(Un-)certainties in radiotherapy of rectal cancer
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Adaptive radiotherapy for long course neo-adjuvant treatment of rectal cancer

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Abstract

Purpose
To quantify the potential margin reduction when using adaptive radiotherapy (ART) during neo-adjuvant treatment of locally-advanced rectal cancer.

Material and methods
Repeat CT scans were acquired for 28 patients treated with 25x2 Gy, daily during the first week, and followed by weekly scans. The CTV was delineated on all scans, and shape variation was estimated. Five ART strategies were tested, consisting of an average CTV over the planning CT and one to five repeat CTs. Required PTV margins were calculated for adapted and non-adapted treatment. The strategy with the least PTV volume over the whole treatment was selected and bowel area dose reduction was estimated.

Results
Substantial systematic and random shape variation demanded for a PTV margin up to 2.4 cm at the upper-anterior part of the CTV. Plan adaptation after fraction 4 resulted in a maximum 0.7 cm margin reduction and a significant PTV reduction from 1185 cc to 1023 cc (p<0.0001). The bowel area volume receiving 15, 45 and 50 Gy was reduced from 436 to 402 cc, 111 to 81 cc and 49 to 29 cc, respectively (p<0.0001).

Conclusions
With adaptive radiotherapy, maximum required PTV margins can be reduced from 2.4 to 1.7 cm, resulting in significantly less dose to the bowel area.
Introduction
The standard of care for patients with locally-advanced rectal cancer is pre-operative long course chemo-radiotherapy (CRT) followed by a total mesorectal excision after a waiting period of 4 to 8 weeks [1]. During 5 weeks of RT changes in bladder and rectal volume and shape occur, leading to substantial shape variation of the clinical target volume (CTV) [2-6].

In clinical practice the CTV is only delineated on a planning CT scan (pCT), and a subsequent planning target volume (PTV) margin is added to take the geometric uncertainties, such as the shape variation, into account. In the PTV margin, geometric uncertainties are divided into systematic and random errors. The systematic errors describe the average differences between what was intended to be treated and what was treated, while random errors describe the day-to-day variation. Systematic errors have a larger effect on coverage of the CTV than random errors and are therefore the major contributors to the size of the PTV margin [7,8]. Systematic errors for CTV shape variation in locally-advanced rectal cancer were estimated to be up to 1.0 cm SD [2].

Dose to the organs at risk (OARs) surrounding the CTV is dependent on the size of the required PTV margins. An approach to reduce dose to the OARs, might be reducing the PTV margins. However, this can only be done safely by estimating and correcting for geometric uncertainties, for example using image-guided RT (IGRT). However, CTV shape variation cannot be corrected using IGRT based couch corrections.

Adaptive RT (ART), as introduced by Yan et al. [9,10], is an approach to estimate and reduce systematic errors using scans from the first few treatment fractions. For CTV shape variation, the average CTV shape from the early fractions can be calculated, resulting in a CTV which is more similar to the actual CTV shape during treatment. Subsequently, a smaller PTV margin can be used for the remainder of the treatment. The reduction in PTV margin can either be used to escalate the dose to the CTV using iso-toxic OAR doses [9,10], or to reduce the dose to the OARs [11,12].

With extensive CTV shape variation, Nuyttens et al. [2] already suggested in 2002 that rectal cancer might be an ideal candidate for ART. The purpose of this study was to develop an ART schedule for neo-adjuvant treatment of rectal cancer patients, evaluate the potential margin reduction and its subsequent effect on dose to the bladder and bowel area. The data was gathered in a prospective repeat CT (rCT) study in which no ART was used.

Material and methods
 Patients, scans and delineations
A total of 28 consecutive patients treated with 25x2 Gy RT were scanned daily in the first week of treatment, followed by weekly scans. Only patients without previous surgery or RT in the pelvic area were selected.

