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Repeat CT assessed CTV variation and PTV margins for short- and long-course preoperative RT of rectal cancer

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ABSTRACT

BACKGROUND

To quantify the inter-fraction shape variation of the CTV in rectal cancer patients treated with 5 x 5 (SCRT) and 25 x 2 Gy (LCRT) and derive PTV margins.

METHODS

Thirty-three SCRT with daily repeat CT scans and 30 LCRT patients with daily scans during the first week followed by weekly scans were included. The CTV was delineated on all scans and local shape variation was calculated with respect to the planning CT. Margin estimation was done using the local shape variation to assure 95% minimum dose for at least 90% of patients.

RESULTS

Using 482 CT scans, systematic and random CTV shape variation was heterogeneous, ranging from 0.2 cm close to bony structures up to 1.0 cm SD at the upper-anterior CTV region. A significant reduction in rectal volume during LCRT resulted in an average 0.5 cm posterior shift of the upper-anterior CTV. Required margins ranged from 0.7 cm close to bony structures up to 3.1 and 2.3 cm in the upper-anterior region for SCRT and LCRT, respectively.

CONCLUSIONS

Heterogeneous shape variation demands anisotropic PTV margins. Required margins were substantially larger in the anterior direction compared to current clinical margins. These larger margins were, however, based on strict delineated CTVs, resulting in smaller PTVs compared to current practice.
INTRODUCTION

The standard of care for early-stage and locally-advanced rectal cancer has evolved to preoperative short-course radiotherapy (RT) followed by a total mesorectal excision (TME) and long-course chemoradiotherapy (CRT) followed by a TME, respectively\(^{24,26,90,98,99}\). The side-effects of RT can be reduced by advanced treatment delivery techniques such as intensity modulated RT (IMRT)\(^{100,101}\). To assure clinical target volume (CTV) coverage with IMRT a proper planning target volume (PTV) margin should be applied accounting for all geometric uncertainties. The known dominant uncertainties in RT of rectal cancer are CTV shape- and delineation-variation with systematic and random errors up to 1 cm SD. Despite the size and impact of these uncertainties, only few publications are available describing them\(^{102-108}\), with the limitation of small numbers and only a part of the CTV investigated. Furthermore, there is no recipe available to calculate the required PTV margin to account for these variations. Available margin recipes are only valid for translations of rigid CTV structures\(^{64,109}\). In clinical practice often a too small uniform 1 cm PTV margin is used, for which the radiation oncologist often delineates the CTV generously to compensate for shape variation\(^{106}\).

The purpose of this study was to evaluate the shape variation of the clinical target volume in both early- and advanced-stage rectal cancer and to establish subsequent planning target volume margins. The data were gathered in a prospective repeat CT (rCT) study.

PATIENTS AND METHODS

PATIENTS, SCANS AND TREATMENTS

The study was initiated in the Netherlands Cancer Institute (NKI) and expanded to the Leiden University Medical Centre (LUMC). For patients with short-course RT (SCRT) of 5 x 5 Gy, daily rCT scans were acquired. For patients with long-course RT (LCRT) of 25 x 2 Gy, daily rCT scans were acquired in the first week followed by weekly scans. The study was designed to include 40 SCRT and 40 LCRT patients, 20 male and 20 female each. Previous surgery or RT in the pelvic area and supine positioning (e.g. due to stoma) were exclusion criteria.

All CT scans were acquired in prone position, on a flat table, ranging from the L2-L3 junction to below the perineum. A rotated knee support was placed under the lower legs for immobilization. When clinically feasible, intravenous contrast enhancement was used for the planning CT (pCT) only. No rectal contrast was used. All patients received instructions to empty the bladder and subsequently drink 350 ml water 1 h before the pCT and every treatment fraction. The rCT scans were planned before the treatment fraction.

STUDY DELINEATIONS

On each CT scan the following structures were delineated: bladder, rectum, and the CTV divided into the mesorectum (MesoRect), the pre-sacral lymph node region (Presacr), and the internal iliac and
obturatorial lymph node regions left and right (LN_L, LN_R) (Figure 1). The rectum was delineated from the dentate line up to the sigmoidal curve.

