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The ART to adapt

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Publication date
2022

Document Version
Final published version

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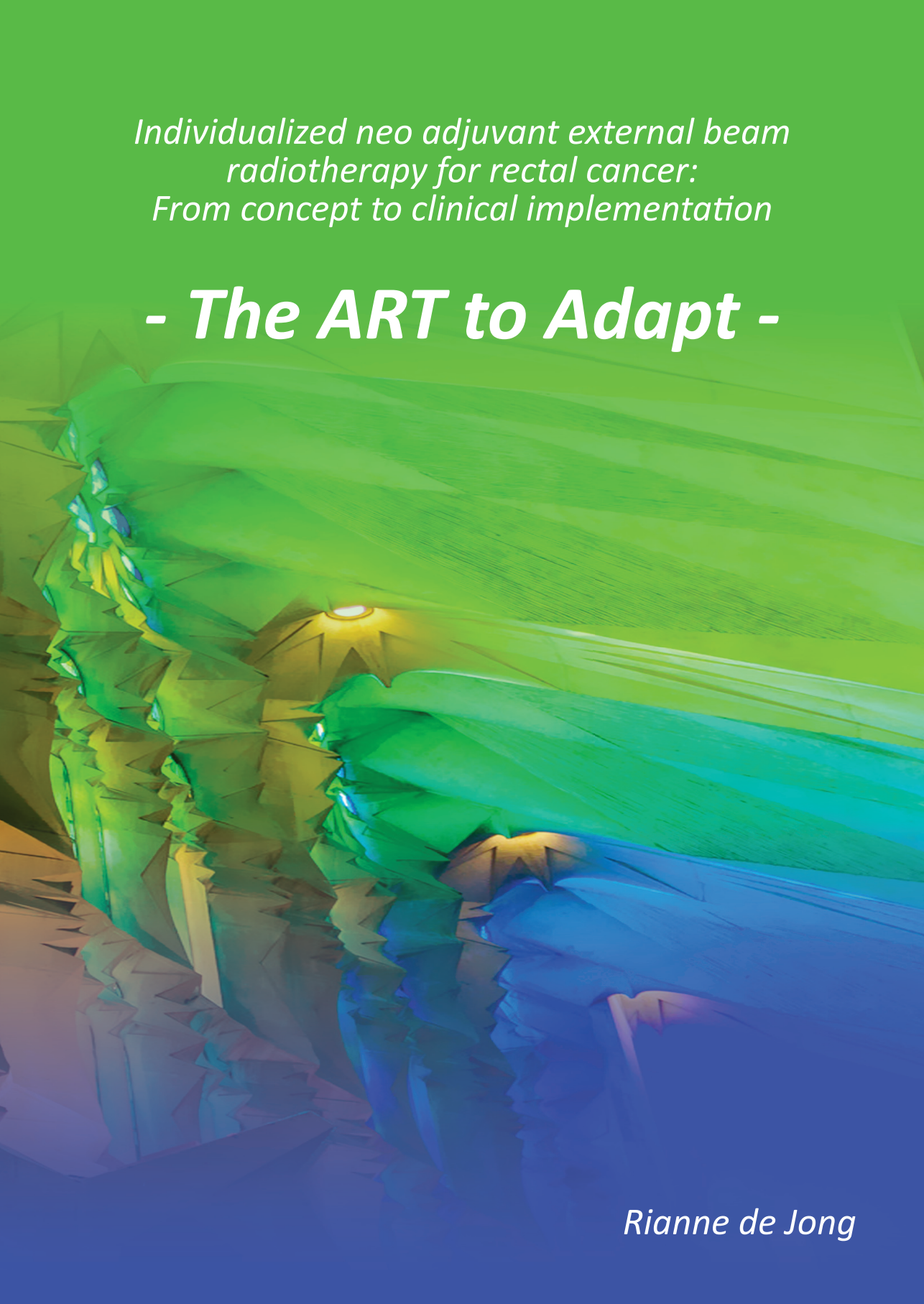

Rianne de Jong

Individualized neo adjuvant external beam radiotherapy for rectal cancer:
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Rianne de Jong

Voor Jelle en Tim

Individualized neo adjuvant external beam radiotherapy for rectal cancer: From concept to clinical implementation

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ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. ir. K.I.J. Maex
ten overstaan van een door het College voor Promoties ingestelde commissie,
in het openbaar te verdedigen in de Agnietenkapel
op woensdag 26 januari 2022, te 16:00 uur

door Maria Antonia Johanna de Jong
geboren te Roosendaal en Nispen

The research in this thesis was performed at the department of Radiation Oncology of the Amsterdam University Medical Center, location Meibergdreef, University of Amsterdam.

Printing of this thesis was financially supported by Elekta and Varian.

ISBN: 978-94-93197-95-4

Design and layout by Jeroen de Vries, jevrie@me.com
Illustratie RTT's ROCK by Elena Giusti 2021
Printing by Off Page

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Contents

Chapter 1

Introduction

Rectal cancer

Epidemiology

In Europe colorectal cancer (Fig 1) is the third most frequent cancer after lung and breast cancer with approximately 350.000 newly diagnosed patients each year [1]. In the Netherlands colorectal cancer is also the third most common cancer with around 13000 newly diagnosed cases. Approximately one third of colorectal cancers are rectal cancers and the majority of patients is over 50 years of age.

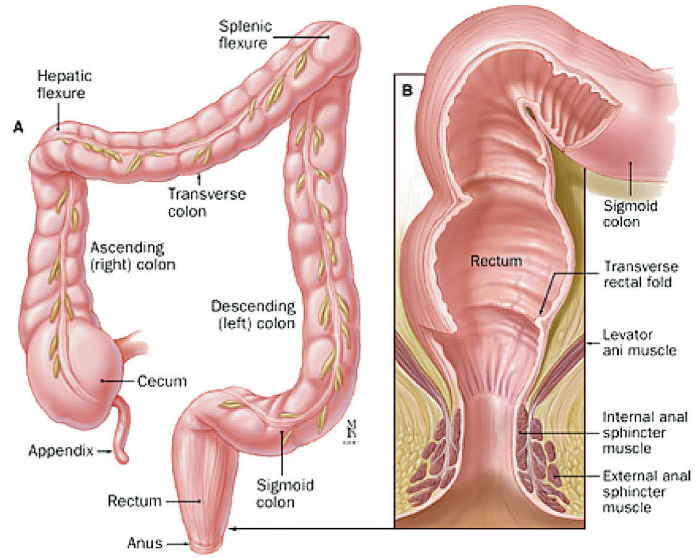

Figure 1. The rectum is part of the lower gastro intestinal tract that consists of the colon, sigmoid colon, rectum and anus (Fig 1, anatomy-medicine.com). The rectum functions as a reservoir for faeces.

The incidence of colorectal cancers has increased as a result of ageing and population growth. Changing life style, such as minimizing smoking, minimizing processed meat and alcohol intake, increasing physical activity and decreasing excess body weight, has the potential to lower incidence [2-4].

Population based screening programs for colorectal cancer have been proven to reduce mortality rate in the population aged 55-74 years and is promising to improve prognoses and decrease treatment related morbidity [2]. It also shows a potential to reduce incidence because of the efficacy of polyp removal in preventing adenomas from evolving into colorectal cancer [5]. In the Netherlands such a population based bowel cancer screening has been

implemented in 2014 [1]. Currently the ten year survival rate for patients diagnosed with rectal cancer is approximately 60%.

Tumor stages and treatment modalities

Depending on tumor stage there are different treatment options for the treatment of rectal cancer [2, 6, 7]. Rectal cancer is classified according to the TNM staging system. Tumor stage does not only depend on local tumor extension but also on location with respect to the sphincter and the peritoneal reflection, presence of positive lymph nodes, potential circumferential resection margins, mesorectal fascia involvement and extra-mural or venous invasion [2, 8]. Through shared decision making comorbidity, age and patient preference will also be factored in when deciding on a treatment option.

In general, low risk early rectal cancer (T1-3N0) can be treated locally with surgery either via local excision trans-anal endoscopic microsurgery (TEM) [9] or radical total mesorectal excision (TME) surgery [10] depending on tumor extension. The TEM procedure is minimally invasive and therefore associated with better quality of life than the radical TME surgery. Because the radical TME surgery is associated with lifelong consequences that impact quality of life there is an interest in exploring a less invasive alternative consisting of radiotherapy only combined with a surveillance policy in case of a complete clinical regression. For early rectal cancer (T1-T2) it is also an option to administer radiotherapy via contact therapy. This is a good option for patients unsuitable for surgery like elderly patients or palliative intent only, but it is scarcely available [11].

For intermediate risk resectable rectal cancer (T1-3N0, T1-3 (MRF-)N1), the consensus is to treat with short course radiation therapy (SCRT; 5 fractions of 5 Gy) followed by surgery. The added benefit of RT is mostly local control compared to surgery alone, as there is only limited evidence of improved survival [8]. Improved local control is the result of sterilizing surgery borders in case of microscopic disease but radiotherapy treatment comes at the cost of increased toxicity after surgery and also increases long term toxicity like fecal incontinence, increased bowel movement and sexual dysfunction [12].

For high risk borderline resectable or not resectable tumors (locally advanced) the consensus is to treat with long course chemo-radiotherapy (LCRT; 25 x 2 Gy) for downstaging to improve chances of complete resection. In case of comorbidity and/or high age SCRT with delayed surgery can be opted for through shared decision making [13].

Target definition

For external beam radiotherapy four definitions lie at the basis of the treatment design. The Gross Tumor Volume (GTV) is defined by the palpable and/or visible primary tumor and positive lymph nodes. The Clinical Target Volume (CTV) includes the GTV plus the surrounding tissue at risk for microscopic disease. For rectal cancer the CTV is the rectum and the fatty tissue including lymph nodes surrounding the rectum. Its borders are anatomical boundaries like muscles and fascia that form the mesorectum. Also the elective lymph nodes regions are part of the CTV, see figure 2. The Planning Target Volume (PTV) is the expansion of the CTV with a margin to incorporate all uncertainties that occur in all steps of radiotherapy. This ensures that the prescribed dose is delivered to the CTV for the majority (e.g. 90%) of patients [14, 15]. Next to the definition of GTV, CTV and PTV also Organs at Risk (OAR) are defined so radiation dose can be minimized for these structures.

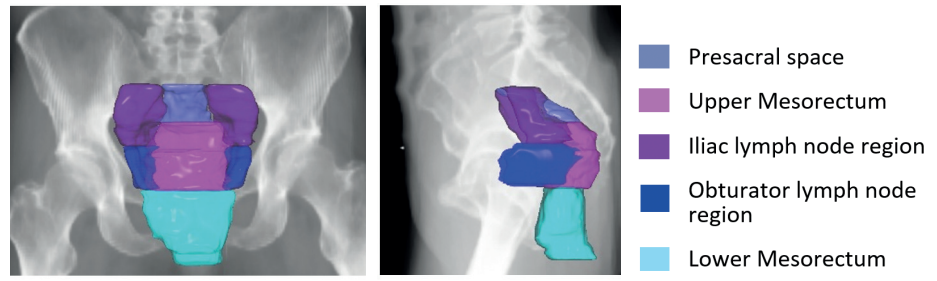

Figure 2. Illustration of the CTV for the treatment of rectal cancer.

Radiotherapy treatment

Radiotherapy treatment is a commonly used treatment modality to treat cancer, often in combination with surgery and systemic chemotherapy. Radiotherapy uses ionizing radiation to kill cells and is delivered using high-energy (MV) photons.

Radiotherapy related toxicity

Because of the physical properties of photons, when a treatment beam traverses the body, neighboring healthy tissue will always receive dose to some extent and comes at the cost of toxicity. In the treatment of rectal cancer dose to small bowel and bladder contributes largely to the toxicity [16-18]. It manifests for example in complaints of diarrhea, increased urinary frequency and/or dysuria and has an impact on quality of life [19].

The severity of toxicity correlates with the amount of dose and the volume that receives that dose; this is described in the dose-volume-effect-relationship. There are two types of toxicities: acute toxicity that occurs during treatment and/or up to three months after treatment, and late toxicity that occurs three months or later after treatment. Knowledge about the relationship between dose/volume and toxicity can be taken into account when designing a treatment plan in order to minimize toxicity. The QUANTEC papers [20] provided an overview of data on such dose volume effect relationships. For rectal cancer the prescribed dose (SCRT 5 x 5Gy and LCRT 25 x 2Gy) is not very high and usually the resulting toxicity is not directly limiting treatment compliance. Still, evidence suggests that lowering dose and volume for a range of dose levels [16, 21-24] will have a positive impact on reducing toxicity and in turn on quality of life for rectal cancer patients.

Improvements in radiotherapy

As mentioned before, to treat the majority of patients with the prescribed dose, the CTV needs to be enlarged to a PTV which directly overlaps with adjacent healthy tissue. The most efficient way of reducing dose to the healthy tissue is minimizing the total volume of the patient that receives the prescribed dose while maintaining delivery of sufficient dose to the CTV. Over the last decades this has been accomplished in two ways: by shaping the dose to the PTV and by decreasing the size of the PTV.

1) *Shaping the dose to the PTV*

Before the introduction of 3D CT scans reference images were in 2D which restricted the definition of the target volume to anatomical borders, usually bony anatomy. The actual target volume was rarely visible so treatment volumes were usually generously defined to ensure target coverage at the expense of dose to healthy tissue. The treatment planning for rectal cancer consisted of three beams encompassing the entire volume of the target, resulting in high doses to the surrounding tissue in the line of the treatment beams. Often the dose distribution was optimized in only one slice of the axial view based on only a schematic representation of the patient.

With the advent of CT scans patient specific anatomy could be visualized and used to create an individualized treatment volume. The shape of each treatment beam could be matched to the shape of the target volume and the number, direction and weight of the beams could be optimized; Conformal radiation therapy (3D-CRT). However, because of the concave shape of the target volume this only improved the dose distribution for rectal cancer marginally as represented in the green color overlay, figure 3a. With the introduction of the multi-leaf collimator, a device consisting of multiple small leafs which positions can be quickly adjusted, it was possible to create different shapes as well as vary the intensity of the beam: Intensity Modulated Radiation Therapy (IMRT), figure 3b. In figure 3c the latest technique is visualized; Volumetric Modulated Arc Therapy (VMAT). This technique enables a slightly tighter dose distribution around the PTV compared to IMRT and deposits the lower dose volumes more evenly. VMAT also allows for a much faster delivery time.

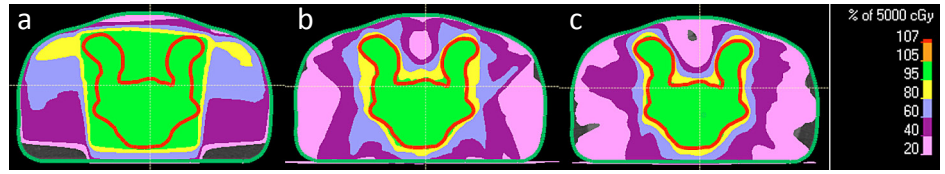

Figure 3. Illustration of dose distribution of a (a) 3 field CRT (with beams at gantry 90, 180 and 270) with in green the 95% dose volume, (b) IMRT with 7 beams and (c) dual arc VMAT in a transversal slice at the level of the upper mesorectum and obturator lymph node region. In red the PTV structure.

2) *Decreasing the size of the PTV*

The PTV is an expansion of the CTV with a margin which depends on (all) geometric uncertainties in the treatment process. Generally, the treatment process consists of three steps: (a) Definition of the CTV on a pretreatment CT scan, (b) creation of a treatment plan on the pretreatment CT scan and (c) patient positioning and delivery of the treatment in multiple fractions. Each step has uncertainties that contribute to the size of the PTV margin. In our department, the same dose is prescribed to the GTV as to the CTV, therefore definition and delineation of the GTV is beyond the scope of this thesis.

For step 1 (a), the definition of the CTV, the inter-observer delineation variation of the CTV has been reduced by improved consensus of the CTV. This was obtained by developing delineation guidelines, atlases and delineation courses which are currently available [25-30]. They allow for reduction of the variations in the definition of the CTV between patients, observers, departments and countries, which in turn helps to investigate treatment outcome.