All CT scans were acquired in prone position, on a flat table, ranging from the L2-L3 junction to below the perineum. All patients received instructions to empty their bladder and subsequently drink 350 ml water 1 hour before the pCT and every treatment fraction. The rCT scans were scheduled before treatment fractions.
On each scan the bladder, rectum, bowel area and CTV were delineated. The rectum was delineated from the dentate line up to the sigmoidal curve. The bowel area was delineated up to 3 cm cranial of the CTV. The CTV was constructed out of 4 separate regions, being the mesorectum including the sphincter complex (MesoRect), the internal iliac and obturatorial lymph node regions left and right (LN_L, LN_R) and the presacral lymph node region (Presacr). The urether left and right were used as anterior border for LN_L and LN_R. All delineations and following analyses were done after bony anatomy registration of the CT scans.

Shape variation and margins

The method for determining the shape variation was similar to earlier studies [4,5]. The PTV margin for shape variation was based on an adapted margin recipe developed using the repeat CT data in a separate study.

In summary, the following model was used. The MesoRect and Presacr delineation were concatenated (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, while LN_L and LN_R were analyzed separately, using 40 slices and 50 dots per slice. The shape variation was calculated by measuring the distance from each point to the surfaces of the rCT CTVs, perpendicular to the surface of the reference CTV. For each point the average distance and the standard deviation over the distances was calculated. Corresponding points between patients were used to calculate the local group mean (GM), systematic (∑) 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.

The margin recipe for shape variation of the CTV was an adapted version of van Herk et al. [13]. Adaptation was needed because the margin for systematic shape variation depends on the correlation between the shape variations on different areas of the surface of the CTV [14,15]. The multiplication factor which needs to be applied to the ∑, 2.5 for 3D rigid errors, was estimated to assure a minimum dose to the CTV of 95% of the prescribed dose for 90% of the patients for shape variation. In the sequel article this factor was estimated to be 3.2, resulting in a PTV margin (m_{PTV}) of:

\[ m_{PTV} = 3.2 \times \Sigma + 1.64 \times \sqrt{\sigma^2 + \sigma_p^2} - 1.64 \times \sigma_p + GM \]

with the SD to describe the penumbra width (σ_p) in the pelvic area taken as 0.32 cm.

Since shape variation was calculated perpendicular to the surface of the reference CTV, the PTV margin is also perpendicular to the surface. In order to also provide clinically applicable PTV margins a translation to non-isotropic rolling ball margins was needed. To calculate the rolling ball expansions the shortest distance from each PTV surface to its corresponding CTV surface was calculated locally. Because of the heterogeneity of CTV shape variation [2], sub-volumes of the CTV were visually derived for which differentiated clinically applicable margins were defined. The resulting PTV sub-volumes were added together, creating PTV_clin.
Adaptive radiotherapy

All following calculations using the CTV were performed for MesoPresacr, LN_L and LN_R separately. The simulated adaptation procedures consisted of a single plan adaptation during treatment, e.g. treatment was started with the CTV and PTV defined on the pCT and adapted once after which the remainder of the treatment was based on the CTV_art and PTV_art. Adaptation consisted of averaging the CTV shape over the pCT and a limited number of the rCT delineations. Five ART scenarios were calculated. In ART_1 an average CTV was calculated using the CTVs of the pCT and the 1st fraction. The shape variation with respect to the ART_1 CTV was calculated using CTV_2 to CTV_9, estimating in the residual GM, $\Sigma$ and $\sigma$ shape variation for fractions 2 to 25. The derived margin recipe for shape variation was used to calculate the PTV_ART margin for the adapted treatment plan using the residual GM, $\Sigma$ and $\sigma$ shape variation. For ART_2 the plan was adapted after the 2nd fraction using the pCT and the first 2 rCT scans, etc, etc, until ART_5 adapting after 5 fractions.

