT treatment. The cranial border was chosen because it is the most cranial anatomical landmark of the mesorectal fat visible on both CT and CBCT. Cranially of the defined MesoRect the clinical
CTV consists of the presacral and iliac lymph node areas.

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.

![Image](image.png)

*Fig. 6.1: Example of the MesoRect delineation. In the upper-left corner the contour of the most caudal-axial slice; in the upper-right corner the middle-axial contour slice; in the lower-left corner the contour of second most cranial-axial slice; in the lower-right corner a sagittal view of the MesoRect delineation.*

**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.

Differences between the treatment plan and during treatment were derived by comparison of the volumes on the pCT and the average volumes on the CBCT-scans per patient.

To evaluate the volume variation within patients, 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, a modified version of virtual rectum unfolding was used [19, 20]. The MesoRect delineation of the pCT was used as the reference structure for each patient. To overcome limitations in comparison caused by differences in patient size all pCT MesoRect delineations were re-sliced on the CC axis into 50 equidistant slices. Doing so, we assumed that shape variation in the cranial, middle and lower part of the MesoRect could be compared between patients, even if there was a difference in physical CC distance. On each slice 100 equidistant dots were placed and numbered starting at the dorsal side of the patient. The dorsal side of the contour was chosen because it was expected to be a reproducible anatomical point for the pCT delineation of all patients. From the centre of each dot on the reference MesoRect the distance to the surface of the five CBCT delineations was calculated after bony anatomy registration. A positive distance was defined when the MesoRect delineation on the CBCT-scan was found outside the delineation on the pCT, and negative when inside.

The mean and SD over the five distances was calculated for each dot and stored in 2D surface maps. 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 means and the root-mean-square of the SDs, respectively.

Influence of rectum and bladder on MesoRect

For each CBCT-scan the bladder and rectum volume difference with respect to the pCT were calculated. The Pearson correlation coefficient was then calculated between the local MesoRect shape changes and overall bladder/rectum volume changes for each dot on the reference MesoRect delineations yielding two new 2D surface maps. The new maps contained the correlation coefficient ($r^2$) between MesoRect shape variation and (1) variation in bladder volume (2) variation in rectal volume. 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 volume of bladder or rectum.

Statistical analysis

The anatomy of males and females in the pelvic area differs considerably. To validate whether differences in anatomy lead to a difference in MesoRect shape variation the methods described above have been performed for males and females separately.

The systematic- and random-error maps for men and women were tested on significant differences. For systematic errors, a two-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 two-sided Student’s 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 $p < 0.05$. 
**Table 6.1:** Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>64</td>
<td>62.5</td>
</tr>
<tr>
<td>Range</td>
<td>48-84</td>
<td>50-77</td>
</tr>
<tr>
<td>Distance of tumor from the anal verge (nr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.1-15 cm</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>5.1-10 cm</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>≤ 5 cm</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>TNM stage (nr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>II</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>III</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>IV</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Type of resection (nr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low anterior</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>Abdominoperineal</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Time between pCT and 1st fraction – days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Range</td>
<td>11-21</td>
<td>11-18</td>
</tr>
</tbody>
</table>

**Table 6.2:** Intra-fraction setup error

<table>
<thead>
<tr>
<th>Translations (mm)</th>
<th>Rotations (dg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LR</td>
</tr>
<tr>
<td>LR</td>
<td>0.0</td>
</tr>
<tr>
<td>CC</td>
<td>2.4</td>
</tr>
<tr>
<td>AP</td>
<td>2.2</td>
</tr>
</tbody>
</table>

**Table 6.3:** Volumes of the delineated structures

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>p-value (t-test, 1sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>206 cc (134)</td>
<td>209 cc (152)</td>
<td>0.44</td>
</tr>
<tr>
<td>Rectum</td>
<td>136 cc (49)</td>
<td>89 cc (32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MesoRect</td>
<td>256 cc (53)</td>
<td>201 cc (36)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Chapter 6

Results

Patients
Details on patient and tumor characteristics are given in Table 6.1. The limited number of abdominoperineal resections can be explained by the fact that those patients nowadays often receive neo-adjuvant chemo-radiotherapy.