The MesoRect included the sphincter complex and the mesorectum with borders defined by the external sphincter, the mesorectal fascia, and had the cranial border at the same level as the rectum. In the cranial region where the mesorectal fascia could not be identified, the anterior border was delineated 0.5 cm anterior of the rectum, excluding small bowel loops.

Figure 1: Example of the delineated structures on the planning CT of a male patient. On the left axial views at two different levels are shown, on the right a sagittal view. The delineated structures are the bladder, the rectum, the MesoRect including the sphincter complex, the presacral region and the lymph node regions left and right.

The LN_L and LN_R regions included the internal iliac, the lateral sacral, and the superior gluteal artery. The caudal border was where the obturator artery entered the obturator canal. The cranial border was the division of the common iliac artery in the external and internal artery. The borders were defined by the ureters anteriorly, the bones/muscles laterally, the MesoRect, seminal vesicles, uterus, neurovascular bundle medially.

The Presacr delineation connects the LN_L and LN_R from the cranial border of the MesoRect and includes the superior rectal artery. Small bowel loops were excluded from all delineations. All structure definitions were the same for SCRT and LCRT patients. The GTV was not delineated. All scans of a patient were delineated by one of five observers. The structures were first delineated on the pCT
and discussed among the observers and one radiation oncologist. The rCT scans were subsequently delineated after bony anatomy registration, using the pCT delineations as example.

SHAPE VARIATION

To compare the CTV shape variation between patients the following model was used. The MesoRect and Presacr delineation were added together (MesoPresacr) to create the central, cylinder-like, part of the CTV. The pCT MesoPresacr was sliced into 80 slices containing 100 equidistant dots per slice, with the first dot of each slice at the dorsal side. LN_L and LN_R were analysed separately, using 40 slices and 50 dots per slice, numbered starting at the mid-lateral side of the slices. The shape variation was calculated by measuring signed distances to the surfaces of the rCT CTVs perpendicular to the surface of the pCT delineation for each point. For each point the average distance and the standard deviation over the distances were calculated.

The assumption was made that the ordered points were comparable between patients, such that corresponding points could be used to calculate the local group mean (GM), systematic (Σ), and random (σ) shape variation by means of the average of the averages, the SD over the averages, and the root-mean-square of the SD’s, respectively. For long-course RT a normalized weighted average and SD were calculated for each patient by using a weight of 1 for the scans in the 1st week and a weight of 5 for the following scans.

MARGINS

In order to calculate the PTV margins for shape variation of the CTV, the margin recipe for rigid CTV motion of van Herk et al.\textsuperscript{64} was adapted. The aim was to define a margin recipe using the local group mean, systematic, and random shape variation surface maps assuring a minimum CTV dose (D\textsubscript{95\%}) of 95% of the prescribed dose for at least 90% of the patients. In the rigid setting the PTV margin can be calculated by
\[ m_{PTV} = \alpha \times \Sigma + \beta \times \sqrt{\sigma^2 + \sigma_p^2} - \beta \times \sigma_p + \text{GM} \] with the SD to describe the penumbra width (\sigma_p) in the pelvic area taken as 0.32 cm, \( \alpha = 2.5 \) and \( \beta = 1.64 \) to meet our demands. Adaptation of the formula was needed because in a rigid setting, systematic translations always result in a movement out of the high dose region on one side, while the other side of the CTV moves within the high dose region. The effect of systematic shape variation depends on the correlation between the shape variations on different areas of the surface of the CTV\textsuperscript{110,111}. Group mean errors are generally small and discarded, but when significant time-trends are present they can be included by simple adding to the PTV margin, taking the margin directions into account.

The effect of random errors in the setting of rigid motion or shape variation is the same, namely blurring of the dose to the CTV as a local effect. For random shape variation \( 1.64 \times \sqrt{\sigma^2 + 0.32^2} - 1.64 \times 0.32 \) was used.

To estimate the remaining unknown factor \( \alpha \), the factor was varied between 2.0 and 4.0 in steps of 0.1 resulting in 21 PTVs. Each PTV was translated into an ideal dose distribution with a homogeneous dose
and a penumbra described by $\sigma_p = 0.32$ cm, resulting in a 95% isodose line at the edge of the PTV\textsuperscript{64}. Within each dose distribution the surface dose to the CTV was accumulated by slicing each rCT CTV into 80 slices with 100 dots per slice. The dose was accumulated over the corresponding points and the $D_{\text{min}}$ was calculated for each patient. The $\alpha$-factor assuring $D_{\text{min}}$ of 95% of the prescribed dose for 90% of the patients was finally used in the adapted margin recipe.