In single plan adaptation the residual errors will become smaller and smaller when the adaptation is timed later in the treatment. Ideally, the systematic error reduction would be a division by $\sqrt{n}$, with $n$ being the scans used for the average. Simultaneously, the amount of remaining fractions in which the reduced margins are beneficial also becomes smaller. To find the optimal timing the weighted average PTV volume was calculated for each ART procedure. Weighting was based on daily scans representing only one fraction, while the weekly scans represented a whole treatment week. The procedure with the least average PTV volume was selected for dosimetric evaluation of the OARs.

For the selected ART strategy clinically applicable PTV margins for sub-volumes were calculated, resulting in a total dataset of perpendicularly expanded PTV and PTV_ART, and the rolling ball PTV_clin and PTV_ART_clin.

Treatment plans and OAR dose evaluation

For a realistic estimate of the ART effect on the dose to the OARs, 7-field intensity-modulated RT (IMRT) plans were calculated for the PTV, PTV_clin, PTV_ART and PTV_clin_ART using Pinnacle (Philips Medical Systems, Eindhoven, The Netherlands version 9.0). For PTV and PTV_clin the bladder and bowel area delineation on the pCT were used as organs at risk during optimization.

For optimization of the ART plans ideally an average bladder and bowel area would be used. For calculation of an average bladder and bowel area, however, reliable models are lacking. To have the best estimate of the average bladder, the delineation of the scan with the bladder volume closest to the average within the ART procedure was selected. Kim et al. [16] showed that the dose delivered to the bowel area is highly correlated to the volume of the bladder. We therefore assumed that the scan selected for the bladder delineation could also be used for the bowel area.

All IMRT plans were calculated as in clinical practice, using direct machine parameter optimisation (DMPO) with a maximum of 35 segments, 10 MV, a minimum field size of 25 cm² and a minimum of 4 MU per segment. Field angles of 0, 50, 100, 150, 210, 260 and 310 degrees were used. All treatment plans had to satisfy ICRU-62 conditions, such
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that 99% of the PTV volume receives at least 95% of the prescribed dose of 50 Gy. Hot spots up to 107% of the prescribed dose were allowed. For the sparing of the bowel area two maximum equivalent uniform dose (EUD) objectives were initially set at a dose level of 28 and 17.5 Gy with an α of 7 and 1 and a weight of 10 and 5, respectively. These constraints were optimized per plan by adapting the dose levels until the above described ICRU conditions were met. A fixed bladder maximum EUD objective of 22 Gy with a weight of 10 and α=1 was used.

The CTV surface dose was accumulated over the rCT delineations by slicing each CTV into 80 slices containing 100 equidistant dots per slice, sampling the dose surface histogram using 8000 corresponding points. For the ART plans the fractions in which the original pCT dose would have been delivered were taken into account.

Dose accumulation should also be done for the bladder and bowel area, but models to define corresponding points are lacking. For exposure evaluation, the bladder and bowel area delineation of the scan with the bladder volume closest to the weighted average volume during the whole treatment was selected. Dose volume histograms (DVHs) were calculated for bladder and bowel area for each plan. For acute toxicity the bowel area volume receiving 15 Gy (V15) was compared [17]. For late toxicity the bowel area volume receiving 45 (V45) and 50 Gy (V50) was compared [18,19]. For the bladder the $D_{\text{mean}}$ was compared.

Statistical analysis
For the bladder, rectum and CTV 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. The GM shape variation errors were tested on difference from 0 using a T-test resulting in a p-value surface map. Finally the average bowel area V15, V45 and V50 were tested on significant difference between the PTV and PTV_ART plan and between the PTV_clin and PTV_ART_clin plan using paired 2-sided student T-tests. Significance level was set to $p < 0.05$.

Results
Patients, scans and delineations
In the dataset of 28 patients, 1 rCT scan was missing for 3 patients, resulting in a total of 277 evaluable CT scans. These rCT scans were taken on average 25 minutes before the treatment fractions. All patients had clinical T3 (25) or T4 (3) disease. Only 3 patients had clinically no nodal involvement.