To minimize the variation of CTV definition radiation oncologists refine the target volume they delineate on de pretreatment CT scan by using additional (imaging) modalities, each with their unique information with respect to the

boundaries of the GTV/CTV. In rectal cancer the consensus is that the radiation oncologist defines the target volume based on the combined information from rectoscopy, CT scan and physical examination [2]. MRI which has superior soft tissue contrast compared to CT is increasingly used nowadays [2]. Still, the process of defining the CTV unavoidably introduces uncertainties: the defined target volume is still not perfect as it is based on images of a tumor with imperfect resolution and the position and the shape of the target volume on the pretreatment CT scan is a snapshot in time and will have changed before the first treatment fraction as well as between treatment fractions.

For step 2 (b), the process of creating a treatment plan on a pretreatment CT scan, there have not been improvements that significantly contributed to a decrease of the PTV margins. There has been a different concept proposed that incorporates motion and uncertainties differently: robust and probabilistic optimization [31].

For step 3 (c) the introduction of in-room CT imaging in the form of Conebeam CT (CBCT) (Fig 4) enabled visualization of the patients anatomy in 3D just prior to each treatment fraction with reasonable soft tissue contrast. Registration algorithms also allowed straightforward accurate 3D to 3D registration of the CBCT scan to the planning CT scan combined with online position correction using remote table displacement. The term Image guided Radiation Therapy (IGRT) was introduced. *"IGRT increases the chance of RT being applied as planned so the intended doses are delivered to the targets"* [32]. CBCT scans also enabled online daily evaluation of target coverage. Additionally, these CBCT scans could be used to asses offline dose distribution and quantify the geometrical uncertainties necessary to calculate a (population based) PTV margin, without acquiring additional scans outside the direct scope of treatment. As stated before, an analytical decision was usually made of treating 90% of patients receiving 95% of prescribed dose [14, 15]. However, daily CBCT guidance allows to do better. The remaining 10% of the patients that would not be covered with the population based PTV margin due to larger deviations from the planning CT scan could be identified and acted upon. This was the very first step of image guidance transitioning into adaptive radiation therapy (ART).

With daily online re-planning being the ultimate goal of ART, intermediate steps of adaptation have been developed first [33]. The first concept is an adaptation using a new plan based on a new CT scan either scheduled after a certain number of fractions [34] to account for changes as a result of the treatment, e.g. regression, or triggered due to unexpected anatomical changes as

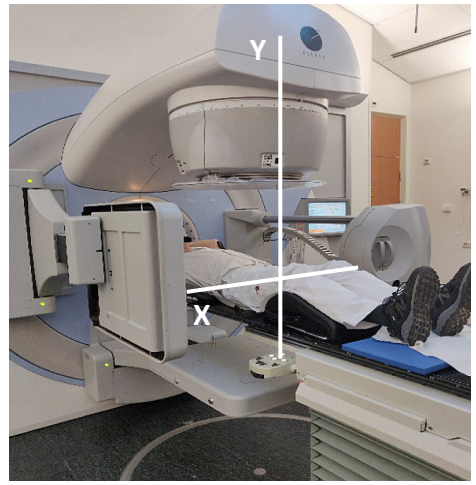

Figure 4. Image of a linear accelerator (Elekta) with on the vertical axis (Y) on the top the MV source and on the bottom the MV imager panel, on the horizontal axis (X) on the right the kV source and on the left the kV imager panel.

identified on CBCT used for patient positioning [35, 36]. The second concept of adaptation is a set of a-priori plans, i.e. plan selection. This is an approach where a number of plans are prepared in advance to account for expected changes. It is mostly applied in the pelvic region where bladder filling influences the shape and position of the target volume, e.g. bladder- and cervix cancer [37-40].

ART with daily online re-planning has only recently become a reality with the newly designed MRI linacs [41-44] and a CBCT-based linac [45, 46]. With daily online re-planning a treatment plan is created just prior to each treatment fraction taking into account all anatomical changes captured on the scan. An online adaptive workflow requires a fast delineation of organs at risk and target volume as well as rapid re-planning. Currently, the entire workflow for one treatment fraction can be achieved below 60 minutes [47, 48].

Resources in modern radiotherapy

Traditionally the radiation oncologist has been responsible for the definition of the target volume on the pretreatment CT scan. This target volume was delineated only once, or with scheduled/triggered adaptation possibly a second time. The radiation oncologist traditionally also reviews and approves the treatment plan, although in clinical practice medical physicists take responsibility as well. The entire workflow usually takes several days before start of treatment. For online ART this procedure needs to be done much

faster, rather within minutes than hours. The current solution for many departments performing online ART, either MRI- [49, 50] or CBCT-based adaptation [45, 46], is to have a multidisciplinary team present at the treatment machine, so radiation oncologists approve the adapted target volume and together with the physicist approve the adapted treatment plan. This makes online ART, next to complex, a labor and cost intensive treatment slowing down widespread implementation.

Thesis outline

The aim of this research has been to decrease the irradiated volume without compromising target coverage for neo adjuvant rectal cancer radiotherapy treatment. In turn this reduction will reduce toxicity and improve quality of life during and after treatment. This thesis describes the course of developments in the last two decades from defining appropriate population based fixed PTV margins to designing strategies to reduce these PTV margins with ultimately adaptive radiotherapy treatment by means of online re-planning.

Chapter 2 and 3 describe the quantification of the geometrical uncertainties for the CTV in both short and long course radiotherapy treatment for rectal cancer. The definition of appropriate PTV margins became extremely important with the introduction of IMRT treatment planning techniques with its highly conformal dose distribution and steep dose gradients.

Chapter 4 explores the possible benefit of a plan selection strategy where multiple margins to the upper ventral side of the mesorectum are available at the treatment machine to select from based on the patients individual anatomy. We analyzed the benefit by retrospectively simulating such a plan selection strategy for 10 short course radiotherapy patients. Such a plan selection procedure requires a multi-disciplinary approach if it comes to the design the strategy, the design of a training program, the training itself, assessing competencies of staff and evaluation of the quality of the procedure. **Chapter 5** describes the implementation procedure that was used for (RTT-led) plan selection strategy, where plan selection is based on a single pretreatment planning CT scan with variable margins to the upper ventral side of the mesorectum.

Chapter 6 retrospectively analyzes the actual benefit of the first ever treated 20 rectal cancer patients (10 SCRT and 10 LCRT) that have been treated with plan selection and compares the dosimetric consequences to the population based fixed margin.

Technical advances speed up the process of structure definition and re-planning, therefore **chapter 7** analyzes the possible benefit of online re-planning compared to plan selection.

Finally **chapter 8** describes the procedure and the feasibility for the first 10 ever treated conebeam-based online adaptive rectal cancer patients, on a ‘conventional’ but newly designed linear accelerator.

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Chapter 2

Target volume shape variation during hypo-fractionated preoperative irradiation of rectal cancer patients

Radiotherapy and Oncology 92 (2009) 202-209

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Corine van Vliet

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Abstract

Purpose: To quantify the day-to-day target volume shape variation in rectal-cancer patients treated with preoperative 5x5Gy radiotherapy.

Materials 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 deforma tion 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, 1-7mm (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 3mm larger than for males. Small correlations, r^2 0.4, were found with changes in bladder volume. Larger correlations, r^2 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 Meso-Rect 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.

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 a 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 × 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.

Materials and Methods

Patients and treatment

A total of 27 patients treated with pre-operative 5 × 5 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. 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.d.J.) and evaluated by a radiation oncologist (C.M.). For the rectum the outer wall was delineated from the dentate line up to the sigmoid colon.

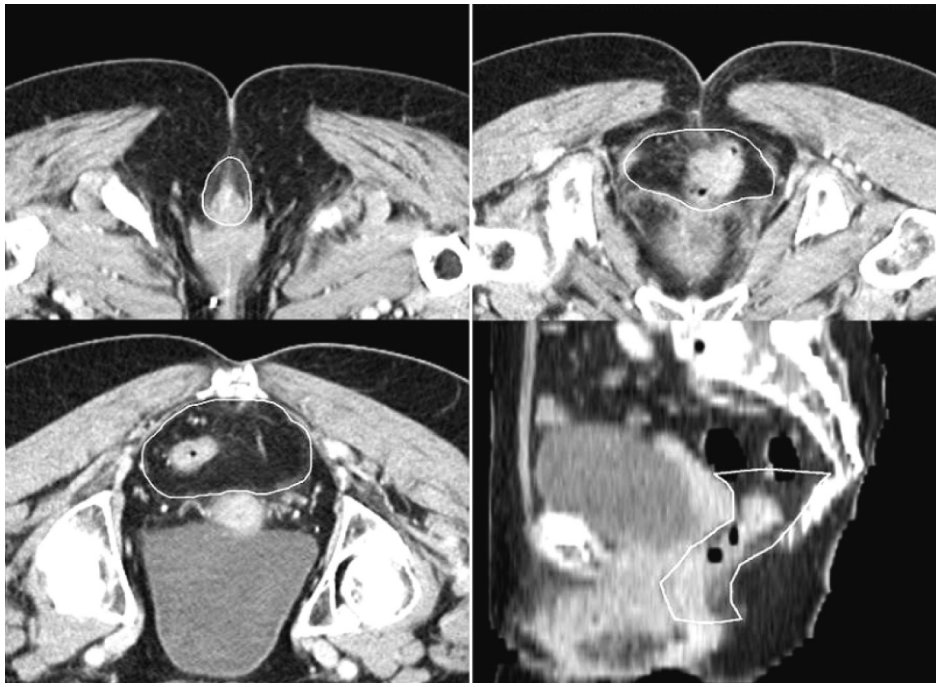

Figure 1. Example of the MesoRect delineation. In the upper-left corner the contour of the most caudal-axial slice; in the upper-right corner the middle-axial contour slice; in the lower-left corner the contour of second most cranial-axial slice; in the lower-right corner a sagittal view of the MesoRect 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 center 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 and (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

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

Table 2. Intra-fraction setup error						
	Translations (mm)			***Rotations (dg)***		
	LR	CC	AP	LR	CC	AP
M	0.0	-0.6	0.5	0.6	0.2	0.0
Σ	2.4	1.0	0.6	0.5	0.6	0.3
σ	2.2	1.0	1.0	0.5	0.6	0.2

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 $p < 0.05$.

Results

Patients

Details on patient and tumor characteristics are given in Table 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 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 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).

Table 3. Volumes of the delineated structures

	Average volume (1SD)		
	Male	***Female***	***p-value (t-test, 1sided)***
Bladder	206 cc (134)	209 cc (152)	0.44
Rectum	136 cc (49)	89 cc (32)	< 0.001
MesoRect	256 cc (53)	201 cc (36)	< 0.001

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. 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. 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. 2b 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.

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. 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. 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. 3c). The correlation between rectum volume and MesoRect shape for male patients (Fig. 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 ($p < 0.05$).

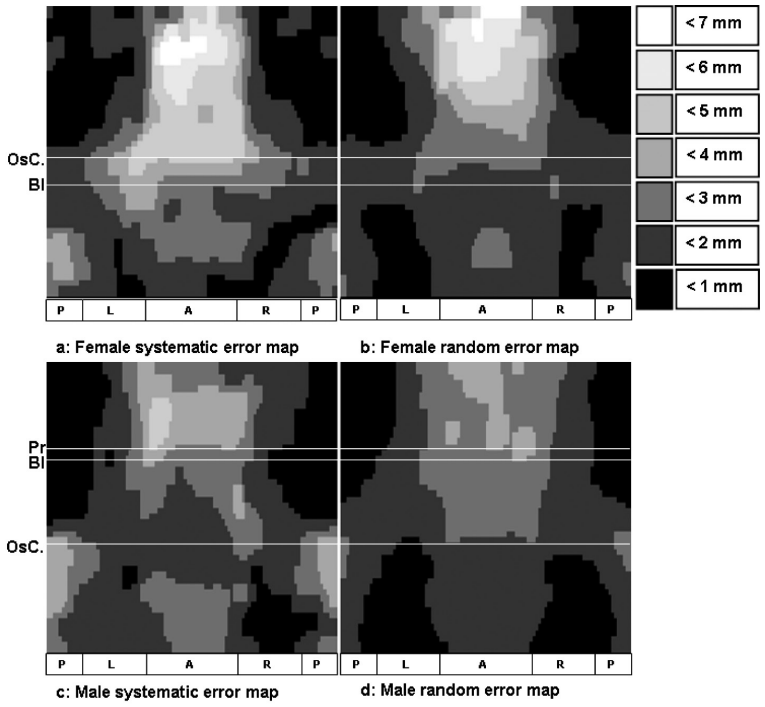

Figure 2. Systematic- and random-error maps for female and male patients. The horizontal lines in each figure depict the level where (1) the tip of the os coccyx, (2) the base of the bladder, and (3) the top of the prostate without seminal vesicles were found on average in both patient groups. The horizontal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

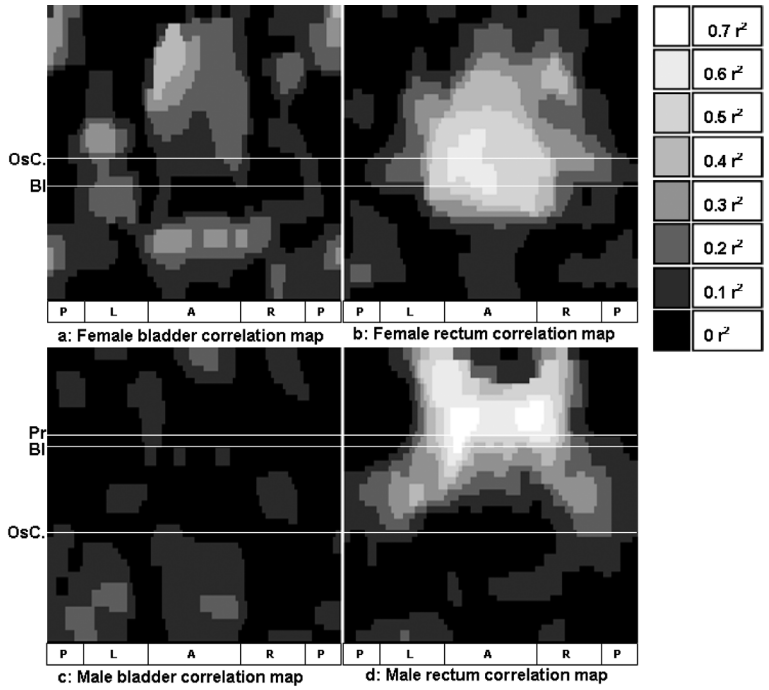

Figure 3. The r^2 correlation maps between bladder volume and MesoRect shape variation (a and c) and between rectal volume variation and MesoRect shape variation (b and d) for both female and male patients.

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 intra-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.

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 $2.5*\Sigma + 0.7*\sigma$ 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.

The deformation errors were combined with other uncertainties to put them in a clinical perspective. Besides the intra-fraction errors from table 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 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.

Table 4. Margin calculation table, with the base of the bladder as divider for upper and lower MesoRect

Millimeters		***Male***			***Female***		
		Anterior	***Posterior***	***Lateral***	***Anterior***	***Posterior***	***Lateral***
Deformation Upper half	∑	4.9	1.4	3.3	6.6	2.2	3.8
	σ	4.0	1.3	2.9	6.2	2.2	3.4
Deformation Lower half	∑	3.3	4.1	2.7	3.2	3.7	3.1
	σ	3.1	2.6	2.4	2.7	2.6	2.1
Setup, inter-fraction	∑	0.5	0.5	0.5	0.5	0.5	0.5
	σ	1.0	1.0	1.0	1.0	1.0	1.0
Setup, intra-fraction	∑	0.6	0.6	2.4	0.6	0.6	2.4
	σ	1.0	1.0	2.2	1.0	1.0	2.2
Inter-observer delineation	∑	3.0	3.0	3.0	3.0	3.0	3.0
Margin Upper half		**17**	**10**	**15**	**23**	**11**	**16**
Margin Lower half		**14**	**15**	**14**	**13**	**14**	**15**

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. 2a and 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 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*Σ 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.

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Target volume shape variation during hypo-fractionated preoperative irradiation

Chapter 3

Target volume shape variation during irradiation of rectal cancer patients in supine position: comparison with prone position

Radiotherapy and Oncology 92 (2009) 202-209

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Abstract

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

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

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

Conclusions: Shape variation of the MesoRect is substantial, heterogeneous and different between male and female patients. Differences between supine and prone orientation, however, are small. Clinical margins should be differentiated in position along the cranio-caudal axis, in anterior-posterior direction and for gender. Margins should also be increased, even when online setup correction is used. Due to the small margin differences between prone and supine treatments, the setup choice should be determined on dose to the organs at risk.