All calculations described above were performed perpendicular to the pCT CTV surface. Most treatment planning systems are not capable of this type of expansion and use rolling ball like algorithms. To get the rolling ball expansions the shortest distance from each PTV surface to its corresponding CTV surface was calculated locally. The median distance over corresponding points in the patient groups was taken to derive the required local rolling ball PTV margin.

Finally, sub-volumes of the CTV were visually derived based on the heterogeneity of locally defined margins. For each sub-volume a clinically applicable margin was defined in orthogonal directions. The PTVs created with these margins were dosimetrically analysed by generating ideal dose distributions and accumulation of the dose over the rCT delineations. Finally, a volumetric comparison to the actual clinical PTVs, which were based on generously delineated CTVs and a 1 cm PTV margin, was done to estimate the impact of strictly delineated CTVs plus the newly derived margins in clinical practice.

STATISTICAL ANALYSIS

For all delineations the absolute volume and the volume relative to the pCT was calculated. The relative volumes were tested to be different from 1 using a 2-sided student T-test for each rCT time point. Systematic shape variation errors between the groups were compared using a 2-sided F-test on corresponding points resulting in a $p$-value surface map. The GM shape errors were tested on difference from 0 using a T-test. For random errors a 2-sided T-test was used to test the means as a surrogate for the root-mean-square. In the analysis four different groups were compared, being the male and female SCRT, and the male and female LCRT patients. Significance level was set to $p < 0.05$.

RESULTS

PATIENTS

Between October 2008 and March 2011 63 patients (40 male, 23 female) were included in the study (Table 1), 60 NKI, and three LUMC. The intended 40 female patients were not reached due to more prevalence of exclusion criteria, more refusals, and less prevalence compared to male patients.

For six SCRT patients one rCT scan was missing. For LCRT one rCT scan was missing for three patients and two female patients withdrew from the study after the 1\textsuperscript{st} and 2\textsuperscript{nd} week, respectively. This resulted in a total of 63 pCT scans and 419 rCT scans. The rCT scans were taken on average 25 min before the treatment fraction.
DELINEATED VOLUMES

The average bladder volume on the pCT was about 300 cc and comparable between the different groups (Table 2). The bladder volumes in the rCT scans were significantly smaller compared to the pCT scan, except for the first week scans of the LCRT female patients (Figure 2). A significant negative time trend in rectal volume was present in the LCRT groups, more predominant in male than in female patients (Figure 2) with a rectal volume reduction of approximately 35% at the end of treatment. The average CTV volume on the pCT was 508 cc for female patients and 580 cc for male patients (Table 2).

SHAPE VARIATION

The local GM, $\Sigma$, and $\sigma$ surface maps for each patient group were projected on the average CTV shape for visualization (Figure 3). The negative time trend in rectal volume resulted in a negative GM error at the upper-anterior border of the MesoRect for both LCRT groups. The GM error was significantly different from 0 for the male patients ($p < 0.01$) and borderline significant for the female patients ($p = 0.06$). Combining all LCRT patients resulted in a significant negative GM error of 0.5 cm ($p < 0.01$).

Table 1: Clinical and pathological characteristics

<table>
<thead>
<tr>
<th></th>
<th>5 x 5 Gy</th>
<th>25 x 2 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs) Median (range)</td>
<td>65 (44-85)</td>
<td>64.5 (44-81)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>13</td>
</tr>
<tr>
<td>Distance from anus</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>&lt; 5 cm</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>5 – 10 cm</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>&gt; 10 cm</td>
<td></td>
</tr>
<tr>
<td>Resection type</td>
<td>LAR</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>APR</td>
<td>7</td>
</tr>
<tr>
<td>cT-stage</td>
<td>T1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>0</td>
</tr>
<tr>
<td>cN-stage</td>
<td>N0</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>N1</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>N2</td>
<td>2</td>
</tr>
<tr>
<td>cM-stage</td>
<td>M0</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>M1</td>
<td>2</td>
</tr>
</tbody>
</table>