The average bladder, rectum and CTV volume on the planning CT was 257 cc (1SD=169), 134 cc (1SD=46) and 556 cc (1SD=96), respectively. The bladder volumes were significantly smaller on the rCT scans, except for the first 2 fractions (Fig. 9.1). The rectal volume on the rCT scans of the 1st treatment week was on average 10% smaller than on the planning CT. A significant further decrease in rectal volume to approximately 60% of the planning CT volume was observed. This time trend resulted in a significant, but relatively smaller, reduction in CTV volume (Fig. 9.1).
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Shape variation and margins

The local GM, $\Sigma$ and $\sigma$ surface maps with respect to the planning CT were projected on the average CTV shape for visualization (Fig. 9.2). The negative time trend in rectal and CTV volume resulted in a significant negative GM at the upper-anterior border of the MesoRect of approximately 0.5 cm ($p<0.01$). The $\Sigma$ was heterogeneous, ranging from 0.2 cm SD close to the bony anatomy to 0.9 cm SD at the upper-anterior border of the MesoRect. The $\sigma$ was similarly heterogeneous, but slightly smaller than the $\Sigma$ (max 0.7 cm SD).

The locally defined rolling ball margin to assure a minimum dose of 95% of the prescribed dose for 90% of the patients is shown in Figure 3. Based on the heterogeneity of the locally defined rolling ball margins 6 sub-volumes of the CTV were visually defined for clinically applicable orthogonal expansions (Table 9.1). The sub-volumes consisted of the separately delineated LN_L, LN_R and Presacr 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 average PTV and PTV_clin volume was 993 cc (1SD=123) and 1185 cc (1SD=122).

Fig. 9.1: Relative bladder, rectum and CTV volume on de repeat CT scans with respect to the planning CT. Bars indicated with a * were statistically significantly different from the planning CT volume ($p<0.05$, 2-sided paired t-test).
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Fig. 9.2: Left anterior view of the group mean (top), systematic (middle) and random (bottom) errors with respect to the planning CT (left) and the residual errors after the five adaptive RT procedures ART_1, ART_2, ART_3, ART_4, and ART_5.
Adaptive radiotherapy

Each of the 5 ART strategies resulted in a significant reduction of the residual $\sum$ compared to no ART (Fig. 9.2). The ART strategies only slightly reduced the GM error (Fig. 9.2), due to the late occurrence of the volumetric time-trend in CTV volume (Fig. 9.1). Since residual errors reduce as more scans are taken into the ART procedure the volume of the PTV based on the residual errors is also decreasing from the ART_1 to the ART_5 procedure (Table 9.2). However, the weighted PTV volume for the whole treatment was minimized at the ART_4 strategy, for which ART_4 was selected as adaptive strategy. The locally defined rolling ball margins for ART_4 and their subsequent orthogonal CTV sub-volume were considerably reduced compared to the initial margins (Fig. 9.3, Table 9.1). The average PTV_ART and PTV_ART_clin volume was 846 cc (1SD=106) and 1023 cc (1SD=114), and both were significantly smaller than PTV and PTV_clin (Table 9.2).

Treatment plans and OAR dose evaluation

All treatment plans were clinically acceptable and coverage of the accompanying PTV was indistinguishable between plans (data not shown). The average accumulated CTV DSH was similar for PTV and PTV_ART plans, and for PTV_clin and PTV_ART_clin plans (Fig. 9.4). The minimum accumulated CTV surface dose for 90% of the patients was 94.1% and 97.1% of the prescribed dose using the PTV and the PTV_clin plans, respectively. The CTV coverage using the adaptive ART_4 strategy was not compromised, with again a $D_{\text{min}}$ of 94.3% and 97.4% of the prescribed dose for 90% of the patients using the ideal PTV expansions and the clinical rolling ball margins, respectively.
With ART, the bladder $D_{\text{mean}}$ was significantly reduced by approximately 2.7 Gy both for expanding perpendicular to the CTV surface as well as for the clinical expansions (Table 9.3). The bowel area exposure was also significantly reduced with ART, where the reduction in V45 and V50 was relatively larger than the reduction in V15 (Table 9.3).