Intra-fraction setup errors
For 26 patients a total of 121 CBCT pairs were used to calculate the intra-fraction setup errors (nine post-treatment scans were missing). Group mean (M), systematic (Σ) and random (σ) errors were small, except for L–R shifts (Table 6.2), where a systematic and random error up to 2.4 mm was found. No significant differences between male and female patients (data not shown) were found. The time between the pre- and post-treatment scan was 13 ± 2 min (1SD) on average.

Volume variation of bladder, rectum and MesoRect
In 2 of the 135 pre-treatment CBCT-scans it was impossible to delineate any structure, due to artifacts caused by motion of gas or breathing during the scan.

There was a wide variety in volumes of the three delineated structures within and between patients (Table 6.3). The bladder volume was comparable between male and female patients, while the rectum and MesoRect volumes were significantly smaller for female patients.

For male patients the bladder volume during treatment was on average 16% smaller than during planning (p = 0.004, two-sided t-test). For female patients the MesoRect volume was on average 5% larger during treatment fractions compared to the pCT (p = 0.02). For all other delineations no significant volume differences between pCT and treatment were found.

The intra-patient variation was large for the bladder (range 25–300% of the patient average volume). As a consequence, the relative bladder volumes had a SD of 0.42 for men and 0.63 for women. The intra-patient variation in rectum volumes was smaller with a relative volume SD of 0.25 and 0.24 for males and females, respectively. The relative volume SD for the MesoRect was even smaller with 0.06 and 0.08 for men and women, respectively.

No time trends during the 5 days course of radiotherapy were found (not shown).

MesoRect shape variation
The average delineated CC length of the MesoRect was 9.2 cm (1SD 1.1) for male patients and 8.6 cm (1SD 0.7) for female patients. For CC orientation on the vertical axis of the 2D error maps (Fig. 6.2), the average 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), have been indicated with horizontal lines. The variation for each of these levels was around 0.9 cm (1SD).

There was large heterogeneity in the systematic- and random-error maps (Fig. 6.2), where maximum values are located at the upper-anterior border of the MesoRect and minimum values are located at the upper-posterior side, and the lower-lateral sides.
In female patients, random and systematic errors up to 7 mm were found. In male patients the maximum random and systematic errors were smaller, being 4 and 5 mm, respectively. In the random-error maps (Fig. 6.2 b and d) the difference between male and female at the upper anterior side was significant (p < 0.05). At the upper anterior side of the systematic-error maps the difference was, however, not significant (p = 0.10). The systematic errors were significantly larger for male patients posteriorly at the level of the os coccyx compared to female patients, while at the anterior side cranial of the os coccyx the systematic errors were significantly smaller for male patients compared to female patients.

**Fig. 6.2**: Systematic- and random-error maps for female and male patients. The horizontal lines in each figure depict the level where (1) the tip of the os coccyx, (2) the base of the bladder, and (3) the top of the prostate without seminal vesicles were found on average in both patient groups. The horizontal axis is divided into posterior (P), left (L), anterior (A), right (R) and posterior (P).
Influence of rectum and bladder on MesoRect

Due to anatomical differences between male and female patients the position of the bladder with respect to the MesoRect was different. On average half of the bladder was located more cranially than the MesoRect for male patients, while this was less than 20% for female patients. Therefore, a larger influence of bladder volume differences on the MesoRect can be expected for female patients compared to male patients. Even though, only a small correlation between bladder volume and MesoRect variation within the female patient group was found (Fig. 6.3a). The maximum contribution of changes in bladder volume on deformation of the MesoRect was 40% in small areas of the map. The rectum correlation map for female patients (Fig. 6.3b) shows one clear area with a maximum contribution of 60% at the anterior side, at the level of the os coccyx. There was hardly any correlation between bladder volume and MesoRect variation within the male patient group (maximum 20%, Fig. 6.3c). The correlation between rectum volume

Fig. 6.3: The $r^2$ correlation maps between bladder volume and MesoRect shape variation (a and c) and between rectal volume variation and MesoRect shape variation (b and d) for both female and male patients.
and MesoRect shape for male patients (Fig. 6.3d) at the upper-anterior side just above the prostate had a maximum contribution of 70%. Note also that at the level of the prostate itself (approximately between OsC and Pr) the changes in rectal filling correlate better at the lateral sides of the MesoRect than at the anterior side. All correlation map areas with an $r^2$ value of 0.2 and higher were significantly different from 0 ($p < 0.05$).