The $\Sigma$ was comparable between the groups. In general the maximum $\Sigma$, of approximately 1.0 cm SD, was found at the upper-anterior region of the MesoRect. Only for the male LCRT patients the maximum $\Sigma$ was somewhat smaller (0.8 cm SD). When comparing the male LCRT and SCRT $\Sigma$, differences
were only significant at the edges of the high variable upper-anterior CTV region of the LCRT group (Figure 4). Differences in $\Sigma$ between male and female LCRT were not significant. Random errors were comparable between the groups (no significant differences), similar in heterogeneity compared to the $\Sigma$, but slightly smaller (max 0.8 cm SD).

**Table 2:** Average volumes delineated/calculated on the planning CT (1SD)

<table>
<thead>
<tr>
<th></th>
<th>5x5 Gy</th>
<th>25x2 Gy</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Bladder</td>
<td>322 cc (204)</td>
<td>301 cc (189)</td>
</tr>
<tr>
<td>Rectum</td>
<td>116 cc (49)</td>
<td>125 cc (56)</td>
</tr>
<tr>
<td>CTV</td>
<td>509 cc (154)</td>
<td>579 cc (101)</td>
</tr>
<tr>
<td>Current clinical PTV</td>
<td>1316 cc (290)</td>
<td></td>
</tr>
<tr>
<td>Proposed PTV (Table 3)</td>
<td>1107 cc (200)</td>
<td></td>
</tr>
</tbody>
</table>

**MARGINS**

To reach a $D_{\text{min}}$ of 95% of the prescribed dose for 90% of the patients a factor $\alpha$ of 3.2 needed to be applied to the systematic errors (Figure 5). The rolling ball margins were calculated with factor $\alpha = 3.2$ for SCRT and LCRT groups separately (Figure 6), because of the difference in GM error (Figure 3) and the significant difference in $\Sigma$ error between the male patients in both groups (Figure 4). The average PTV volumes were 997 cc (1SD = 184) and 944 cc (1SD = 127) for SCRT and LCRT (p = 0.19), respectively.

The CTV was divided into six sub-regions to define more practical orthogonal PTV margins (Table 3). The sub-regions were the earlier defined LN_L, LN_R, and presacral regions, and a division of the MesoRect in the sphincter region (caudal 4 cm) and an upper and lower half of the remainder of the MesoRect.

The proposed margins (Table 3) were also applied to the dataset to re-evaluate the accumulated $D_{\text{min}}$ to the CTV, which resulted in a $D_{\text{min}}$ of 95% of the prescribed dose to 94% of the patients. The average PTV volumes were 1233 cc (1SD = 198) and 1186 cc (1SD = 131) for SCRT and LCRT, respectively.

The actual clinical PTVs that were used during treatment had an average volume of 1316 cc (1SD = 290) and 1484 cc (1SD = 285) for SCRT and LCRT, respectively (Table 2). The proposed PTVs (Table 2), adapted to the same cranial and caudal border as the clinical PTVs, were significantly smaller with an average 1107 cc (1SD = 200) and 1128 cc (1SD = 127) ($p < 0.0001$) for SCRT and LCRT, respectively (Table 2).
Figure 2: Relative bladder and rectum volume on the repeat CT scans with respect to the planning CT for the four groups. Bars indicated with a * were statistically significantly different from 1 (p<0.05 in a 2-sided z-test).
Figure 3: Left anterior view of the group mean (top), systematic (middle) and random (bottom) errors for the four groups of patients.

Figure 4: Anterior view of the systematic error for the 5x5 Gy male patients (left), 25x2 Gy male patients (middle) and the p-value results (right) of a locally calculated 2-sided f-test where only regions with systematic error differences of ≥ 0.2 cm were taken into account.
Repeat CT assessed CTV variation and PTV margins for short- and long-course preoperative RT

Figure 5: Minimum dose to the clinical target volume for the total dataset of 63 patients. This when applying $m_{PTV} = \alpha \Sigma + 1.64 \sqrt{\sigma^2 + 0.32^2} - 1.64 \times 0.32 + GM$ when applying the $\Sigma$, $\sigma$ and GM errors shown in Figure 1 for each group separately. With $\alpha=3.2$, 90% of patients assured a minimum dose of 95% of the prescribed dose to the CTV.