Introduction

The standard of care for primary resectable rectal cancer has evolved to total mesorectal excision (TME) surgery in combination with pre-operative (chemo-) radiation [1-5].

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

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

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

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

For organ motion/shape variation 2 studies are available, for prone setup only [17, 18]. Both studies investigated treatment schedule of 5 weeks for 10 patients each on either repeat CT or MV–CBCT. The majority of the patients in the repeat CT study [17] were treated post-operatively, while in the other study [18] shape variation was only presented averaged over all levels on the

cranio–caudal axis and averaged over all patients, which makes it difficult to translate the data into a PTV margin.

In our hospital, the lack of knowledge about the different uncertainties has led to an arbitrary uniform 10 mm CTV to PTV margin which is compensated by very generous delineation of the CTV. Parts of the cervix, uterus, bladder and prostate are included in the CTV to account for uncertainties. In the RTOG delineation atlas for anorectal cancer it is advised to include 1 cm of the back of the bladder into the CTV to compensate for day-to-day variation [19]. This incorporation of motion uncertainties into CTV generation, rather than PTV expansion, represents a conceptual break with ICRU 62 conceptual guidelines. This approach also causes large observer variation, because the border of the delineated CTV is not visible as an anatomical border. Furthermore, it is not clear if this approach leads to a sufficient PTV. Till what extent this departmental approach is also used in other hospitals is not known. Until now, treatment planning studies comparing small bowel exposure for prone and supine position used the same CTV to PTV margin for both types of setup [9-11, 20]. It is, however, not certain that the required margins are the same for both options.

In a recent study we investigated the inter-fraction shape variation of the mesorectal part of the CTV in 27 rectal cancer patients treated with hypo-fractionated RT in prone position on a flat table [13] (this study is named “prone study” in the remainder of this paper). In this study large and anisotropic shape variation was observed. Furthermore, a difference in shape variation between male and female patients was found, with variation being larger for female patients.

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

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

Materials and methods

Patients and treatment

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

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

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

CBCT acquisition

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

Delineation

Three volumes were delineated on each pCT and pre-treatment CBCT scan: the mesorectal part of the CTV, the bladder and the rectum. Due to reduced image quality in CBCT and a low expected day-to-day variation in the nodal regions [17] a sub-part of the CTV (called MesoRect in the remainder of this study) was delineated. The MesoRect encompassed the rectum and mesorectal fat starting at the dentate line up to the last CT-slice where the lateral borders of the mesorectal fascia were still visible (Fig. 1). The borders of the MesoRect were defined by the mesorectal fascia. The CBCT delineations were performed after bony anatomy registration to the pCT. During delineation on the CBCT scans, the MesoRect delineation of the pCT was available to guide the observer when necessary. All delineations were performed by one observer (R.d.J.) and evaluated by a radiation oncologist (C.M.).

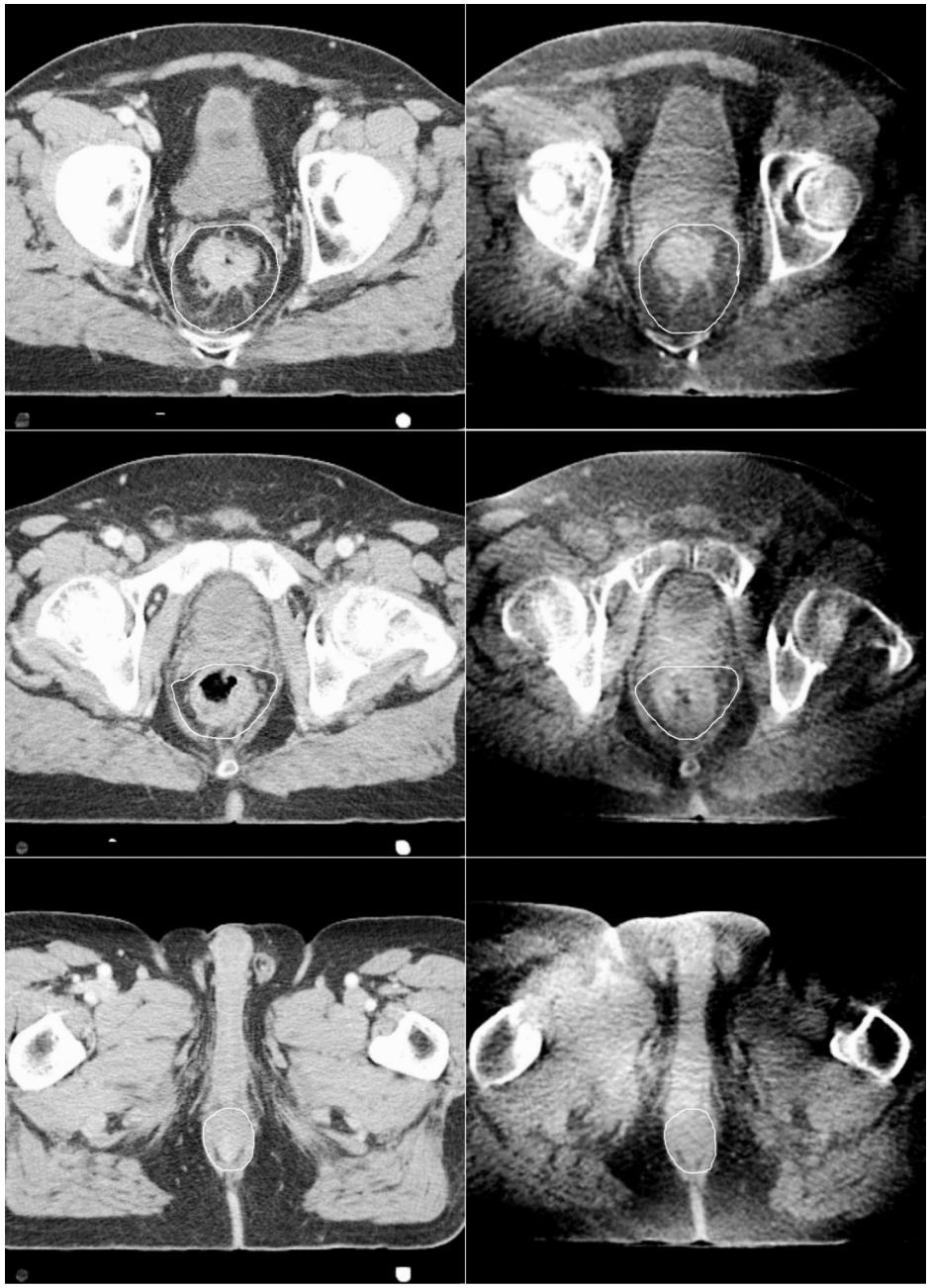

Figure 1. Example of the CT (left) and CBCT (right) delineation of the MesoRect in a superior (top), middle (cente) and an inferior slice (bottom) for one patient.

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

Volume variation in bladder, rectum and MesoRect

For the bladder, rectum and MesoRect delineations the inter-patient volume variation was calculated by taking the mean and standard deviation (SD) over all scans.
Systematic volume differences between the treatment planning and treatment delivery were derived by comparison of the volumes on the pCT and the average volumes on the CBCT scans per patient.
To evaluate the intra-patient volume variation, first the relative volumes were calculated. The relative volume was defined as the volume on the delineated scan divided by the average volume of the patient. The intra-patient variation was determined by taking the SD over these relative volumes.

MesoRect shape variation

To quantify the shape variation in MesoRect the delineation of the pCT was used as the reference structure for each patient. These reference MesoRect delineations were re-sliced on the CC axis to 50 slices, and 100 equidistant dots were placed and numbered on each slice, starting at the dorsal side of the patient. From the center of each dot on the reference MesoRect the distance to the five CBCT delineations was calculated perpendicular to the surface.
The mean and SD over the five distances was calculated for each dot and stored in 2D surface maps by virtually cutting and unfolding the delineation at the dorsal side. The horizontal axis of the maps represents the 100 equidistant dots of each slice starting at the dorsal side via left, anterior and right back to dorsal. The vertical axis of the maps represents the 50 slices on the CC axis from the anus up to the cranial border of the MesoRect.
With the mean and the SD map of each patient the systematic- and random-error maps of the total group could be calculated by taking the SD of the mean maps and the root-mean-square of the SD maps, respectively, similar to the prone study.

Influence of rectum and bladder on changes in the MesoRect shape

For each CBCT scan the bladder and rectum volume differences with respect to the volume on the pCT were calculated. The Pearson correlation coefficient was then calculated between the changes in the MesoRect shape and bladder/rectum volume for each dot on the reference MesoRect delineations yielding

two new 2D surface maps. The r^2 value of a pixel in the map represents the portion of the MesoRect shape variance that can be attributed to changes in the volume of bladder or rectum.

Intra-observer variation

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

Required margins

It is not straightforward to combine shape variability with rigid uncertainties into a required PTV margin. Since the MesoRect is a deforming organ only the changes in the shape outside the original delineated volume affect the dose to the target volume. To, nevertheless, get a first order approximation of the required margins the rigid margin recipe of $2.5 * \sum + 0.7 * \sigma$ was applied [21].
The MesoRect was divided into six regions, the upper- and lower half, divided at the base of the bladder, and anterior, posterior and lateral sides as assigned at the bottom of each map.
The shape variation errors were combined with other uncertainties to obtain a clinically relevant margin. Besides intra-fraction errors from a group of bladder cancer patients treated supine [22], an estimate of the residual inter-fraction setup error (0.5 mm systematic and 1 mm random) and an optimistic estimate of the inter-observer variation (3 mm) were used [16]. Intra-observer variation was not incorporated for margin calculation, as it only served for validation of reproducibility using only one observer.

Statistical analysis

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

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

Results

Patient characteristics

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

Intra-observer variation

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

Volume variation of bladder, rectum and MesoRect

Over all the patients, the bladder volume was comparable between male (210 ± 153 cc) and female (226 ± 154 cc) patients, while the rectum (108 ± 31 cc vs. 92 ± 38 cc) and MesoRect (226 ± 39 cc vs. 199 ± 76 cc) volume were significantly smaller for female patients ($p < 0.01$, 2-sided t-test).
The intra-patient variation was large for the bladder (range 25–338% of the patient average volume). The relative bladder volumes had a SD of 0.41 for male and 0.54 for female patients. The intra-patient variation for males and females in rectum volumes was 0.17 and 0.21 and in MesoRect volumes was 0.06 and 0.07, respectively.
For 7 patients with the 250 cc drinking protocol the average bladder volume was 184 ± 128 cc (1 SD), while for the 350 cc protocol the average was 229 ± 159 cc ($p = 0.05$, 1-sided t-test).
No significant time trends in any of the volumes were found during the 5 day course of radiotherapy.

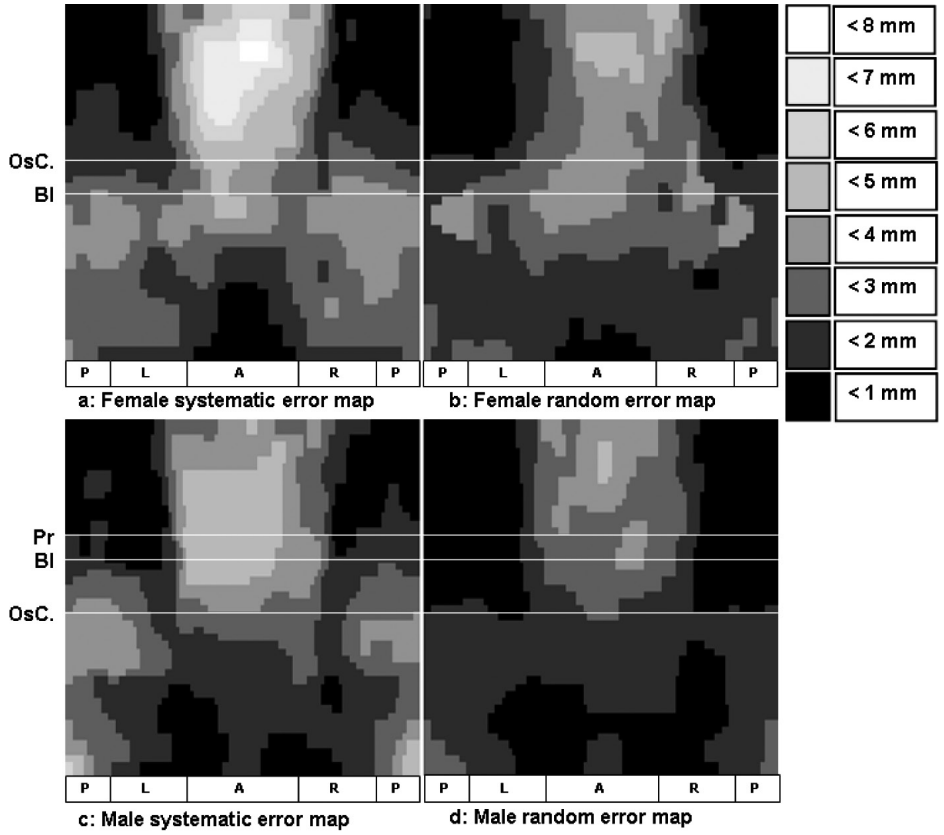

Figure 2. Systematic- and random-error maps for female and male patients. The horizontal lines in each figure depict the level where (1) the tip of the os coccyx [Osc.] (2) the base of the bladder [Bl] and (3) the top of the prostate without seminal vesicles [Pr] were found on average in both patient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

MesoRect shape variation

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

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

Required margins

An overview of the systematic and random-shape variation values in the six regions is shown in Table 1. The required margins in the lower half are approximately 16 mm in all directions for both male and female. For the upper anterior region in female patients a 24 mm margin was required, while for male patients in the same region a 5 mm smaller margin was required.

Table 1. Margin calculation table, with the base of the bladder as divider for upper and lower MesoRect

Millimeters		*Male*			*Female*		
		Anterior	*Posterior*	*Lateral*	*Anterior*	*Posterior*	*Lateral*
Deformation Upper half	∑	5.4	1.8	3.8	7.5	3.3	4.1
	σ	4.5	1.3	2.9	4.8	2.0	3.6
Deformation Lower half	∑	4.7	4.4	3.7	4.3	4.2	4.2
	σ	3.1	2.8	2.2	3.7	4.1	3.7
Setup, inter-fraction	∑	0.5	0.5	0.5	0.5	0.5	0.5
	σ	1.0	1.0	1.0	1.0	1.0	1.0
Setup, intra-fraction [22]	∑	0.5	0.5	0.5	0.5	0.5	0.5
	σ	0.6	0.6	0.9	0.6	0.6	0.9
Inter-observer delineation	∑	3.0	3.0	3.0	3.0	3.0	3.0
Margin Upper half		**19**	**10**	**15**	**24**	**13**	**15**
Margin Lower half		**16**	**16**	**14**	**16**	**16**	**16**

Influence of rectum and bladder on changes in the MesoRect shape

Changes in the MesoRect shape were mainly caused by changes in rectal volume (Fig. 3). For both male and female patients the highest correlation of 50% was found at the anterior side of the MesoRect cranial of the tip of the os coccyx. Hardly any correlation between changes in bladder volume and MesoRect shape was observed in female patients (Fig. 3a). For male patients the maximum bladder correlation was 30%, which is still a minor influence.