**Table 9.1:** 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. PTV margins are described for the start of the treatment, and after plan adaptation after fraction 4

<table>
<thead>
<tr>
<th>Start of treatment (PTV_clin)</th>
<th>Anterior</th>
<th>Posterior</th>
<th>Left</th>
<th>Right</th>
<th>Cranial</th>
<th>Caudal</th>
</tr>
</thead>
<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>
<td>1.0 cm</td>
</tr>
<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>0.7 cm</td>
<td>0.7 cm</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>
<td>1.0 cm</td>
<td>1.0 cm</td>
<td>1.0 cm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Plan adaptation after the 4th treatment fraction (PTV_ART_clin)</th>
<th>Anterior</th>
<th>Posterior</th>
<th>Left</th>
<th>Right</th>
<th>Cranial</th>
<th>Caudal</th>
</tr>
</thead>
<tbody>
<tr>
<td>LN_L</td>
<td>1.0 cm</td>
<td>0.7 cm</td>
<td>0.5 cm</td>
<td>0.7 cm</td>
<td>0.7 cm</td>
<td>0.7 cm</td>
</tr>
<tr>
<td>LN_R</td>
<td>1.0 cm</td>
<td>0.7 cm</td>
<td>0.7 cm</td>
<td>0.5 cm</td>
<td>0.7 cm</td>
<td>0.7 cm</td>
</tr>
<tr>
<td>Presacral</td>
<td>1.3 cm</td>
<td>0.7 cm</td>
<td>0.5 cm</td>
<td>0.5 cm</td>
<td>0.7 cm</td>
<td>0.7 cm</td>
</tr>
<tr>
<td>MesoRect upper half</td>
<td>1.7 cm</td>
<td>0.7 cm</td>
<td>0.5 cm</td>
<td>0.5 cm</td>
<td>0.7 cm</td>
<td>0.7 cm</td>
</tr>
<tr>
<td>MesoRect lower half</td>
<td>1.0 cm</td>
<td>0.7 cm</td>
<td>0.5 cm</td>
<td>0.5 cm</td>
<td>0.7 cm</td>
<td>0.7 cm</td>
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<tr>
<td>Sphincter</td>
<td>0.7 cm</td>
<td>1.0 cm</td>
<td>0.7 cm</td>
<td>0.7 cm</td>
<td>0.7 cm</td>
<td>0.7 cm</td>
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**Table 9.2:** PTV volumes based on the residual errors and the weighted average volume for the entire treatment when using no adaptive RT or one of the 5 adaptive strategies

<table>
<thead>
<tr>
<th></th>
<th>pCT</th>
<th>ART_1</th>
<th>ART_2</th>
<th>ART_3</th>
<th>ART_4</th>
<th>ART_5</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTV for residual errors</td>
<td>993 cc</td>
<td>901 cc</td>
<td>872 cc</td>
<td>859 cc</td>
<td>847 cc</td>
<td>841 cc</td>
</tr>
<tr>
<td>PTV weighted average</td>
<td>993 cc</td>
<td>905 cc</td>
<td>882 cc</td>
<td>875 cc</td>
<td>870 cc</td>
<td>872 cc</td>
</tr>
<tr>
<td>Weighted average different with previous strategy (2-sided paired t-test)</td>
<td>n.a.</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>p=0.012</td>
<td>p=0.219</td>
</tr>
</tbody>
</table>

**Discussion**

In this first study on adaptive radiotherapy during neo-adjuvant treatment of rectal cancer we have shown the potential benefit of adaptive radiotherapy in terms of reduction in dose to the organs at risk. Systematic shape variation was confirmed to be large, with a maximum of 0.9 cm SD. Plan adaptation after 4 fractions resulted in a significant reduction in PTV volume and subsequently also in bowel area dose and bladder dose, without compromising CTV coverage.
CTV shape variation and margins
The CTV shape variation in locally advanced rectal cancer was previously investigated by Nuyttens et al. [2] for the anterior border of the CTV. They showed that the variation of the anterior border of the mesorectum ranged from 0.4 cm SD at the anus, to 1.0 cm SD at 10 cm from the anus, similar to our results. Shape variation of entire CTV including the internal iliac, obturatorial and presacral lymph node regions has, to the best of our knowledge, never been investigated, and can therefore not be compared to literature.