Figure 6: Locally defined rolling ball margins for the 5x5 Gy patients (left) and the 25x2 Gy patients (right).
**Table 3:** Required PTV margins for sub-regions of the CTV to assure a $D_{\text{min}}$ of 95% of the prescribed dose to at least 90% of the patients.

<table>
<thead>
<tr>
<th></th>
<th>Anterior</th>
<th>Posterior</th>
<th>Left</th>
<th>Right</th>
<th>Cranial</th>
<th>Caudal</th>
</tr>
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<tbody>
<tr>
<td>LN_L</td>
<td>1.5 cm</td>
<td>0.7 cm</td>
<td>0.7 cm</td>
<td>1.0 cm</td>
<td>1.0 cm</td>
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<tr>
<td>LN_R</td>
<td>1.5 cm</td>
<td>0.7 cm</td>
<td>1.0 cm</td>
<td>0.7 cm</td>
<td>1.0 cm</td>
<td>1.0 cm</td>
</tr>
<tr>
<td>Presacral</td>
<td>1.5 cm</td>
<td>0.7 cm</td>
<td>0.7 cm</td>
<td>0.7 cm</td>
<td>1.0 cm</td>
<td>1.0 cm</td>
</tr>
<tr>
<td>MesoRect upper half</td>
<td>2.4 cm</td>
<td>0.7 cm</td>
<td>0.7 cm</td>
<td>0.7 cm</td>
<td>1.0 cm</td>
<td>1.0 cm</td>
</tr>
<tr>
<td>MesoRect lower half</td>
<td>1.5 cm</td>
<td>0.7 cm</td>
<td><strong>0.7 cm</strong></td>
<td><strong>0.7 cm</strong></td>
<td>1.0 cm</td>
<td>1.0 cm</td>
</tr>
<tr>
<td>Sphincter</td>
<td>1.0 cm</td>
<td>1.4 cm</td>
<td>1.0 cm</td>
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<td>0.7 cm</td>
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<tr>
<td>LN_R</td>
<td>1.5 cm</td>
<td>0.7 cm</td>
<td>1.0 cm</td>
<td>0.7 cm</td>
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<tr>
<td>Presacral</td>
<td>1.5 cm</td>
<td>0.7 cm</td>
<td>0.7 cm</td>
<td>0.7 cm</td>
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<tr>
<td>MesoRect upper half</td>
<td>3.2 cm</td>
<td>0.7 cm</td>
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<tr>
<td>MesoRect lower half</td>
<td><strong>1.8 cm</strong></td>
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<tr>
<td>Sphincter</td>
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**DISCUSSION**

The first aim of this study was to evaluate shape changes of the clinical target volume during pre-operative RT of early- and advanced-stage rectal cancer patients. With a dataset of 483 CT scans in a group of 63 patients we have shown that shape variation of the CTV is a substantial and heterogeneous geometric uncertainty. In long-course RT a volumetric negative time trend could be found for the CTV (Figure 2), as well as a significant difference in systematic error between the male patients in both groups (Figure 4).

The second aim was to establish PTV margins for CTV shape variation. With an adapted version of the van Herk margin recipe\textsuperscript{64} it was shown that a multiplication factor of 3.2 for the systematic shape variation error could be used to reach a 95% $D_{\text{min}}$ for 90% of the patients (Figure 5). The acquired locally defined PTV margins were pragmatically translated into clinically applicable margins for sub-regions of the CTV (Table 3) with sufficient CTV coverage and smaller PTV volumes compared to clinical PTVs.

**CTV SHAPE VARIATION**

In LCRT, Nuyttens et al\textsuperscript{107} described the motion of the anterior border of the CTV, ranging from 0.4 cm SD at the anus, to 1.0 cm SD at 10 cm from the anus, which is similar to our results. Shape variation in LCRT was also described by Tournel et al\textsuperscript{108} with a mean shift of 0.2 cm (1SD = 0.7 cm) and 0.04 cm...
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(1SD = 0.4 cm) in anterior and posterior directions, respectively. These results were averaged over all measurements on the cranio-caudal axis and over all patients, ignoring the heterogeneity of shape variation and the influence of inter-patient variation. The 0.7 and 0.4 cm SD in anterior and posterior directions do confirm that shape variation is substantial and heterogeneous.