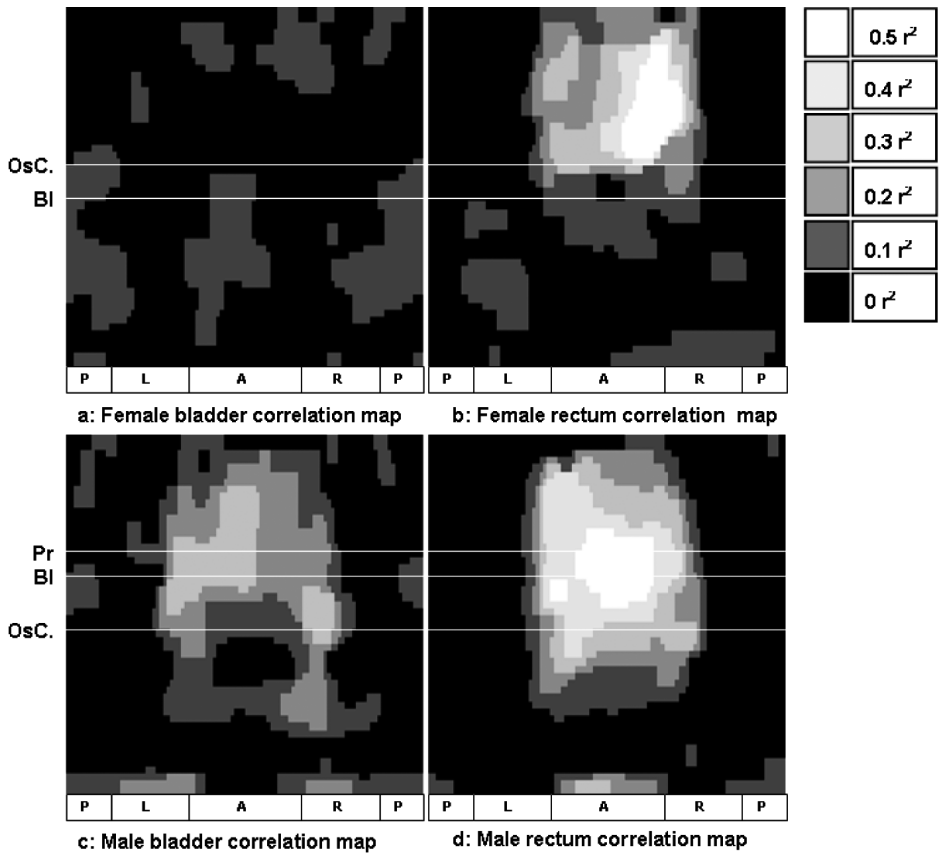

Figure 3. The r^2 correlation maps between bladder volume and MesoRect shape variation (a and c) and between rectal volume variation and MesoRect shape variation (b and d) for both female and male patients.

Comparison of results with prone study

In the current study slightly larger systematic changes in the MesoRect shape were found (Fig. 2a and c), while for female patients the random changes in shape were smaller compared to those in prone position (Fig. 2b). The maximum systematic error in male patients was 5 mm at the upper anterior side, which is comparable between prone and supine (Fig. 2c), but the region is larger and also extends inferiorly to the level of the prostate for supine setup.
The first order approximation of required margins shows slightly larger margins for supine position compared to prone position. For both types of setup the required margin at the upper anterior side of the MesoRect is approximately 5 mm larger for female patient compared to male patients.

Since patients in this study were suitable for both prone and supine orientation treatments, a comparison of data from this study with those of the prone study can be made. In Fig. 4 the systematic changes in shape in the current study and the prone study are combined to validate if differences in position and gender are significant. The systematic error map for all prone patients together (4a) is tested on significant differences (4c, 2-sided f-test) with the systematic error map for all supine patients together (4b). The same comparison has been made comparing all male patients with all female patients (4d–f). Although differences due to patient orientation are similar to the differences in gender, being in the order of 2–3 mm, the difference in the upper anterior region is mainly significant when stratifying for gender. For patient position the differences are mainly significant at the posterior side at the level of the os coccyx and at the lower-anterior region, where the magnitude of shape variation is smaller, and clinically less relevant.
The correlation between changes in rectal volume and MesoRect shape is also different between prone and supine positions in male patients. Where in prone position a change in rectal volume primarily influenced the MesoRect shape to anterior and lateral cranially of the prostate, in supine position a clear influence only towards anterior is found which also extents to the level of the prostate. For female patients the opposite is found with the highest correlation more cranially for supine orientation compared to prone orientation.

Discussion

This is the first study to evaluate the changes in the mesorectum shape, the most variable part of the CTV, in rectal cancer patients treated in supine position. In addition changes in the target volume shape between prone and supine positioning were compared, which is the main source of errors when online setup correction is used. Large systematic and random-shape variation up to 7 and 5 mm was observed. To account for different systematic- and random-shape variability in different areas of the MesoRect anisotropic margins are needed, similar to the prone study. Differences between prone and supine positions were: smaller random errors for changes in MesoRect shape in female patients treated in supine position (≤5 mm vs. ≤7 mm), and the MesoRect was also clearly more movable at the border with the prostate in male patients treated in supine position.

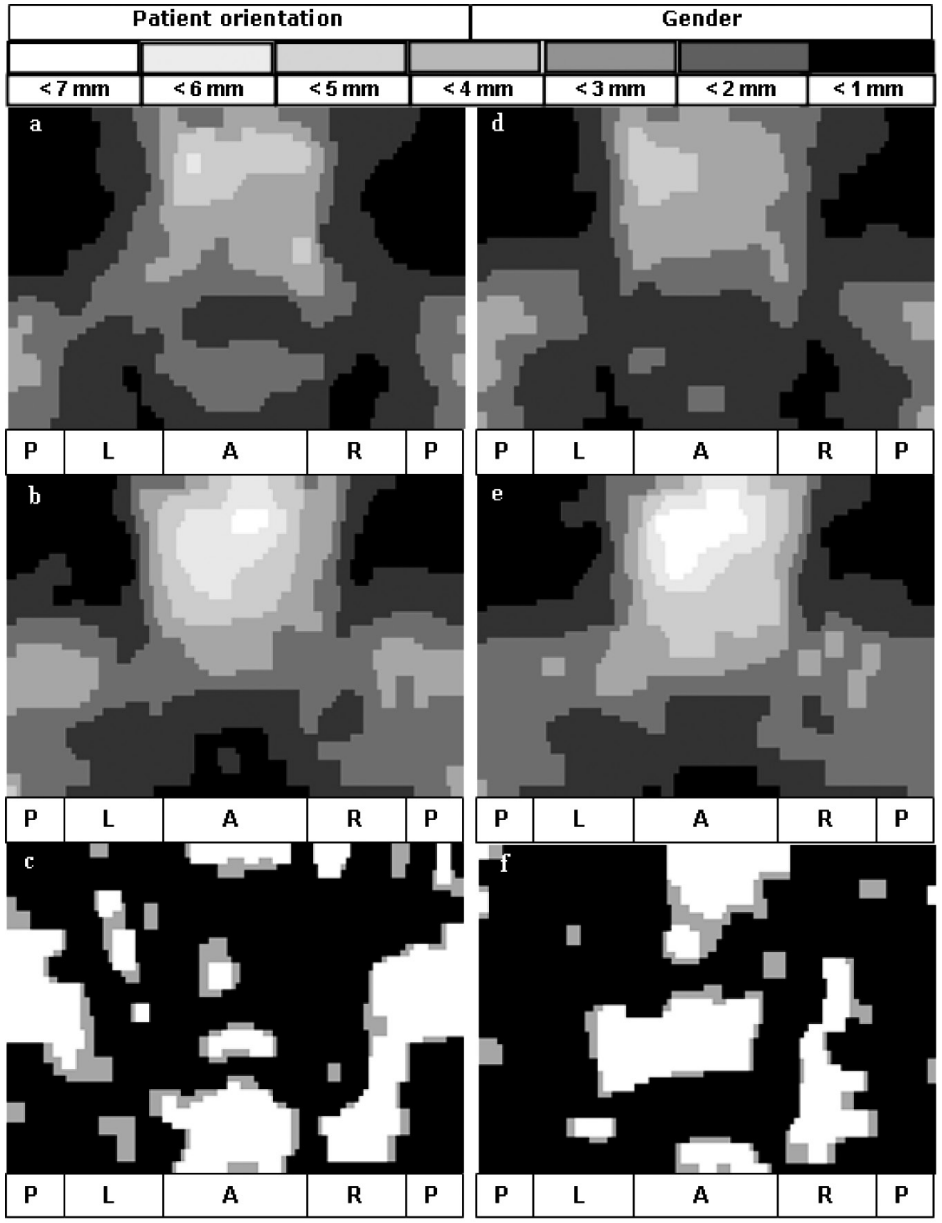

Fig. 4. Systematic error maps for prone (top left), supine (middle left), male (top right) and female (middle right) patients. Statistically significant different areas (white: $p < 0.05$, grey: $p < 0.10$, 2-sided f-test) between prone and supine are shown in bottom left and between male and female bottom right. Horizontal axis runs from posterior via left, anterior and right back to posterior. Vertical axis runs from anus up to the end of the mesorectal fascia.

Volume variation of bladder, rectum and MesoRect

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

Shape variation of the MesoRect

The MesoRect mostly deforms at the anterior side cranially from the tip of the os coccyx and, to a lesser extent, at the posterior part caudal of the os coccyx. In other regions the border of the MesoRect is adjacent to bony anatomy which prevents deformation. The upper anterior region of the MesoRect is the most clinically important region. Since in this region the difference was only significant between male and female and not between prone and supine setups (Fig. 4), PTV margins should be differentiated in gender, and not in orientation of the patient.

For male patients the change from prone to supine resulted in a larger area with the maximum systematic error of 5 mm. This area was located cranial of the prostate in prone position [13], while in supine position it is also located at the level of the prostate (Fig. 2c) suggesting that in prone setup the prostate is blocking the MesoRect from deforming because its movement is restricted by the os pubis.

Intra-observer delineation variation

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

Bladder/rectum volume correlation with changes in the MesoRect shape

Similar to patients in prone position, changes in rectum filling was found to

be the major cause of changes in the shape of the MesoRect. However, the location with the highest correlation was different between prone and supine orientations. For female patients the high rectum correlation region changed from widespread anterior and lateral at the level of the tip of the os coccyx in prone setup, to anterior-right entirely above the tip of the os coccyx in supine setup. For male patients in prone setup the rectum correlations were high at the anterior and lateral areas cranial of the prostate and to a lesser extent to lateral at the level of the prostate. In supine setup a change in rectal filling correlates best with a change in the MesoRect shape at the border with, and above the prostate (Fig. 3). These differences support the theory that the prostate is less affected by rectal filling in prone setup due to gravity and anatomy.

Margins

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

The required margins up to 19 mm and 24 mm for male and female patients are much larger than the clinically used uniform margin of 10 mm. This increase in required PTV margin, however, does not necessarily increase the PTV. The current clinical margin is applied on top of a generously delineated CTV implicitly accounting for anisotropic rectum shape variability, while in the prone and supine study the anatomical borders of the CTV were used for delineation of the MesoRect. This is illustrated in Fig. 5 with an example of a male patient

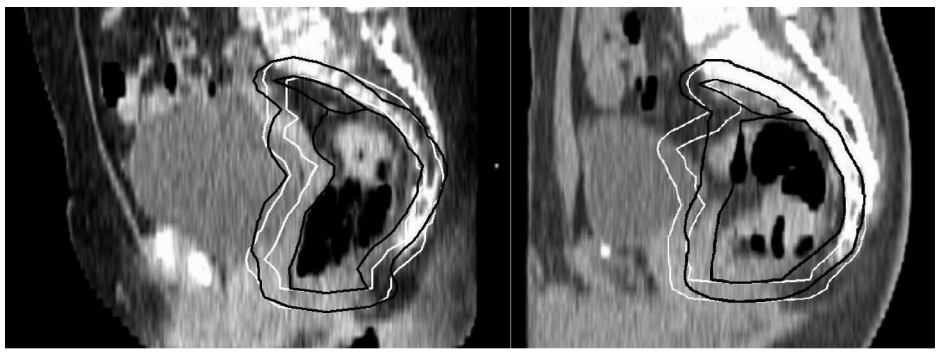

Figure 5. Examples of the CTV and PTV (white) and the mesorectal CTV, pre-sacral region and the PTV (black) based on a strictly delineated CTV plus 10 mm margin in the lymph node areas and the margins from Table 1 and the prone study on the mesorectal part for a female patient in supine position (left) and a male patient in prone position (right).

in prone position and a female patient in supine position with the CTV and PTV (white) and the CTV (MesoRect + pre-sacral region) and PTV according to this study (black), which are in the case of the female patient very close to each other, while for the male patient the new approach led to a smaller PTV at the whole anterior border.

Limitations of the study

This study was conducted on a dataset of 28 patients divided into two groups of 14 patients. Determination of systematic and random errors on a group of 14 patients gives a reasonable, but not definite estimate of the errors. The results of this study were compared to those of a similar limited study on 27 patients in prone position. Larger studies, but also studies from other hospitals, are required to confirm the results and improve the statistical power of the analyzed variations. Current study does, however, give a good estimate of the order of magnitude and especially the heterogeneity of systematic and random errors for shape variation in supine position.

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

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

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

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

Further investigation is needed to quantify if there is a difference.
Inter-observer variation potentially has a larger impact on margins needed. This is however never investigated for rectal cancer patients. Inter-observer variation studies are generally performed on planning CT scans. Since image quality differences of CT scans in prone and supine are small, inter-observer variation is expected to be similar for both types of setup. Therefore, the influence of inter-observer might be different than the assumed variation of 3 mm, but also comparable for prone and supine.

Conclusions

In conclusion, inter-fraction shape variation of the mesorectum was found to be substantial, heterogeneous and anisotropic. As a result, the PTV margin should be differentiated in position on the cranio–caudal axis, in anterior–posterior direction. Differences in shape variation are smaller for prone versus supine compared to male versus female. Therefore, margins should be differentiated for gender. The CTV to PTV margin should be increased above the standard 10 mm in combination with a strict delineation of the CTV. Since required treatment margins are similar for prone and supine when using online setup correction, decision making on patient setup can be based on dose to the organs at risk.

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Target volume shape variation during irradiation in supine position: comparison with prone position

Chapter 4

Potential dosimetric benefit of an adaptive plan selection strategy for short-course radiotherapy in rectal cancer patients

Radiotherapy and Oncology 119 (2016) 525-530

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Abstract

Purpose: An adaptive plan selection strategy can account for daily target volume variations for radiotherapy in rectal cancer patients. The aim was to quantify the daily dosimetric consequences of plan selection compared to a non-adaptive approach.

Materials and Methods: Ten patients with rectal cancer, treated with 25Gy in five fractions to the mesorectum and pelvic lymph nodes, were selected. The adaptive strategy was simulated by creating three plans per patient, with varying upper ventral PTV margins, and selecting the smallest PTV covering the entire mesorectum on every daily CBCT scan. Subsequently, mesorectum, bladder, and bowel cavity were delineated on these scans. Daily dose volume histograms were calculated for both the adaptive and non-adaptive plan, with a ventral PTV margin of 20 mm. Coverage of the mesorectum, defined as V95% > 99%, was calculated, as well as bladder and bowel cavity V95% and V15Gy.

Results: In one patient, mesorectum coverage improved. A reduction in bladder V95% and bowel cavity V15Gy was found, of 6.9% and 18.4 cm^3 ($p<0.01$), respectively.

Conclusion: Plan selection for radiotherapy in rectal cancer can improve coverage of the target volume. Overall dosimetric sparing of bladder and bowel cavity was limited but could be beneficial for individual patients.

Introduction

For patients with intermediate risk rectal cancer, preoperative short-course radiotherapy followed by immediate total mesorectal excision is the primary treatment option [1]. Short-course radiotherapy consists of five daily fractions of 5 Gy, resulting in a total dose to the mesorectum of 25 Gy. The addition of preoperative radiotherapy results in a high local control rate compared to surgery alone, but also leads to higher rates of toxicity [2-6]. It has been shown that toxicity reduces for smaller volumes of irradiated normal tissue [4, 5, 7, 8]. Several efforts to reduce the irradiated normal tissue volume have therefore been implemented, such as more conformal treatment techniques, or the use of a bellyboard when irradiating in prone position [9-11]. However, during the course of treatment substantial changes in bladder and rectum volume occur, requiring large margins to maintain coverage of the target [12, 13]. Further reducing these margins can only be achieved safely when the geometric uncertainties can be assessed and corrected for, by using daily image-guidance. This also enables the implementation of adaptive radiotherapy (ART).

Adaptive plan selection strategies have already successfully been implemented, for instance for bladder and cervical cancer [14-18]. For such strategies, multiple plans are created prior to treatment using CT scans with different bladder filling states. The daily acquired cone beam CT (CBCT) scans are used to select the best fitting plan, based on the bladder volume of that day. For rectal cancer, rectum volume is the main cause of target volume variation, which is more difficult to vary on the planning CT scan than bladder volume. An adaptive strategy based on a single plan adaptation during treatment, was described for long-course rectal cancer radiotherapy by Nijkamp et al. [19], with 25 fractions of 2 Gy. This resulted in a significantly smaller planning target volume (PTV) and simultaneous reduction in dose to the organs at risk (OARs). However, since the benefit of ART was largest with plan adaptation after the fourth fraction, this strategy is not applicable for short-course radiotherapy.