Margin recipes to translate shape variation of the CTV into a PTV margin are rare. Tournel et al. [3] and Brierly et al. [6] previously estimated PTV margins for the shape variation of the mesorectal part of the CTV in rectal cancer. In both papers the PTV margin was estimated to cover 95% of the shape variation, where its normal distribution was based on all measurements of all fractions and all patients together. Doing so, the effect of random and systematic errors under the presence of a realistic dose distribution is ignored, which is contradicting to the generally accepted margin recipes for rigid translations of the CTV [13, 20]. With the adjusted margin recipe provided in the current study we were able to reach an accumulated CTV surface dose of 94% of the prescribed dose for 90% of the patients, which is close to the intended 95% of the prescribed dose, confirming validity of the adapted margin recipe.

The provided rolling ball margins (Table 9.1) were taken conservatively to assure target coverage, because only shape variation was taken into account. The conservativeness of the clinical margins was also shown by an accumulated CTV surface dose of 97% of the prescribed dose for 90% of the patients. Although setup errors can be corrected online, as assumed in the current study, and intra-fraction setup errors are small compared to shape variation errors [4], they should be taken into account in the margin recipe. Further investigation is needed on how to combine the rigid setup errors with shape variation errors in a margin recipe. This is also the case for incorporation of target volume delineation errors, which were out of the scope of the current investigation.

<table>
<thead>
<tr>
<th>Table 9.3: Dosimetric parameters for comparison of the 4 treatment plans. The p-values were calculated using a paired 2-sided students T-test.</th>
</tr>
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<tbody>
<tr>
<td>Parameter</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>Bladder $D_{mean}$ (Gy)</td>
</tr>
<tr>
<td>Bowel area V15 (cc)</td>
</tr>
<tr>
<td>Bowel area V45 (cc)</td>
</tr>
<tr>
<td>Bowel area V50 (cc)</td>
</tr>
<tr>
<td>PTV$_{clin}$ (1SD)</td>
</tr>
<tr>
<td>Bowel area V15 (cc)</td>
</tr>
<tr>
<td>Bowel area V45 (cc)</td>
</tr>
<tr>
<td>Bowel area V50 (cc)</td>
</tr>
</tbody>
</table>
Fig. 9.4: Relative DVH for the bladder and the 4 defined PTVs (top), and absolute DVHs for the bowel area (bottom) using the 4 treatment plans. The DVHs for the PTVs are virtually the same and can therefore not be distinguished.
Adaptive radiotherapy for long course neo-adjuvant treatment of rectal cancer

Adaptive radiotherapy and OAR dose

The potential of ART for rectal cancer was shown by the significant reduction in $\Sigma$ using the ART_1 strategy (Fig. 9.2). By averaging the CTV of only two CT scans the maximum residual $\Sigma$ was reduced from 0.9 cm SD to approximately 0.7 cm SD, which is close to theoretically expected value predicting a reduction of $0.9/\sqrt{2}=0.64$. The ART procedures involving more scans before adaptation further reduced the residual $\Sigma$ to a maximum of 0.5 cm SD. The ideal reduction at ART_5 of $0.9/\sqrt{6}=0.37$ cm SD was probably not reached because of the time trend in rectal and subsequent CTV volumes (Fig. 9.1).