**Discussion**

This is the first study to evaluate shape changes in the mesorectal part of the CTV in rectal cancer patients treated with hypo-fractionated pre-operative radiotherapy. With the mesorectal part being the most variable part of the CTV, large systematic and random deformations up to 7 mm were found. Due to the heterogeneity of the systematic and random errors in different areas of the MesoRect anisotropic margins can be advised. The current clinical uniform PTV margin of 1 cm seems to be insufficient. Deformations of the MesoRect were mainly driven by changes in rectal volume, while there was a minor influence of changes in bladder volume. With treatment in prone position, substantial intra-fraction setup errors in left-right direction were found.

**Intra-fraction setup errors**

Relative high intra-fraction setup errors of 2.4 and 2.2 mm systematic and random in the LR direction, respectively, were found. This is twice the size of intra-fraction organ position/setup errors from abdominal/pelvic patients in supine position, where variation of 1.1 mm (1SD) was found in LR direction [21]. With small values for rotations around CC axis, patients are probably shifting to the left and right because of the lack of bony structures for stable positioning. Errors for all other directions were small and therefore of little influence on the treatment.

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

Despite the use of standardized bladder instructions still a large variation in bladder filling between patients and fractions was found, which is consistent with the literature [22]. The bladder volume was comparable between men and women, but the in-patient variation was larger for female patients with a relative volume SD of 0.63 (versus 0.42 for males). Previous studies have shown a clear relationship between dose to the small bowel and toxicity [9–11]. Therefore it is still important to aim for a full bladder, as it prevents the small bowel from entering the high dose region. The patients were instructed to drink 250 ml of water 1 h before treatment, which might be insufficient for a real full bladder. Increasing the amount to drink will increase the average volume, but the day-to-day variation might also increase. Patient tolerance needs to be investigated to find the optimum amount to drink.

With a treatment time of 5 days, no time trends in bladder, rectum and MesoRect volume were expected, nor found. There was, however, a significant difference between the bladder volume on the pCT and the treatment fractions for male patients (16% reduction), which demonstrates that bladder filling instructions have a limited effect on reproducibility of the bladder volume [22].
Shape variation of the MesoRect

The systematic and random shape changes were relatively small for the lower half of the MesoRect (1–4 mm) and comparable for male and female patients. In the upper-anterior part of the MesoRect, however, substantial shape changes were observed (up to 7 mm) that were different between male and female, with systematic and random errors up to 3 mm smaller for male patients. These differences are likely due to differences in anatomy: the anterior border in this region is determined by the uterus in females, while in males this border is determined by the bladder wall (full bladder) or small bowel (empty bladder). The uterus position and shape can change several centimeters from day-to-day, as shown in a MR-based study on cervical cancer patients [23]. These anatomical differences are likely to influence the shape variability of the MesoRect.

The location and magnitude of the systematic and random errors at the anterior side of the MesoRect are comparable to the findings of 8 mm SD at 6–8 cm from the anus as found in a study by Nuyttens et al. [17].

Bladder/rectum volume correlation with MesoRect shape changes

Rectum volume changes were found as the major cause of changes in the shape of the MesoRect. For irradiation of prostate cancer patients introduction of a diet and mild laxatives have been shown to reduce the variation in filling of the rectum [24]. With large rectal volume correlation values of 70% and 50% in large areas for male and female patients, diet and mild laxatives might be helpful to reduce the systematic and random errors in MesoRect shape. Whether the bowel regimen is tolerable for rectal cancer patients, with already severe bowel dysfunction, remains to be seen.