We therefore designed a novel adaptive plan selection strategy for short-course rectal cancer radiotherapy, for which multiple PTVs are created by using variable target margins for the upper-anterior side of the mesorectum, since maximum deformations are found for this part of the target volume [12, 20]. Subsequently, for each of these PTVs a treatment plan is created. By simulating this treatment strategy on patients treated previously for rectal cancer with a non-adaptive strategy, the potential dosimetric benefit of ART can be

evaluated. The aim of this study was therefore to quantify the daily dosimetric consequences of an adaptive plan selection strategy compared to a non-adaptive strategy, for short-course radiotherapy for rectal cancer.

Materials and Methods

Patients, planning CT and delineations

For this simulation study, patients treated between December 2014 and August 2015 with short-course radiotherapy for rectal cancer were selected. Standard treatment position was prone on a bellyboard, but patients were treated in supine position when pain or presence of a stoma inhibited prone position. Only patients with CBCT scans available which imaged the entire target volume were included, resulting in the inclusion of 10 patients: five consecutive patients treated in prone position, and five consecutive patients treated in supine position. Eight patients had cT2-3N0-2M0 rectum carcinoma [1] and had surgery after radiotherapy, whereas two patients were staged as cT2-3N2M1 and received palliative treatment. Further patient characteristics are presented in Table 1. Patients were treated in five fractions of 5 Gy, receiving a total of 25 Gy to the mesorectum and lymph nodes. Prior to treatment, a CT scan was acquired for planning purposes for which patients were instructed to have a full bladder, by drinking 0.5 l of water 1.5 h prior to scanning and refraining

Table 1: Patient characteristics

Patient	*Age*	*Sex*	*Position*	*Tumor stage*			*GTV location*	*Further treatment*
1	35	Female	Supine	T3	N2a	M1a	Proximal	Chemotherapy
2	67	Male	Supine	T3b	N0	M0	Proximal	LAR
3	61	Male	Supine	T2/3	N1b	M0	Proximal	LAR
4	73	Male	Supine	T3	N1	M0	Distal	LAR
5	82	Female	Supine	T3	N2	M0	Distal	LAR*
6	59	Female	Prone	T3	N1	M0	Proximal	LAR
7	55	Male	Prone	T2	N1b	M0	Distal	LAR
8	55	Female	Prone	T3	N1	M0	Proximal	LAR
9	63	Male	Prone	T3	N1b	M0	Distal	LAR
10	44	Male	Prone	T2	N2	M1	Proximal	Chemotherapy

LAR: low anterior resection. * radiotherapy with down-staging purposes, therefore prolonged interval between radiotherapy and surgery.

from voiding. On the planning CT scan, the radiation oncologist contoured the mesorectum, presacral space, internal iliac lymph node regions and, when applicable, obturator lymph node region according to the rectal cancer delineation guidelines by Roels et al. [21]. The gross tumor volume (GTV), possible pathologic lymph nodes, bladder, bowel cavity, and both femur heads were delineated as well, using RTOG guidelines [22].

Treatment planning and delivery

The planning CT scan and all delineations were imported in the treatment planning system (Oncentra, version 4.5, Elekta AB, Stockholm, Sweden). For planning and evaluation purposes, the mesorectum was divided in an upper and a lower part, for which the border was located at the CT slice showing the base of the bladder. The clinical target volume (CTV) was created by combining the delineations of the mesorectum, presacral space, and lymph node regions. To obtain the PTV, anterior margins of 20 mm and 15 mm were added to the upper and lower mesorectum, respectively, while the margin in the other directions was 10 mm. The pelvic lymph nodes were expanded uniformly with 9 mm, and the presacral space with 10 mm.

Patients were treated with a non-adaptive strategy. For this, a dual arc volumetric modulated arc therapy (VMAT) plan was created for each patient. Planning objectives were used to aim for a homogeneous fractional dose of 5 Gy in the PTV, while keeping dose to the OARs as low as possible. For each daily fraction, patients were given similar drinking instructions as for the planning CT scan. A CBCT scan was acquired daily, and registered to the pelvic bony anatomy (XVI, Elekta). The resulting setup correction was applied by shifting the treatment couch before starting treatment.

Simulation of adaptive strategy

To obtain the PTVs for simulation of the adaptive plan selection strategy, the ventral margin for the upper mesorectum was varied to be either −25 mm, −15 mm, 0 mm, 15 mm or 25 mm (Fig. 1). To reduce the treatment planning workload with regard to clinical implementation of this strategy, three margin sizes were chosen for each patient depending on bladder and rectum volume on the CT scan. The choice of plans was determined as follows: a margin of 0 mm was always selected, and it was assessed that a full bladder or empty rectum on the planning CT scan required target volumes tailored to either an emptier bladder or a more filled rectum, i.e. positive ventral margins. Conversely, negative ventral margins were required for either an empty bladder

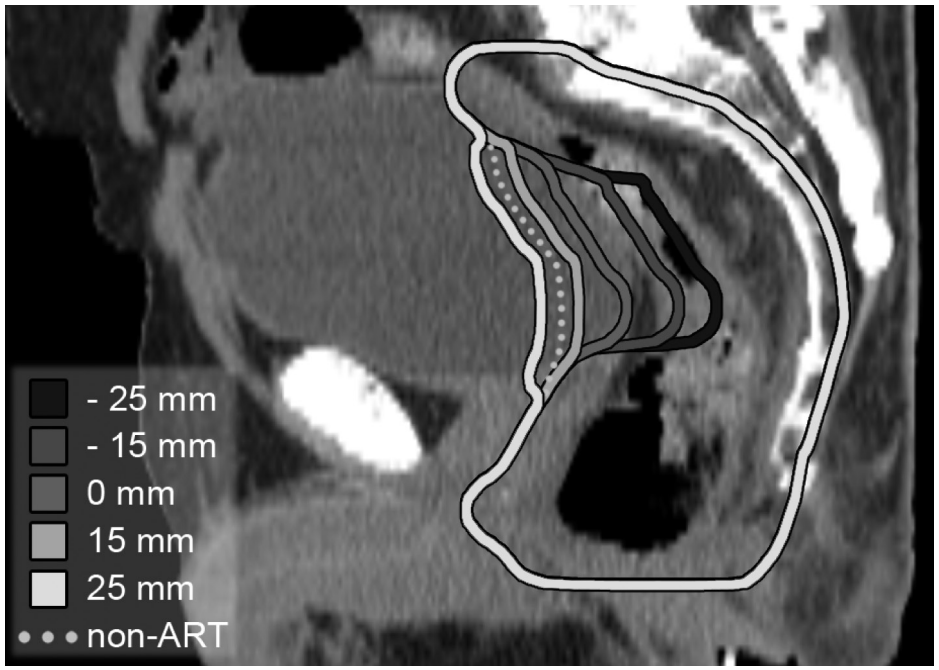

Figure 1. Different PTVs for the adaptive strategy (solid lines, representing CTV to PTV margins of −25 to 25 mm), as well as the non-adaptive strategy (dotted line) (CTV-PTV margin of 20 mm).

or full rectum on the planning CT scan. Therefore, when visual assessment of the planning CT scan showed a very full bladder or very empty rectum, the 0 mm, 15 mm and 25 mm ventral margins were selected. The 0 mm, −15 mm and −25 mm margins were selected in case of the opposite anatomy, and margins of 0 mm, −15 mm and 15 mm were chosen for mixed situations or a bladder and rectum with intermediate filling. All other CTV to PTV margins were identical to the non-adaptive treatment procedure. This resulted in three PTVs per patient, for which dual arc VMAT plans were created, similar to the non-adaptive treatment procedure. These plans were not used clinically. Plan selection was simulated by selecting the smallest PTV covering the entire mesorectum on each CBCT. Plan selections were obtained from an ongoing study regarding interobserver variability. In this study, plan selection was performed independently by a group of 20 observers consisting of physicians, radiation therapists and physicists. During a discussion session, visibility of the mesorectum on CBCT was evaluated to be sufficient for plan selection purposes and a consensus regarding the selected plan for each fraction was established.

Dose calculation and comparison

Each CBCT was resampled to the frame of reference of the CT, according to the clinically employed shift of the treatment couch, and subsequently imported in VelocityAI (version 3.1.0, Velocity Medical Solutions, Atlanta, USA). The mesorectum, bladder and bowel cavity were delineated by a single observer. For the mesorectum, the target volume delineation guidelines by Roels et al. [20] were used, whereas for bladder and bowel cavity the RTOG guidelines were followed [21, 22]. Each CBCT was in the same reference frame as the CT, therefore the dose distribution for each plan as calculated on the CT could be used to calculate the daily dose–volume histogram (DVH) for each structure, thereby disregarding possible changes in dose distribution due to anatomical variations. For each CBCT scan, daily DVHs were calculated for the non-adaptive, clinically used treatment plan, as well as the selected adaptive plan, using Matlab (version R2015b, MathWorks, Natick). For the bowel cavity, an absolute volume scale was used since the CBCT scans did not include the entire cavity.

Statistical analysis

For the upper mesorectum, bladder and mesorectum delineations, the absolute volume as well as the volume relative to the volume on the planning CT was calculated. To facilitate comparison between the adaptive and non-adaptive PTV volumes, all daily PTV volumes for the adaptive strategy were averaged for each patient. Coverage of the mesorectum was assessed by calculating the daily V95%, i.e. the volume receiving at least 95% of the prescribed daily dose. Dose to the bladder was assessed by calculating the V95% and mean dose (D_{mean}). For the bowel cavity, the V95% and V3Gy were assessed. The V3Gy corresponds to the V15Gy for 5 fractions, and will therefore be referred to as its fractionated substitute, i.e. V15Gy-fx. Similarly, the daily V95% and daily Dmean will be referred to as the V95%-fx and Dmean-fx, respectively. Since daily DVH parameters do not contain spatial information and can therefore not be directly summated, the differences in these dose parameters for the adaptive and non-adaptive strategies were calculated per fraction. Differences were tested using the Wilcoxon signed-rank test, which was also used to calculate 95% confidence intervals (CI). To summarize the findings, median dose parameter values over all fractions were calculated. A p-value < 0.05 was considered statistically significant. Statistical analysis was performed using R (version 3.1.0, The R Foundation for Statistical Computing, Vienna, Austria).

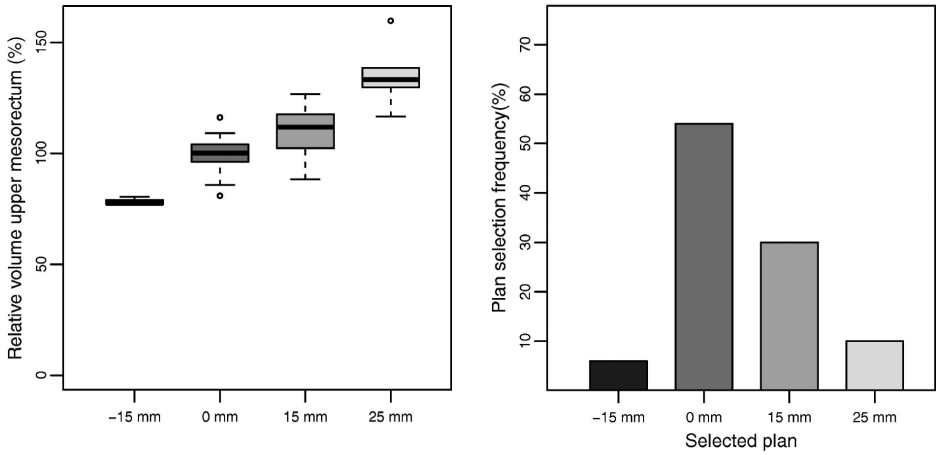

Figure 2. Top: the volume of the upper meso-rectum relative to the volume on the planning CT, for each selected plan. Bottom: frequency of plan selections.

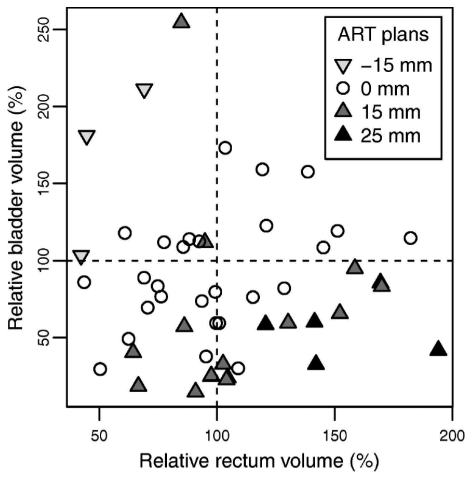

Figure 3. Plan selections for each fraction, with the respective relative bladder and rectum volume for each fraction. The vertical dotted line represents a relative rectum volume of 100%, i.e. the rectum volume during that daily fraction was the same as on the planning CT scan. The horizontal dotted line represents a relative bladder volume of 100%.

Results

Plan selection

For the adaptive strategy, the selected plan increased with increasing relative volume of the upper mesorectum (Fig. 2). The −25 mm plan was never selected, whereas the 0 mm plan was selected most often (54% of fractions) (Fig. 2 and Supplementary Fig. 1). In 40% of all fractions, a plan with a positive margin was chosen, whereas in only 6% of all fractions a plan with a negative margin was selected.

Of all plans with a positive margin, for 60% the rectum filling was larger than on the CT scan, and for 90% the bladder filling was less compared to the CT scan (Fig. 3). The three plans with a negative margin were only selected when the bladder filling was larger, and rectum filling was smaller, compared to the CT scan.

Target coverage

For the non-adaptive strategy, a mesorectum coverage ≥99% was obtained in all but two fractions for two different patients. For one of these fractions, the adaptive plan improved coverage to at least 99% of the volume. For the other fraction, the suboptimal coverage of the non-adaptive plan (97.7%) could be increased to 98.1% using the 25 mm margin adaptive plan, but not to the desired 99%.

Sparing of OARs

For both bladder and bowel cavity, the mean DVH-graph of the adaptive strategy lies below the graph of the non-adaptive strategy (Fig. 4). This illustrates that the bowel cavity V95%-fx and V15Gy-fx, as well as the bladder V95%-fx and D_{mean}-fx, were reduced significantly for ART, but the reductions were small (Table 2). The median volume of the PTV for the non-adaptive strategy was 1032 cm^3, compared to 1002 cm^3 for the adaptive strategy, resulting in a small but significant median reduction in PTV volume of 30 cm^3 (95% CI: 22–69 cm^3, $p < 0.01$) for ART.

The DVH parameters for the adaptive strategy were different for patients treated in prone or supine position (Supplementary Table 1), and showed a larger difference between both strategies. However, these patients had significantly larger bladder volumes during treatment compared to patients treated in supine position (Supplementary Fig. 2), which is most likely the cause for the difference in dose parameters [11].

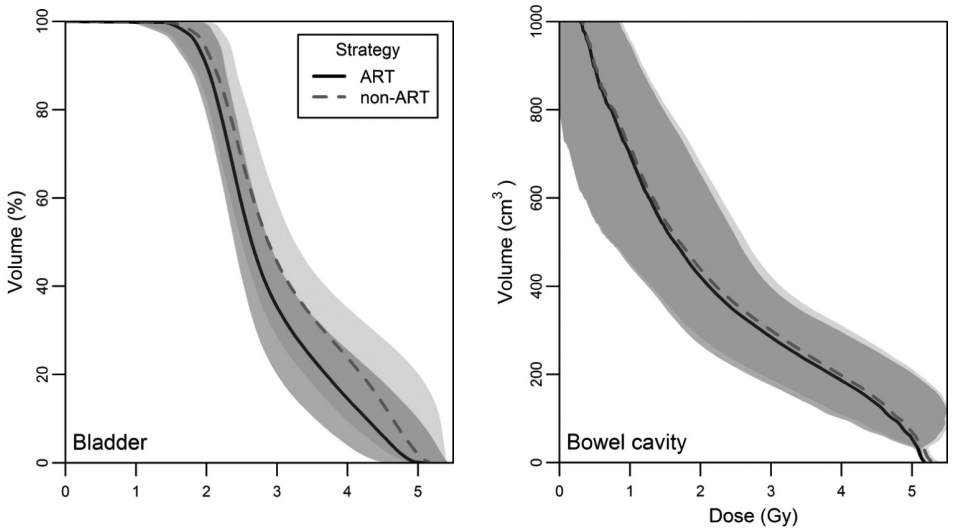

Figure 4. Mean DVH for both the adaptive strategy (solid line) and non-adaptive strategy (dotted line), for bladder (top) and bowel cavity (bottom). Shaded areas indicate the standard deviation around the mean. Mean DVHs represent a worst case scenario for the high doses, and a best case scenario for the low doses, since it is implied that volumes with equal doses are located at the same position for each fraction, which is not the case in reality.