In two previous studies we investigated the shape variation of the mesorectal part of the CTV during SCRT using CBCT scans\textsuperscript{104;105}. We found heterogeneous shape variation with up to 0.8 cm $\Sigma$ and 0.7 cm $\sigma$ at the anterior part of the mesorectum. In the current study repeat CT imaging was chosen instead of CBCT, because of better image quality and the ability to investigate the entire CTV. When comparing the systematic and random SD for the same regions in the current study, results are comparable in terms of heterogeneity and size. Where systematic errors in the CBCT studies were slightly larger for female patients\textsuperscript{104;105}, differences in the current study were not statistically significant.

One major significant difference comparing the four groups was the negative time trend in rectal volume for the LCRT (Figure 2). The negative time trend in rectal volume was previously shown in repeat-CT studies on prostate cancer patients, indicating a RT dose-effect on rectal volume\textsuperscript{112;113}. The LCRT patients in the current study also received chemotherapy, which might also have influenced the rectal volume.

In addition, we found a difference in systematic errors between both male groups (Figure 4), which might be explained by a difference in tumour location. In SCRT more upper rectal tumours were present, in LCRT more low seated. When evaluating the first week scans of all 63 patients divided into low-, mid-, and high seated tumours, high seated tumours showed statistically significant larger systematic errors at the anterior side of the CTV compared to mid- and low-seated tumours (data not shown). A more elaborated multi-variate analysis is needed, since tumour stages and treatment types were differently distributed in the three groups.

MARGINS

PTV margins to account for CTV shape variation in rectal cancer patients have been previously estimated by Tournel et al\textsuperscript{108} and Brierly et al\textsuperscript{102}, for the mesorectal part of the CTV. In both papers the shape variation of the mesorectum was averaged over the cranio-caudal axis and over all patients. Doing so, the different effects of $\Sigma$ and $\sigma$ on the $D_{\text{min}}$ to the CTV were ignored, as well as the heterogeneity of systematic and random shape variation.

An important additional issue is that margins for shape variation should take the correlation of variation in different regions of the CTV into account\textsuperscript{110;111}. Attempts have been made to estimate correlation by use of principal component analysis\textsuperscript{114} and by a point distribution model based on corresponding points modelled using spherically parameterized and canonical aligned outlines\textsuperscript{115}. Due to the complexity of these models and the lack of clinical implementation we have chosen for a more pragmatic approach calculating local $\Sigma$ and $\sigma$ position variability and deriving a margin recipe by calculation of the CTV coverage.
The derived margin recipe included a ∑ multiplication factor $\alpha$ of 3.2 based on the total group of 63 patients. When estimating $\alpha$ for the 4 groups separately a range of 3.2, 2.8, 3.0, and 3.4 was found for LCRT male and female and SCRT male and female, respectively, with smaller statistical certainty. The small range of $\alpha$ with the extremes coming from the small female groups with only 10 and 13 patients suggests the applicability of the margin formula to other rectal cancer patients, but validation on a completely independent dataset is preferred. Note that applying a fixed multiplication factor to the heterogeneous systematic errors does not necessarily lead to the smallest possible PTV volumes. Increasing the multiplication factor in the least variable regions will substantially increase local coverage, while the PTV volume will only increase moderately. The gain in coverage could be used to decrease the multiplication factor in more variable regions, resulting in a larger reduction of the PTV volume.

In the current study ideal dose distributions were used to calculate CTV coverage. In clinical practice it is very hard to get the 95% isodose line on the edge of the PTV, especially in the anterior region where the horse-shoe shape results often in a somewhat broader dose distribution. The proposed clinical margins (Table 3) resulted in a 95% $D_{\text{min}}$ to 94% of the patients, which was higher than the intended 90% of patients. These results do not include intra-fraction setup errors, intra-fraction shape variation, and delineation variation. We previously described intra-fraction setup errors in SCRT being 0.24, 0.10, and 0.06 cm ∑ and 0.22, 0.10 and 0.10 cm $\sigma$ in LR, CC and AP directions, respectively. We simulated the effect of intra-fraction setup errors on the proposed clinical margins (Table 3) using a Monte Carlo simulation. This resulted in a 95% $D_{\text{min}}$ probability for 92% of simulated treatments, being closer to the intended 90%.