It is interesting to see that a change in rectal filling has an effect on the MesoRect at a more cranial level in male patients compared to female patients, typically above the prostate. During irradiation of prostate patients, generally in supine position, the position of the prostate is mostly influenced in AP and CC direction by changes in rectal filling. The lack of correlation between changes in rectal filling and shape changes of the MesoRect adjacent to the prostate for patients in prone position might be caused by prostate movement in CC direction, because the prostate cannot move into the pubic bone.

Low correlation values between bladder filling and MesoRect deformation for male patients were found. In this group, about half of the bladder was located more cranially than the delineated MesoRect. An increase in bladder volume for male patients seems to have an effect on the upper half of the bladder, and therefore hardly have any effect on the shape of the MesoRect. For female patients, more than 80% of the bladder was located at the level of the MesoRect. In this group, somewhat higher correlation values up to 40% between bladder filling and MesoRect deformation were found, but these values were scattered in small islands all over the map. The uterus, which is located between bladder and MesoRect, seems to dim the effect of an increase in bladder filling on the MesoRect shape. The asymmetry for bladder correlation in female patients in the upper anterior region was not statistically significant.
As shown in this study the full bladder protocol leads to a large day-to-day volume variation. Due to the small correlation between bladder volume changes and MesoRect shape changes, the large day-to-day variation has a limited effect on changes of the target volume. The full bladder protocol is therefore feasible to use, as it mainly affects the dose to the small bowel. The use of a full bladder protocol with larger volumes to drink might increase the correlation with the shape of the MesoRect and should be investigated when the protocol is going to be changed.

### Table 6.4: Margin calculation table, with the base of the bladder as divider for upper and lower MesoRect

<table>
<thead>
<tr>
<th>Millimeters</th>
<th>Male Anterior</th>
<th>Male Posterior</th>
<th>Male Lateral</th>
<th>Female Anterior</th>
<th>Female Posterior</th>
<th>Female Lateral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deformation Upper half</td>
<td>4.9</td>
<td>1.4</td>
<td>3.3</td>
<td>6.6</td>
<td>2.2</td>
<td>3.8</td>
</tr>
<tr>
<td>Deformation Lower half</td>
<td>3.3</td>
<td>4.1</td>
<td>2.7</td>
<td>3.2</td>
<td>3.7</td>
<td>3.1</td>
</tr>
<tr>
<td>Setup, inter-fraction</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Setup, intra-fraction</td>
<td>0.6</td>
<td>0.6</td>
<td>2.4</td>
<td>0.6</td>
<td>0.6</td>
<td>2.4</td>
</tr>
<tr>
<td>Inter-observer delineation</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Margin Upper half</td>
<td>17</td>
<td>10</td>
<td>15</td>
<td>23</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>Margin Lower half</td>
<td>14</td>
<td>15</td>
<td>14</td>
<td>13</td>
<td>14</td>
<td>15</td>
</tr>
</tbody>
</table>

**Margins**

It is not straightforward to combine shape variability with rigid setup uncertainties into a required PTV-margin. Margin recipes described in the literature [25] generally assume translations of rigid bodies. The MesoRect, however, is a deforming organ, and only deformation extending outside the original MesoRect can lead to a reduction of coverage. To get a first-order approximation of the required margins the margin recipe of $2.5\sum + 0.7\sigma$ was applied [25].

In order to develop usable clinical margins the systematic and random error maps were divided into six regions with each a representative value. 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. Although there is some asymmetry between left and right, the differences are not significant ($p > 0.1$), therefore left and right could be joined to lateral.
Chapter 6

The deformation errors were combined with other uncertainties to put them in a clinical perspective. Besides the intra-fraction errors from table 6.2, an estimate of the residual inter-fraction setup error (1 mm) and an optimistic estimate of the inter-observer variation (3 mm) were used [13] (Table 6.4). The calculated margins provide a clear rationale for anisotropic margins that vary in the AP direction along the CC axis and between male and female patients.