Table 2: Differences in dose parameters for bowel cavity and bladder

		ART	non-ART	Median difference	95% CI
Bowel cavity	V95%-fx (cm^3)	184	191	8.10*	6.15 – 9.60
	V15Gy-fx (cm^3)	250	264	13.9*	13.1 – 23.1
Bladder	V95%-fx (%)	6.77	15.7	6.70*	5.13 – 8.40
	D_{mean}-fx (Gy)	2.92	3.23	0.27*	0.20 – 0.32

Median values (over all fractions of all patients) are reported.
fx = fractionated substitute of dose parameter, e.g. V15Gy-fx equals the V3Gy per fraction.
* $p < 0.01$.

Discussion

This study is the first to investigate the potential dosimetric benefit of an adaptive plan selection strategy using multiple target margins for short-course rectal cancer radiotherapy. This strategy improved coverage of the target volume, and yielded a minor sparing of the OARs. The dosimetric sparing of the bladder and bowel cavity was limited, since the median reduction in PTV volume was only 30 cm^3. Both rectum and bladder volume influenced which plans were selected.

The only other adaptive strategy for the entire rectal cancer target volume has been described by Nijkamp et al. They used an adaptive CTV from fraction five onward, created by averaging the CTV shape over the delineations from the first four fractions, rendering this strategy not applicable to short-course treatments. Since their strategy adapts the entire CTV instead of merely the upper ventral margin of the mesorectum, they find a reduction in average PTV of 162 cm^3. With a median reduction in bowel cavity V15Gy of 34 cm^3 compared to 13.9 cm^3 in the present study, and a median reduction in bladder D_{mean} of 2.5 Gy compared to 0.27 Gy, their strategy has a higher potential for sparing the OARs.

For other target volumes such as bladder and cervix, plan selection strategies have proven to result in increased coverage and reduced normal tissue dose [14, 16-18, 23-28]. Strategies using variable margins for large parts of the target volume to build a plan library result in PTV volume reductions ranging from approximately 100 to 150 cm^3 [24, 25], resulting in a higher sparing potential.

The improvement we found in target coverage for two out of 50 fractions is clinically relevant for short-course radiotherapy, since target underdosage in even a minority of fractions is not permitted due to its hypo fractionated nature. For a more conventional treatment schedule with 2 Gy fractions such as long-course radiotherapy, the clinical consequences of a minor coverage improvement will be less significant. However, the negative time trend regarding rectal and bladder volume during long-course treatment [29] could result in larger anatomical deviations from the planning CT than observed in the current study. The clinical benefit of our adaptive strategy regarding target coverage and OAR dose for long-course rectal cancer radiotherapy therefore remains unclear.

Most toxicity after radiotherapy for rectal cancer originates from dose to the bowel cavity [3, 4, 7]. Banerjee et al. found that a bowel cavity V15Gy of less

than 830 cm^3 would result in a less than 10% risk of grade ≥ 3 acute toxicity [30]. All values for V15Gy-fx we found for both strategies were below this cutoff value. These results do not indicate a significant clinical advantage for ART regarding bowel toxicity. Whether late urinary toxicity such as urinary incontinence is caused by radiotherapy or surgery remains debatable [3, 4, 6]. However, since a high fraction dose can result in substantial injury to the bladder due to fibrosis in the bladder, the urethral sphincter or innervation of both [31], a reduction in V95%-fx will be beneficial. Therefore, even the minor reduction in V95%-fx we found, from 15.7% to 6.8%, could be clinically relevant. Despite the limited overall sparing of OARs in the current study, sparing for individual patients can still be substantial. The largest difference in PTV volume between both strategies found was 115 cm^3, corresponding to a 13% reduction in bladder V95%-fx. For the patient with the largest reduction in dose to the bowel cavity, the PTV volume was only reduced by 23 cm^3, but the V15Gy-fx reduced by 59 cm^3, and the V95%-fx by 11 cm^3. This shows that the benefit of a plan selection strategy is patient dependent.

Limitations of the study include the small patient number, and inclusion of patients treated in different positions. This increases the variability in dose parameters, since the dose to OARs is different for treatment in prone or supine position (Supplementary Table 1), independent of strategy. In addition, a distinction was not made between male or female patients, even though shape variation is significantly different for each gender [12, 13]. However, this study showed that a plan selection protocol could be applied independent of the treatment position or patient sex. All CBCT scans were delineated by a single observer, which minimized interobserver variation but could also introduce a systematic error. Nevertheless, delineating was done using the planning CT scan and its delineations as a guide, thereby increasing the consistency of delineations. The PTV margin not only accounts for geometrical variations, but also delineation uncertainties, which renders plan selection based on coverage of the target volume by the PTV theoretically incorrect. However, this selection process is in agreement with our current clinical practice, where decisions regarding position verification also depend on coverage of the target on the CBCT by the PTV, without additional margins. Plan selection was not performed under clinical conditions, which entails time pressure to limit intrafraction motion [32], and plan selection by two specialized radiation therapists, supervised by a physician and medical physicist, instead of the 20 observers that were involved in the current study. Training of observers will therefore be essential. Finally, the set of five margin sizes for the adaptive plans was pragmatically chosen, but whether these sizes were optimal remains unknown. Further optimization could result in minor improvements of the dosimetric outcome.

The sparing is mainly limited due to the minor reduction in average PTV volume over the course of treatment, since the upper mesorectum volume comprised less than half of the entire target volume (median: 43%, range: 38–56%). Currently no evidence exists that the other target margins, around the lower mesorectum, presacral space and lymph nodes, can be safely reduced or varied based on predictable anatomical variations. Therefore, further improvement of the dosimetric results of our adaptive strategy by varying and reducing other PTV margins does not seem achievable, but online replanning with the use of sophisticated daily imaging techniques and automated planning could lead to an additional reduction in margins and therefore result in more sparing of the OARs.

Conclusion

For short-course rectal cancer radiotherapy, an adaptive plan selection strategy using multiple ventral margins for the upper mesorectum has the potential to improve coverage of the target volume. Overall dosimetric sparing of bladder and bowel cavity is limited, but can be clinically relevant for individual patients.

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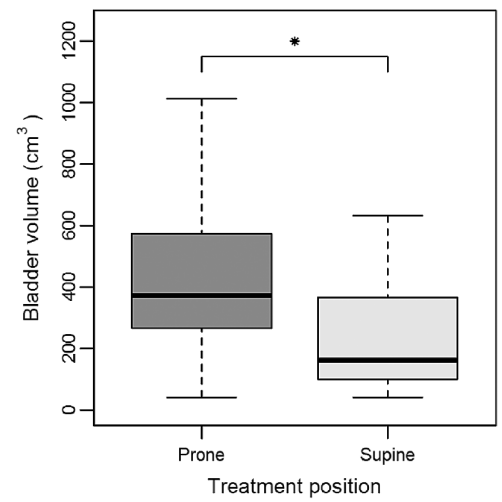
Supplementary Material

Supplementary figure 1. Accessible through
https://www.sciencedirect.com/science/article/pii/S0167814016310581

Supplementary table 1: Differences in dose parameters for bowel cavity and bladder, for patients treated in either supine or prone position

		Position	ART	non-ART	Median difference	95% CI
Bowel cavity	V95%-fx (cm^3)	*Supine*	209	216	7.00*	4.00 – 9.40
		Prone	146	156	9.90*	6.80 – 10.9
	V15Gy-fx (cm^3)	*Supine*	294	302	8.20*	4.85 – 23.1
		Prone	191	202	25.2*	18.4 – 29.8
Bladder	V95%-fx (%)	*Supine*	3.63	6.43	2.11*	2.85 – 7.03
		Prone	9.22	20.4	9.59*	6.36 – 11.1
	D_{mean}-fx (Gy)	*Supine*	2.73	2.82	0.12*	0.11 – 0.23
		Prone	3.08	3.43	0.32*	0.26 – 0.43

* $p < 0.01$. Note that the bowel cavity parameters are lower for patients in prone position (for both the adaptive and non-adaptive strategy). The bladder parameters are higher for patients in prone position, also for both strategies. The estimated differences between parameters for both strategies, i.e. the sparing due to the adaptive strategy, appears to be larger for patients treated in prone position. This is most likely caused by the difference in bladder volumes between the patient groups (see supplementary figure 2), since plans with larger margins are selected for smaller bladder volumes.



Supplementary figure 2: Bladder volumes as assessed on CBCT for all patients treated in either prone or supine position. Bladder volumes for patients treated in prone position were significantly larger compared to supine position, with median volumes of 373 cm^3 and 162 cm^3, respectively ($p = 0.01$, indicated by asterisk).

Chapter 5

Plan selection strategy for rectum cancer patients: an interobserver study to assess clinical feasibility

Radiotherapy and Oncology 120 (2016) 207-211

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Abstract

Background and Purpose: In radiotherapy for rectum cancer, the target volume is highly deformable. An adaptive plan selection strategy can mitigate the effect of these variations. The purpose of this study was to evaluate the feasibility of an adaptive strategy by assessing the inter-observer variation in CBCT-based plan selection.

Material and Methods: Eleven patients with rectum cancer, treated with a non-adaptive strategy, were selected. Five CBCT scans were available per patient. To simulate the plan selection strategy, per patient three PTVs were created by varying the anterior upper mesorectum margin. For each CBCT scan, twenty observers selected the smallest PTV that encompassed the target volume. After this initial baseline measurement, the gold standard was determined during a consensus meeting, followed by a second measurement one month later. Differences between both measurements were assessed using the Wilcoxon signed-rank test.

Results: In the baseline measurement, the concordance with the gold standard was 69% (range: 60%-82%), which improved to 75% (range: 60%-87%) in the second measurement (p=0.01). For the second measurement, 10% of plan selections were smaller than the gold standard.

Conclusion: With a plan selection consistency between observers of 75%, a plan selection strategy for rectum cancer patients is feasible.

Introduction

The standard of care for non-metastasized locally advanced rectal cancer is chemo-radiotherapy combined with surgery [1-3]. In radiotherapy, sparing the organs at risk with the use of state-of-the-art planning techniques such as intensity-modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT), is often compromised by the large population-based margins that are necessary to compensate for the large shape changes of the target volume over the time of treatment. In rectum cancer patients, like in most patients treated in the pelvic region, day-to-day variation in rectum and bladder filling often causes large deformation of the target volume, which cannot be corrected for with a treatment couch adjustment [4-6]. Minimizing shape changes of the mesorectum with the use of drinking protocols to manage bladder filling, or dietary instruction to manage bowel motion, have been limited in their success [7].

An adaptive strategy with multiple plans made prior to treatment and tailored to a range of possible shapes can mitigate the effects of these variations in target volume, by selecting the best-fitting plan based on daily cone beam CT (CBCT) scans, and allows for smaller margins per plan. This strategy has been successfully applied for radiotherapy in bladder and cervical cancer, in which bladder filling is the predominant factor in the shape changes [8-11]. To create multiple plans, often a full and empty bladder pretreatment CT scan are acquired from which a patient-specific model for bladder filling is derived, which is used to create intermediate target volume structures.

In rectum cancer, however, shape changes of the mesorectum are mostly driven by changes in rectum volume and shape, and to a much lesser extent by bladder filling [4-6]. Because of this, creating multiple plans based on varying the bladder filling is not useful. However, by applying different PTV margins to the upper anterior side of the mesorectum, which is the part of the target volume showing the largest deformations [4-6], multiple PTVs can be created based on a single CT scan. This can also correct for the shape changes that are encountered. A similar plan selection strategy based on a variable margin has been investigated for cervical cancer and was proven to be dosimetrically beneficial compared to a single population-based margin [12].

Selecting the optimal plan entails daily selection of the smallest PTV encompassing the entire mesorectum on CBCT images. This requires adequate visibility of the regions of interest. In the pelvic region, CBCT image quality can be hampered by imaging artefacts caused by moving air or bowel [13].

Table 1 Patient characteristics

X	Age	Sex	Treatment position	Tumor stage			GTV location	Treatment scheme	Further treatment	Bladder Volume cm³	Rectum volume cm³	Available margins (mm)		
1	60	F	supine	T3	N0	M0	distal	28x1.8 Gy	APR	313	121	-15 mm	0 mm	15 mm
2	82	F	supine	T3	N2	M0	distal	5x5 Gy	LAR	212	82	-15 mm	0 mm	15 mm
3	73	M	supine	T3	N1	M0	distal	5x5 Gy	LAR	265	68	-15 mm	0 mm	15 mm
4	72	F	supine	T3	N2a	M0	mid	28x1.8 Gy	LAR	130	46	-25 mm	-15 mm	0 mm
5	61	M	supine	T2/3	N1b	M0	proximal	5x5 Gy	LAR	493	117	0 mm	15 mm	25 mm
6	66	M	supine	T2/3	N2	M0	distal	28x1.8 Gy	APR	399	79	-15 mm	0 mm	15 mm
7	44	M	prone BB	T2	N2	M0	proximal	5x5 Gy	CRT	637	76	0 mm	15 mm	25 mm
8	55	F	prone BB	T3	N1	M0	proximal	5x5 Gy	LAR	271	189	-15 mm	0 mm	15 mm
9	63	M	prone BB	T3	N1b	M0	distal	5x5 Gy	LAR	706	123	0 mm	15 mm	25 mm
10	55	M	prone BB	T2	N1b	M0	distal	5x5 Gy	LAR	378	56	-15 mm	0 mm	15 mm
11	59	F	prone BB	T3	N1	M0	proximal	5x5 Gy	LAR	282	54	0 mm	15 mm	25 mm

LAR: Low Anterior Resection

APR: AbdominoPerineal Resection

CRT: Chemoradiotherapy

BB: Bellyboard

Identifying the boundaries of a complex target volume like the mesorectum can therefore be challenging.

The purpose of this study was to evaluate the feasibility of an adaptive plan selection strategy for radiotherapy in rectum cancer patients by assessing the interobserver variation in CBCT-based plan selection.

Materials and Methods

Patient data

Retrospectively, 11 consecutive patients with resectable rectum cancer, treated between December 2014 and August 2015 at our department, were selected. Patients were included if the target delineation was in accordance with delineation guidelines and when the total target volume was visible on the CBCT. Patients were treated with a standard, non-adaptive strategy. In our institution, prone position on a bellyboard was the first choice of patient orientation, as historically this was considered the optimal position to spare small bowel [14], but supine position was used when pain or presence of a stoma prohibited prone position. Therefore, 6 patients treated in supine position were included, as well as 5 patients treated in prone position with bellyboard (Table 1, Figure 1). Three patients were treated with long-course radiotherapy, consisting of 28 fractions of 1.8 Gy, whereas 8 patients were treated with short-course radiotherapy, in which 5 fractions of 5 Gy were delivered. Further patient details can be found in Table 1. For the patients treated with short-course radiotherapy, all CBCT scans were included. For patients treated with long-course radiotherapy, one randomly selected CBCT scan from each week was included, resulting in 5 available CBCT scans per patient. Both treatment schemes were included in this study as both were the intended patient groups for the plan selection strategy.

Imaging data

For the pretreatment CT scan, patients were instructed according to the clinical drinking protocol. They were therefore asked to drink 500 ml of water 1.5 hours prior to the CT scan after voiding the bladder, and refrain from voiding. This protocol was adopted to improve chances of a large bladder filling, as this is considered the optimal anatomy to treat since it minimizes dose to the organs at risk, i.e. bladder and small bowel. For all patients, daily CBCT scans were acquired prior to treatment for online positioning and

evaluation of target coverage. CBCT scans were acquired using XVI 4.5 (Elekta Oncology systems, Crawley) in full rotation scans with a field of view of 18x40cm², or 25x40cm² depending on the length of the target volume.

Target volume delineation

For each patient, the target volumes were delineated on the pretreatment CT scan according to delineation guidelines as proposed by Roels et al. [15]: the gross tumor volume (GTV), the mesorectum, suspected pathologic lymph nodes, presacral space, internal iliac lymph node regions and, when applicable, obturator lymph node region. In addition, organs at risk such as the bladder, bowel cavity, and femur heads were delineated using RTOG guidelines [16].
The mesorectal fat was divided in a lower and upper mesorectum, as suggested by Nijkamp et al. [4-6]. The border between the two structures was located at the slice showing the base of the bladder. The clinical target volume (CTV) was created by combining the delineations of the mesorectum, presacral space, and lymph node regions.