The difference in required margin between SCRT and LCRT patients was mainly due to the negative time trend in rectal and subsequent CTV volume in LCRT patients, for which the margin can simply be reduced.

Intra-fraction shape variation needs real-time imaging and is not easily performed. To our knowledge it has never been investigated and can therefore not be included in the analyses. However, we do assume that intra-fraction motion of the bladder and rectum is small compared to inter-fraction motion.

CTV delineation variation in rectal cancer is found to be comparable to shape variation errors when evaluating inter-observer variation. In the current study observer variation was minimized by having one observer per patient, discussion of pCT delineations before delineation of the rCT scans, and availability of the pCT delineations during rCT delineation. Intra-observer variation using this approach was previously shown to be in the order of 0.2-0.3 cm SD for delineation of the Mesorectum on CBCT scans, for which the image quality is generally inferior to CT scans.

The proposed PTV margins (Table 3) are larger than current clinical margins of 1 cm. Despite the margin increase, PTV volumes were smaller compared to the clinical PTV volumes, with 16% and 24% volume reduction for SCRT and LCRT, respectively (Table 2). A strictly delineated CTV plus larger
margins therefore resulted in a smaller PTV, compared to observer based generous delineation of the CTV plus a 1 cm PTV margin. An advantage of using strict anatomical borders instead of observer dependent generous delineations for the CTV is the possible reduction in inter-observer variation. It is important to realize that the derived results are mainly of advantage when using IMRT. With conventional 3- or 4-field conformal techniques dose outside the PTV will minimize the PTV volume reduction effect.

Another factor is that a large part of the CTV will contain only microscopic disease, at most. It is therefore questionable if the $D_{\text{min}}$ of 95% of the prescribed dose is really needed for the entire CTV. Unfortunately, it is currently not possible to define the exact GTV within the CTV. Until further advances in GTV definition have been made it is unsafe to relax the constraints on the CTV coverage.

LIMITATIONS OF THE STUDY

The study is based on rCT data taken on average 25 minutes before the actual treatment fractions resulting in significantly smaller bladder volumes (Figure 2). In an earlier study we investigated the correlation between bladder and rectum volume changes and CTV shape variation, and demonstrated that shape variation is mainly driven by rectal filling, and not by bladder filling. Influence of the scan timing was therefore expected to be limited.

The number of female patients in the study was limited due to low accrual. Differences between male and female patients might therefore lack statistical power, as was already seen in the derivation of the $\alpha$-factor. This is, however, the largest available study so far.

In order to combine data of different patients a corresponding point model was used based on fixed amount of slices and points per structure. Variation was measured perpendicular to the surface of the reference structures. This model is dependent on the definition of the different structures. Results are therefore only applicable to rectal cancer patients where the CTV is delineated according to the guidelines in the current study. All derived results are of course not applicable to patients meeting the exclusion criteria of previous surgery or RT in the pelvic area.

CONCLUSIONS

Clinical target volume shape variation is a major geometric uncertainty both in short- and long-course radiotherapy of rectal cancer patients. The shape variation was heterogeneous, with systematic shape variation ranging from 0.2 cm SD close to bony structures to 1.0 cm SD at the anterior-cranial end of the mesorectum. To assure 95% of the prescribed dose to the CTV for 90% of the patients $m_{\text{PTV}} = 3.2 \times \Sigma + 1.64 \times \sqrt{(\sigma^2 + 0.32^2)} - 1.64 \times 0.32 + GM$ was established, where shape variation is determined perpendicular to the surface of planning CT CTV delineation. The derived margins were pragmatically translated to orthogonal margins for sub-regions of the CTV ranging from 0.7 cm margin in posterior direction up to 2.3 and 3.1 cm PTV margin at the upper anterior region of the mesorectum for long- and short-course RT, respectively. Anterior margins for long-course RT were smaller due to a significant
negative time trend in rectal volume. The proposed larger PTV margins in combination with a strict CTV delineation resulted in significant PTV reduction compared to the current clinical PTVs based on generous delineated CTVs and 1 cm PTV margin.