The hypothetical margins are larger than the clinically used PTV margins. This was already partly taken into account in clinical practice by including up to 1 cm of the bladder, prostate, uterus and/or cervix in the CTV and adding a 1 cm PTV margin on top of that. With the results of this study the CTV could be delineated according to the anatomy, reducing the observer dependency, and a more sufficient PTV margin could be added on top of that.

Limitations of the study
This study was performed on a dataset of 27 patients divided into two groups of 17 and 10 patients, respectively. Determination of systematic and random errors on a group of 10 patients gives a reasonable, but not definite estimate of the errors. Larger studies are required to improve the statistical power of the analyzed variations. The study does, however, give a good estimate of the order of magnitude and especially the heterogeneity of systematic and random errors for shape variation.

Although delineation was only done by a single observer, all delineations were supervised by an oncologist, thereby minimizing the observer variation. In addition, the delineation of the pCT was used as a guideline for the CBCT delineations. Choices made on the pCT were therefore also applied on the CBCT scans (especially the cranial and caudal border of the MesoRect). Therefore, a minor influence from intra-observer variation can be expected on the size of the found systematic and random deformations.

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 clinical CTV is defined by the presacral- and iliac-lymph node areas. Variation in the position of the iliac vessels is usually limited [17] and the presacral lymph nodes are located adjacent to the bony anatomy, thus corrected by online setup corrections. Therefore, variation in the clinical CTV beyond the MesoRect can be expected to be smaller than the measured deformations. This is supported by the position of the maximum systematic error area, which is located approximately 1 cm away from the cranial border (Fig. 6.2 a & c). This suggests that the maximum systematic error for the clinical CTV has been found within our MesoRect study. Because of the high impact of systematic errors on the required treatment margins compared to random errors the described margins (Table 6.4) are probably not going to be larger in a full CTV shape variation study.

The margin recipe used in the discussion is not developed for shape variation of target volumes. Because shape variation only has an effect on target coverage when extending outside the original shape an overestimation of the required margins was expected. To validate the calculated margins on the dataset a retrospective analysis was performed, using the six representative values of the systematic- and random-error maps to calculate PTV margins for deformation only. This yielded coverage of 99.6%
of the MesoRect volume during the treatment. Dosimetric coverage would be close to 100% because there is a dose gradient at the edge of a PTV, therefore $2.5 \times \Sigma$ to account for MesoRect deformation overestimates the margins needed.

The use of a 250 cc drinking protocol led to an average bladder volume of 200 cc with a lot of day-to-day variation. The use of an increased drinking protocol should be investigated to aim for real full bladders.

Future studies with multiple observers, repeat-CT data and a correct margin recipe will provide full insight on these matters. Until then, this study provides insight into the magnitude of shape variation which should be taken into account in the development of appropriate CTV to PTV margins.

Clinical application
As described in the limitations, the study was focused on the mesorectal part of the target volume in rectal cancer patients. The total CTV extends further to the lymph node areas described. Since shape variation is limited in these regions [17] the current clinical margin of 1 cm seems to be sufficient in these regions. To apply the results of this study in the clinic the CTV should be split up in a mesorectal part and a lymph node part. If the mesorectal CTV would be delineated according to definition, a large volume reduction could be obtained, because currently the CTV delineation is very generous in our clinic. With the found shape variation, PTV margins will increase, but on the whole we expect planning target volumes to be more consistent and equal or smaller in volume compared to the current clinical situation.

Conclusions
In conclusion, we found substantial, heterogeneous and anisotropic deformation of the MesoRect. As a result, the PTV margin should be differentiated in position on the cranio-caudal axis and in anterior–posterior direction. Because deformations in female patients were found to be larger than in male patients, the PTV margin should also be differentiated for gender.

The largest influence on MesoRect deformations in this study was found to be changes in filling of the rectum. Besides deformation of the MesoRect, the large intra-fraction setup error in the left-right direction due to prone treatment needs to be included in CTV to PTV margin.

A first-order approximation of the required margins showed that when the MesoRect would be delineated according to definition, margins up to 1.7 and 2.3 cm should be applied in the upper-anterior part for male and female patients, respectively.
References