Simulation of adaptive strategy

To simulate the adaptive plan selection strategy, three PTVs were created by varying the anterior margin for the upper mesorectum. Margins could either be -25 mm, -15 mm, 0 mm, +15 mm and +25 mm. The -25 mm and 25 mm margins were chosen based on the expected maximum variations reported by Nijkamp et al. [4-6]. This range was pragmatically divided into 5 steps. To minimize the additional workload at the treatment planning stage, three margins were used for each patient, based on the anatomy on the planning CT scan. For a full bladder and/or empty rectum anatomy on the CT scan, the 0 mm, 15 mm and 25 mm ventral margins were used. Conversely, for an empty bladder and/or full rectum, the 0 mm, -15 mm and -25 mm margins were used. For mixed situations, or for a bladder and rectum with intermediate filling, the 0 mm, -15 mm and 15 mm margin sizes were used. All other PTV margins were identical to the non-adaptive treatment strategy, resulting in 3 PTVs per patient. An example for three typical patients is shown in Figure 1. For this retrospective study, the associated treatment plans were not generated.

Observers and design of the study

Twenty observers (16 radiation therapy technologists (RTTs), 4 physicists) were asked to perform plan selection for all available CBCTs. For each CBCT, the observers were asked to select the smallest PTV that encompassed the

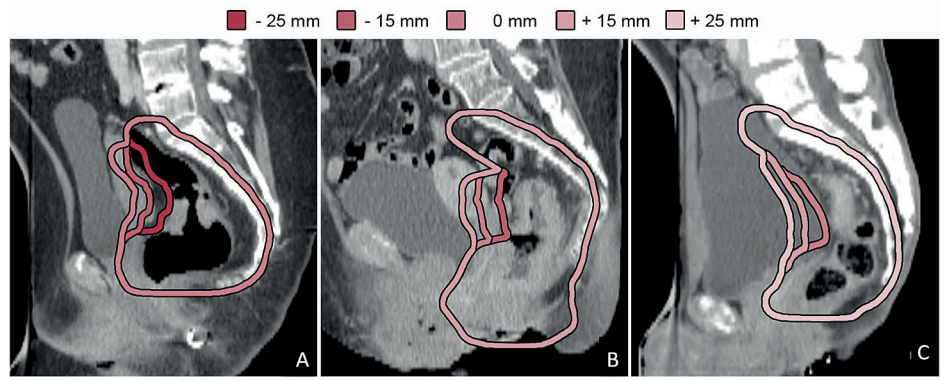

Figure 1. Examples of possible margin selections. (A) for a patient with a full rectum and empty bladder on the planning CT scan, margins of –25 mm, –15 mm and 0 mm were used. (C) shows the opposite anatomy (full bladder and empty rectum) which warrants margins of 0 mm, 15 mm and 25 mm, and (B) shows a mixed situation for which margins of -15 mm, 0 mm and 15 mm were used. Patients were treated in prone position on a belly board (A + C), or in supine position (B).

complete target volume. 7 RTTs already had experience with online plan selection based on CBCT, as this is routine for bladder and cervix cancer treatment in our department [8]. The physicists are involved in all steps of the plan selection protocol during development and clinical introduction and therefore also participated in the observer study. For the first 20 patients, a physicist, a physician and an RTT together will perform plan selection together in the first week of the treatment. A baseline measurement was performed following a lecture on target definition by an expert radiation oncologist. The baseline measurement entailed plan selections by all observers individually, without the possibility of discussion between observers. After the baseline measurement, all observers and 2 expert radiation oncologists determined the gold standard during a consensus meeting. During this meeting, all CBCT scans of all patients were discussed, and for each CBCT the consensus for the best fitting PTV was determined, ultimately based on the decision of the expert radiation oncologists. One month later, a second measurement was conducted, in which the same observers repeated plan selection for all CBCTs on the same data set as the baseline measurement. Observers did not have the possibility to discuss with each other, and were blinded to both the gold standard as well as their own selections from the baseline measurement.

Statistical analysis

Both the baseline and the second measurement were compared to the gold

standard and analyzed in consistency and uniformity. Differences between both measurements were assessed using Wilcoxon signed-rank tests and a p-value < 0.05 was considered statistically significant.

Results

The anatomy on the planning CT scan for each patient and the resulting anterior margins that were chosen are detailed in Table 1. During the consensus meeting, 55 CBCT scans were discussed.
In the baseline measurement, the concordance with the gold standard was 69% (range: 60% - 82%), which improved to 75% (range: 60% - 87%) in the second measurement (p=0.01) (Figure 2).

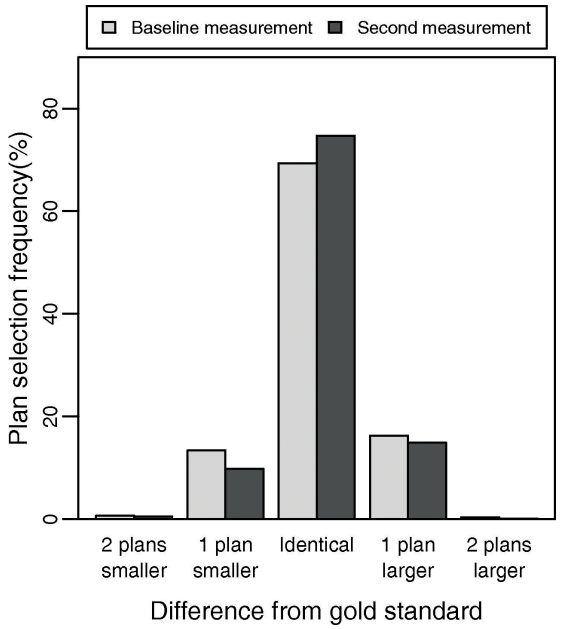

Figure 2. Results of plan selection by the observers in the baseline measurement and the second measurement: concordance with gold standard.

The 0 mm plan was selected in 56% and 59% of cases for the baseline measurement and second measurement, respectively. The -25 mm plans were never selected (Figure 3 and Supplementary Table).

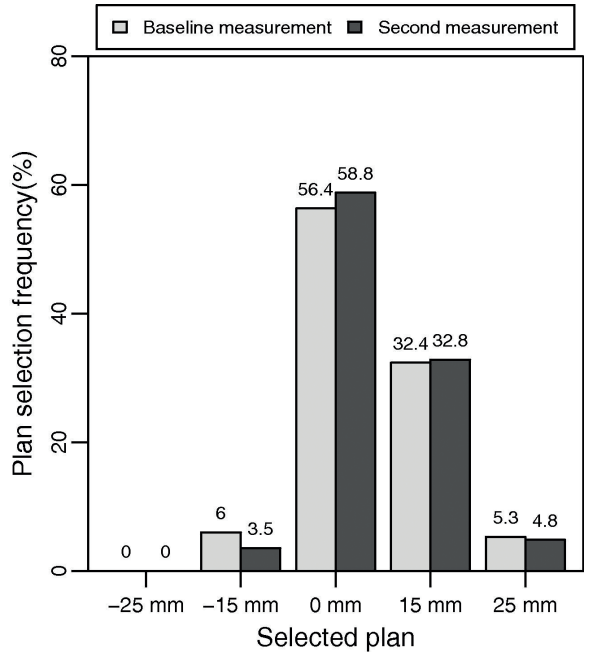

Figure 3. Results of plan selection by the observers in the baseline measurement and the second measurement: distribution of selected plans.

In the baseline measurement, 17% of selected plans were larger compared to the gold standard. After the consensus meeting, this decreased to 15% (p=0.13). Conversely, 14% of all selected plans in the baseline measurement were smaller than the gold standard, which improved to 10% in the second measurement (p<0.01).
A non-significant trend towards more interobserver uniformity was seen for patients treated in the supine position compared to prone position. The agreement with the gold standard was 72% for the supine position and 62% for the prone position in the baseline measurement. In the second measurement, the agreement for supine and prone position was 79% and 70%, respectively.

Discussion

This observer study is the first to evaluate the feasibility of daily plan selection for rectum cancer patients. This plan selection strategy is based on a single pretreatment CT scan with variable PTV margins, for the upper anterior mesorectum. Shape changes are accounted for by selecting the smallest PTV encompassing the entire target volume on the daily CBCT scan. The design of the study reflects the common clinical workflow in which RTTs perform plan selection without offline review by physicians, once the workflow is clinically implemented. Despite a sometimes poor image quality of the CBCT scan due to artefacts caused by moving bowel or air and a complex target volume, uniformity and concordance to the gold standard amongst the observers were high. The agreement with the gold standard was initially 70%, and improved to 75% after a consensus meeting. The observer study also showed that a -25 mm margin was never selected and will be omitted for the clinical implementation.

In a similar study [17], for 4 patients with cervical carcinoma observers selected the best fitting CTV on daily CBCT scans out of 5 CTV structures per patient. In the baseline measurement, 77% of selected plans were in concordance with the gold standard increasing to 84% after a consensus meeting. The larger concordance with the gold standard compared to our study can be explained by the more complex definition of the target volume in this study, i.e. the mesorectum, as compared to the cervix and uterus. Next to plan selection by human observers based on CBCT images, literature describes (semi-) automatic plan selection for bladder cancer radiotherapy, by segmentation of the bladder on CBCT [18, 19]. This method is similarly accurate, with minor manual interaction. However, its usefulness for rectum cancer is limited as the bladder itself is not a good surrogate for plan selection. Progress is made in the automatic segmentation of the rectum on CT images [20, 21], but the automatic segmentation of the mesorectum is highly challenging due to the lack of clear borders and is not described in literature.

Lutkenhaus et al. investigated the potential dosimetric benefit of this adaptive strategy for rectum patients and found that it improved coverage to the target volume, and yielded minor sparing of the organs at risks. However, for individual patients there could be a significant gain [22]. Further follow-up should reveal if this dosimetrical improvement translates into real clinical benefits.

Selection of plans with multiple margins is not the first proposed adaptive strategy for rectum cancer patients. Nijkamp et al. [22] investigated the impact of replanning strategies on the required margin size and therefore the dose to the organs at risk. Their strategy required the acquisition of multiple CT scans over the course of treatment, as well as delineation of these scans. Replanning was done after one week of treatment, based on an average CTV over the planning CT and one to five repeat CTs. Our plan selection strategy also requires the creation of multiple plans, but it is based on a single pretreatment CT scan. The delineation workload does not increase compared to a non-adaptive strategy. The creation of 3 plans for plan selection triples the workload for treatment planning compared to the non-adaptive strategy adding up to 120 minutes of total treatment planning time at our department. Although our strategy has a smaller workload, is more patient-friendly and is more straightforward compared to the strategy by Nijkamp et al, compensation for anatomical changes is limited to the upper mesorectum which impacts the potential sparing of organs at risk.

PTV margins should be calculated by incorporating all errors in the chain of radiation therapy. In this observer study, we selected the smallest PTV that fits the daily mesorectum shape, thereby disregarding all other errors, such as intrafraction motion or delineation uncertainty [23, 24]. Whereas this is theoretically incorrect, it matches current clinical practice. Currently, in our clinic, images for position verification are also used to evaluate changes in anatomy compared to the planning CT. If the target volume is encompassed completely by the PTV after setup correction, it is acceptable to start the daily irradiation. When the target volume is partially outside of the PTV, additional patient-specific actions will be discussed. In practice, this entails that action will depend on site-specific protocols and take into account the cause of the misalignment and/or the number of misalignments in the treatment, as well as its effects on the total dose to the CTV. Plan selection based on selecting the smallest PTV encompassing the entire mesorectum is therefore at least as accurate as current clinical practice. Furthermore, to minimize the influence of intrafraction motion as much as possible, the intention is to combine this adaptive strategy with VMAT. This would limit the time between end of acquisition of CBCT and end of treatment to a maximum of 10 minutes.

Limitations of this study are the inclusion of short and long fractionation schemes and different patient orientations, without sufficient patient numbers to analyze possible differences. For patient orientation, there was a trend in favor of supine position with respect to concordance to the gold standard but this was not statistically significant. A possible explanation could be a better image quality in supine position due to fewer streak artifacts caused by

patients breathing and artifacts caused by the bellyboard. Current literature is inconclusive as to the clinical benefit of treating rectum in prone position with bellyboard for the dose to the organs at risk when treating with IMRT or VMAT [25-28]. However, all patient subgroups encounter large shape changes and could therefore benefit from a plan selection strategy. Therefore, even though patient position and fractionation scheme have an impact on target shape variation [4-6], impact of these variables on plan selection was limited and plan selection was proven to be feasible. A second limitation of the study is that it was not performed under clinical conditions where a plan needs to be selected in an online setting, with time pressure due to the patient on the table waiting for treatment. This could have resulted in a smaller interobserver variation, or better adherence to the gold standard, compared to what can be expected in a clinical setting. However, in a clinical setting, plan selection will be performed by two well-trained RTTs, which will improve consistency and uniformity [7]. A concern is the fact that 10% of selected plans were smaller than the gold standard. Therefore, in clinical practice, an experienced RTT will retrospectively check all selected plans once a week, as a safety net system. This will provide valuable feedback to the RTTs responsible for plan selection for the remainder of treatment. Furthermore, the gold standard is a consensus driven by expert radiation oncologists, based on CBCT images which have a relatively low contrast. Recent developments in MRI-guided radiotherapy [29] with far better image quality compared to CBCT will, almost certainly, reduce possible bias in the 'gold standard' as well as improve the consensus in plan selection.

Our observer study did not only provide the answer regarding the feasibility of a plan selection strategy for rectum cancer patients with a concordance of 75% to the gold standard, it also proved to be a valuable method in the implementation process. All of the observers reported that they have gained expertise and confidence to select the appropriate plan on CBCT images in clinical practice. This observer study, however, involves a heavy workload. Each observer spent 1 hour on a lecture on anatomy, 6 hours on plan selection for each measurement and 5 hours on the consensus meeting. Such an intense implementation strategy, in turn, will provide a competent multi-disciplinary well-trained group at the start of clinical routine. The observer study furthermore provided an image database for demonstration purposes to maintain expertise in the future [29]. Although the combination of the observer study with a consensus meeting was optimal for gaining expertise and confidence during the implementation process, we believe that the demonstration database will suffice for future training of RTTs for plan selection.

Conclusion

With a consistency of 75% in selecting the smallest PTV volume encompassing the entire mesorectum, despite the suboptimal image quality of the CBCT scan and the complex definition of the mesorectum, plan selection for rectum cancer patients has proven to be feasible.

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Supplementary Material

Supplementary Table Results of plan selection for all observers: concordance with gold standard (GS) in %

	Baseline measurement					Second measurement				
Observer	**-2**	**-1**	**0**	**1**	**2**	**-2**	**-1**	**0**	**1**	**2**
1	0	21.8	67.3	10.9	0	1.8	10.9	74.5	12.7	0
2	0	9.1	74.5	14.5	1.8	1.8	14.5	78.2	5.5	0
3	0	0	67.3	32.7	0	0	7.3	74.5	18.2	0
4	0	14.5	63.3	21.8	0	0	14.5	76.4	9.1	0
5	0	3.6	50.9	45.5	0	0	5.5	60	34.5	0
6	0	21.8	74.5	3.6	0	0	9.1	72.7	18.2	0
7	1.8	30.9	67.3	0	0	0	14.5	83.6	1.8	0
8	0	7.3	80	12.7	0	0	7.3	87.3	5.5	0
9	3.6	9.1	70.9	16.4	0	0	10.9	83.6	5.5	0
10	1.8	12.7	72.7	11.7	0	0	1.8	61.8	36.4	0
11	0	20	69.1	10.9	0	0	3.6	83.6	12.7	0
12	0	14.5	63.6	21.8	0	0	10.9	76.4	12.7	0
13	1.8	9.1	78.2	10.9	0	1.8	9.1	78.2	10.9	0
14	0	5.5	61.8	32.7	0	0	9.1	69.1	21.8	0
15	1.8	10.9	65.5	20	1.8	1.8	5.5	67.3	25.5	0
16	0	7.3	67.3	21.8	3.6	0	14.5	65.5	18.2	1.8
17	0	10.9	76.4	12.7	0	0	5.5	69.1	25.5	0
18	0	21.8	70.9	7.3	0	0	18.2	78.2	3.6	0
19	1.8	18.2	81.8	7.3	0	0	10.9	81.8	7.3	0
20	0	18.2	70.9	10.9	0	1.8	12.7	72.7	12.7	0
Overall	0.6	13.4	69.4	16.3	0.4	0.5	9.8	74.7	14.9	0.1

-2: 2 plans smaller than GS

-1: 1 plan smaller than GS

0: Identical to GS

1: 1 plan larger than GS

2: 2 plans larger than GS

Chapter 6

Dosimetric benefit of an adaptive treatment by means of plan selection for rectal cancer patients in both short and long course radiation therapy

Radiation Oncology 15; Jan 13 (2020)

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Abstract

Background: To compare target coverage and dose to the organs at risk in two approaches to rectal cancer: a clinically implemented adaptive radiotherapy (ART) strategy using plan selection, and a non-adaptive (non-ART) strategy.