The ART_4 strategy was found to give the minimum weighted average PTV volume for the whole treatment (Table 9.2), although differences with, for example, ART_2 can be questioned on clinical relevance. The purpose of the study was to evaluate the potential PTV margin reduction using ART, for which treatment plans for the ART_4 procedure were evaluated. The bowel area dose between the reference plans on the planning CT and the ART_4 plans was significantly reduced for all relevant volume parameters (Table 9.3). Also the bladder $D_{\text{mean}}$ was significantly reduced due to the reduction of the PTV volumes in the ART plans. A translation of the reduction in bowel exposure into clinical relevance is difficult, since relationships between bowel toxicity and dose are based on exposure of the small bowel only [17-19]. In a previous study the small bowel was estimated to be somewhere between one third and half of the bowel area volume [21]. When converting the results of the current study (Table 9.3) to small bowel volumes, late toxicity endpoints, with small bowel cutoff points of 78 cc V45 and 17 cc V50 [18,19], were reduced significantly with ART_4, with the bowel area V45 reduced from 111 to 81 cc and V50 from 49 to 29 cc.

In the study rCT scans acquired on treatment days were used. An alternative approach could be to acquire multiple planning CT scans on different days before the start of treatment, and design a treatment plan using the average CTV of the dataset. The exact required PTV margins would have to be investigated, but based on the significant margin reduction already with using ART_1, these will definitely be smaller than the proposed margins using only one planning CT (Table 9.1).

This study was conducted using rCT scans, instead of, for example, cone-beam (CB) CT scans taken just prior to treatment for setup correction of the patient. The CBCT image quality is however inferior to CT scans [5], making delineation of the entire CTV challenging. In previous studies only delineation of the mesorectal part of the CTV was found to be feasible [4,5] on CBCT. Automatic contour propagation using deformable image registration could help reducing the workload of CTV delineation. This is, however, challenging in the pelvic area where bladder and rectal filling changes hamper the accuracy of deformable image registration, even when using CT to CT registration.
Limitations of the study
The ART procedures as simulated in the study, with a new treatment plan on the following fraction, would demand very high dedication in clinical practice. A more practical procedure would be to start treatment on Monday, make rCT scans during the first 4 fractions, use the remainder of day 4 and day 5 to create a new treatment plan and start with the adapted plan in the second treatment week. This approach would be more practical, but would also slightly reduce the benefit from ART.

In this study no bowel contrast was used for the planning CT or the rCT scans. Therefore only bowel areas could be delineated, instead of small bowel, which is more predictive for acute and late toxicity [17-19]. Simultaneously, dosimetric evaluation of ART was done using the bladder and bowel area delineation of the scan with the bladder volume closest to the treatment average volume, instead of a real average or full dose accumulation. To the best of our knowledge, no simple reliable procedures are available to create these averages, and we assume that the selected delineations are our best available estimate.

The study is based on rCT data taken on average 25 minutes before the actual treatment fractions resulting in significantly smaller bladder volumes (Fig. 9.1). In an earlier study we investigated the correlation between bladder and rectum volume changes and CTV shape variation [4], 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.

For the sake of patient burden and imaging dose, rCT scans were not acquired for all fractions. Estimates of the GM, and might deviate slightly from reality, but it is the best estimate available in literature.

Conclusions
With systematic and random CTV shape variation up to 0.9 and 0.8 cm SD, respectively, adaptive radiotherapy can be used to significantly reduce required PTV margins in neo-adjuvant treatment of locally-advanced rectal cancer. In the optimal adaptive radiotherapy strategy an average CTV was created based on the CTV from the planning CT and repeat CT scans during the first 4 fractions of treatment. The average CTV with a significantly reduced PTV margin could be used for the remainder of the treatment. With adaptive radiotherapy the exposure of the bowel area was significantly reduced, especially for relevant late toxicity dose levels of 45 and 50 Gy, while CTV coverage was not compromised. Further investigations are needed to balance the increased complexity with adaptive radiotherapy against the clinical relevance.
Adaptive radiotherapy for long course neo-adjuvant treatment of rectal cancer

References