Methods: The inclusion of the first 20 patients receiving adaptive radiotherapy produced 10 patients with a long treatment schedule (25x2Gy) and 10 patients with a short schedule (5X5Gy). We prepared a library of three plans with different anterior PTV margins to the upper mesorectum, and selected the most appropriate plan on daily Conebeam CT scans (CBCT). We also created a non-adaptive treatment plan with a 20 mm margin. Bowel bag, bladder and target volume were delineated on CBCT. Daily DHVs were calculated based on the dose distribution of the selected and non-adaptive plans. Coverage of the target volume was compared per fraction between the ART and non-ART plans, as was the dose to the bladder and small bowel, assessing the following dose levels: V15Gy, V30Gy, V40Gy, V15Gy and V95% for long treatment schedules, and V15Gy and V95% for short ones.

Results: Target volume coverage was maintained from 98.3% (non-ART) to 99.0% (ART)($p=0.878$). In the small bowel, ART appeared to have produced significant reductions in the long treatment schedule at V15Gy, V40Gy, V45Gy and V95% ($p<0.05$), but with small absolute differences. The DVH parameters tested for the short treatment schedule did not differ significantly. In the bladder, all DVH parameters in both schedules showed significant reductions ($p<0.05$), also with small absolute differences.

Conclusions: The adaptive treatment maintained target coverage and reduced dose to the organs at risk.

Background

Due to the inevitable dose to organs at risk (OAR) such as the small bowel and bladder, radiation therapy for rectum cancer is associated with toxicity [1]. While treatment-planning techniques with intensity modulation (IMRT/VMAT) make it possible to reduce the dose to OARs by steep dose gradients, the benefit is counteracted by the large population-based margins that are necessary to compensate for large inter-fraction shape-changes caused by changing rectum and bladder filling [2-6]. Drinking protocols to stabilize the volume of the bladder have had only limited success [7, 8]. Because the digestive system is both complex and deregulated by a tumor [9], there are also no clear instruments for stabilizing rectal volume. Although a diet (i.e. directions on fluid and fiber intake) or laxatives may help [7, 10-12], they burden the patient. Nijkamp et al [3, 4, 6] report geometrical uncertainties of the mesorectum that, in rectal cancer, require population-based margins up to 24 mm.

To cope with inter-fraction shape changes in cervix and bladder cancer patients several groups introduced adaptive strategies with plan selection [13-17]. This entails creating multiple plans tailored to possible shapes and for these two sites the shape of the target volume can largely be predicted by acquiring two planning CT scans capturing the extreme bladder fillings (full and empty bladder). Structures of the target volume based on these two CT scans can be interpolated to generate intermediate structures (or even extrapolated if necessary) for treatment planning. For each of these plans smaller margins than used for non-ART will suffice. Subsequently, the best fitting plan will be selected based on daily CBCT [18].

For rectal cancer patients, the shape-changes in the target volume are driven mainly by the rectal volume [3, 4] and for that reason creating multiple based plans on varying bladder filling is not useful. Therefor we developed plan selection based on variable margins to the upper anterior side of the mesorectum, which is the part of the target volume with the largest deformations. The remaining part of the upper mesorectum is enclosed by bony anatomy (dorsal) or the elective lymph node region (lateral) and for that reason not eligible for variable margins. These multiple PTV margins were based on a single planning CT scan with spontaneous rectum filling. For implementation purposes, our group has already simulated this strategy for its potential dosimetric effect [19] and also to test the feasibility of selecting a margin based on CBCT images [20]. So far this strategy has not been evaluated within a clinical setting for long-course (LCRT) and short-course radiotherapy treatment (SCRT) in which patients are

Table 1: *Patient characteristics*

X	Age	Sex	Tumor stage	Treatment scheme	Chemo	GTV location	Surgery	Bladder volume cm³ planning CT	Upper mesorectum volume cm³ planning CT	Upper mesorectum length mm planning CT	Available margins (mm)			Average bladder volume CBCT relative to planning CT	Average upper mesorectum volume CBCT relative to planning CT
1	65	M	cT3N1M0	5x5 Gy	N	proximal	LAR	185	259	55	-15	0	15	1.13	1.03
2	70	F	cT3N0M0	5x5 Gy	N	mid	LAR	558	143	60	0	15	25	0.66	1.05
3	63	M	cT4N1M0	5x5 Gy	Y	distal	ns	203	269	60	-15	0	15	0.84	1.06
4	71	M	cT3N1M0	5x5 Gy	N	mid	LAR	622	184	86	0	15	25	0.70	1.14
5	74	M	cT3N0M0	5x5 Gy	N	proximal	LAR	557	226	65	0	15	25	0.57	1.06
6	56	F	cT3N1M0	5x5 Gy	N	mid	LAR	135	156	41	-15	0	15	0.42	1.02
7	73	M	cT3N2M1	5x5 Gy	Y	proximal	LAR	160	357	71	0	15	25	1.02	0.97
8	70	M	cT3N2M0	5x5 Gy	N	distal	APR	295	244	65	0	15	25	0.59	1.03
9	40	F	cT3N1M0	5x5 Gy	N	mid	LAR	941	131	57	0	15	25	0.52	1.25
10	78	M	cT4N1M0	5x5 Gy	N	rectosigmoid	LAR	613	289	70	0	15	25	0.33	1.06
11	71	F	cT3N1M0	25x2 Gy	Y	proximal	LAR	791	393	80	-15	0	15	0.63	0.71
12	66	M	cT3N2M0	25x2 Gy	Y	mid	LAR	150	185	46	-15	0	15	1.05	0.9
13	64	F	cT3N2M0	25x2 Gy	Y	distal	APR	403	223	65	0	15	25	0.31	0.95
14	65	M	cT3N2M0	25x2 Gy	Y	proximal	LAR	446	309	65	0	15	25	0.65	1.09
15	55	F	cT4N0M0	25x2 Gy	Y	distal	LAR	595	186	67	0	15	25	0.42	0.91
16	59	M	cT3N0M0	25x2 Gy	Y	mid	LAR	166	170	52	-15	0	15	1.27	1.00
17	72	M	cT3N2M0	25x2 Gy	Y	proximal	LAR	420	373	85	0	15	25	0.65	1.05
18	69	F	cT4N1M0	25x2 Gy	Y	mid	LAR	511	442	97	0	15	25	0.79	0.99
19	77	M	cT3N2M0	25x2 Gy	Y	distal	ns	456	128	58	0	15	25	0.55	1.10
20	60	M	cT3N2M0	25x2 Gy	Y	distal	ns	392	261	67	-15	0	15	0.75	0.92

ns: not specified

LAR: low anterior resection

APR: abdominal perineal resection

treated in a supine-only position.

We therefore compared target coverage and dose to the organs at risk in two approaches to rectal cancer: a clinically implemented adaptive radiotherapy (ART) strategy using plan selection, and a non-adaptive (non-ART) strategy.

Methods

In this study we used the same methodology as that used in our previous study [19], but applied to a clinical cohort of LCRT (25x2Gy) and SCRT (5x5Gy).

Patients

We included 20 patients, who were treated consecutively between May and August 2016. LCRT and SCRT were both eligible for plan selection. This resulted in the inclusion of 10 LCRT patients and 10 SCRT patients, with a total of 300 CBCT scans. Patient details are shown in Table 1.

The upper mesorectum lies between the presacral space and lower mesorectum. As these each have a 1 cm caudal and cranial margin, we made a pragmatic decision only to include patients for plan selection if the length of the upper mesorectum (measured from the base of the bladder) was over 4.5 cm. This would leave at least 2.5 cm for variable margins to the ventral side of the upper mesorectum. Patients were positioned supine with knee support and a device to position the arms above the head (Posirest, CIVCO).

Planning CT and delineations

A planning CT scan was acquired with a full bladder, instructions having been to empty the bladder 1.5 h before scanning and then to drink 0.5 l of water. As no instructions had been given with regard to rectal filling, spontaneous rectum filling was used.

For GTV, the gross tumor volume and pathologic lymph nodes were delineated. For CTV the mesorectum, presacral space, internal iliac lymph node regions and, when applicable, obturator lymph node regions, were delineated by a radiation oncologist according to the guidelines by Roels et al. [21] (Advantage SIM, GE or VelocityAI 3.2, Varian Medical Systems). To be able to differentiate margins between the upper and lower mesorectum based on the geometrical uncertainties reported by Nijkamp et al [3, 4, 6], the mesorectum was divided into an upper and lower part, with the transition at the base of the

bladder (Fig. 1). Total CTV volume was created by combining all CTV regions. Radiation therapists (RTTs) contoured the OARs (i.e., the bladder, bowel bag and femur heads) according to RTOG guidelines [22].

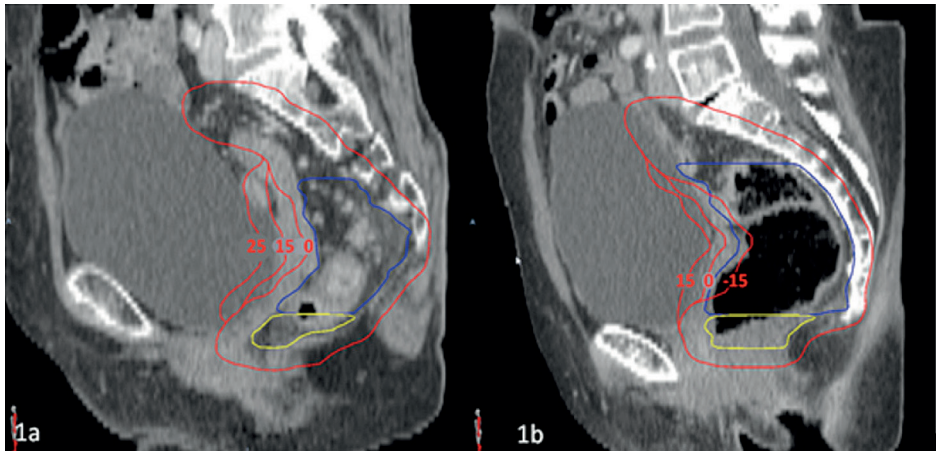

Figure 1. Margin sets based on anatomy as captured on planning CT. a shows an empty rectum with a set of 25 mm, 15 mm, and 0 mm margins (red) for the upper mesorectum (blue). b shows a full rectum with a set of 15 mm, 0 mm, and – 15 mm anterior margins (red) for the upper mesorectum (blue). Yellow is the lower mesorectum.

Treatment planning

Planning CT and delineations were imported into the treatment-planning system (Oncentra 4.5, Elekta AB, Sweden). PTV margins were created (VelocityAI) by expanding the lymph-node regions by 8 mm and the presacral space by 10 mm. The upper and lower mesorectum were expanded in all directions by 10 mm, except for the anterior side. The anterior side of the lower mesorectum was expanded by 15 mm. The anterior margin to the upper mesorectum was variable. To simplify the plan-selection process, we chose 15 mm as the difference between the PTV margins, except for the largest PTV margin, for which – on the basis of the maximum uncertainty found by Nijkamp – we chose 25 mm.

To reduce the number of PTVs in order to minimize workload at treatment planning, two sets of margins were defined, according to the anatomy captured on the planning CT scan: If a rectum was deemed empty after visual inspection on planning CT we used PTV margins of 25 mm, 15 mm, 0 mm, as − 15 mm was unlikely to be needed. Conversely, if a rectum was deemed full after visual inspection on planning CT, we used 15 mm, 0 mm and − 15 mm, as 25 mm was unlikely to be needed. Per patient, this resulted in 3 PTV margins, and thus 3 plans from which we could select during treatment (Fig. 1).

To compare this adaptive treatment with the former non-adaptive strategy, we generated an extra treatment plan in which all margins were kept the same, but in which a fixed anterior margin of 20 mm to the anterior upper mesorectum was used rather than a variable margin. Previously, before the implementation of the plan-selection strategy, this margin was the standard of care. Patients were planned with a 10 MV dual-arc VMAT technique. All treatment plans were checked for clinical acceptability by an experienced RTT and a medical physicist.

Plan selection

Conebeam CT (CBCT) scans were registered on pelvic bony anatomy (XVI5.0, Elekta) including translations and rotations with a maximum tolerance on rotations of 4 degrees. If set-up exceeded rotational tolerance, a patient was re-aligned. The registration results including rotations were converted into a correction with translations-only by taking out the rotations using a rotation point at the center of gravity of the PTV.

This resulted in a table translation, which was then applied. At the treatment machine, trained RTTs selected the smallest PTV that encompassed the complete clinical target volume on daily CBCT scans [20]. Retrospectively, the selected margins were reviewed by a single expert to check concordance with the clinical guidelines.

Dose calculation and comparison

Each CBCT scan was exported to VelocityAI. The patient's position on this CBCT scan is as it was during irradiation, i.e. translational errors were corrected using an online position verification protocol. Rotational errors are still present, as these cannot be corrected using our treatment couch. On each CBCT, a single observer delineated the upper and lower mesorectum based on the original clinical delineations of the radiation oncologist, as well as the bladder and bowel bag for the small bowel. Using identity transformation, delineations were propagated to the planning CT scan. The dose distribution planned was used to calculate daily DVHs for the delineations propagated, both for the selected treatment plan and for the fixed margin plan (20 mm) (version R2015b, MathWorks, Natick). Since the dose was not recalculated, we disregarded changes in dose distribution that resulted from changing anatomy.

Statistical analysis

Descriptive statistics were used to describe the distribution of plan selection for the total cohort and per individual patient.

To test the correlation of rectum volume with the selected plan, we calculated volumes relative to the planning CT scan of the upper mesorectum on daily CBCT. Because 6 combinations of different margins were tested, we used Bonferroni correction for multiple comparison testing after one-way ANOVA resulting in a confidence level of 0.05/6 = 0.008.

Using Wilcoxon signed-rank the difference in coverage between ART and non-ART was tested per fraction for the combined upper and lower mesorectum. Coverage was expressed as V95%, the volume receiving at least 95% of the prescribed dose.

Because deformable registration was not considered accurate enough [23], dose accumulation was not used to assess dose to OARs. For this reason, the difference of the dose to the OARs between the ART and non-ART strategy had to be tested per fraction. Because the literature on predictive dose volume parameters is relatively sparse we used a range of DVH parameters based on the parameters suggested in the QUANTEC papers [24, 25] and the DVH parameters suggested by Moutet-Audoard et al. [26] and Devill et al. [27, 28] (i.e., the volume receiving at least 15Gy (V15Gy), 30Gy (V30Gy), 40Gy (V40Gy), 45Gy (V45Gy)) per fraction. For LCRT, these were the following: 1.) the volumes that received at least 0.6Gy (V0.6Gy); 1.2Gy (V1.2Gy); 1.6Gy (V1.6Gy); and 1.8Gy (V1.8Gy) per fraction; 2.) the volume that received at least 95% of the prescribed dose (V95%); and 3.) the mean dose (Dmean) for bladder. For SCRT, 15Gy equals 3.0Gy per fraction; other dose levels are higher than the dose prescribed for SCRT. The V95% for LCRT is therefore the only dose level we evaluated together with the V95% for SCRT. We also tested Dmean for the bladder. All dose levels were tested for significant differences using the Wilcoxon signed-rank test.

Significance for coverage and dose to the OARs was set at $p < 0.05$. Statistical analysis was performed using SPSS24.

Results

Patients and plan selection

For clinical adaptive treatment, the margin set of 25 mm, 15 mm and 0 mm was used for 13 patients, and the margin set of 15 mm, 0 mm, and − 15 mm was used for 7 patients. Overall, based on daily CBCT scans, the − 15 mm margin was selected in 2% of fractions, the 0 mm margin was selected in 41%, the 15 mm margin in 40%, and the 25 mm margin in 17%. The distribution of selected margins per patients is shown in Fig. 2. For one patient only, one specific plan (25 mm margin) was used for all 5 fractions. All available plans were used for 7 patients.

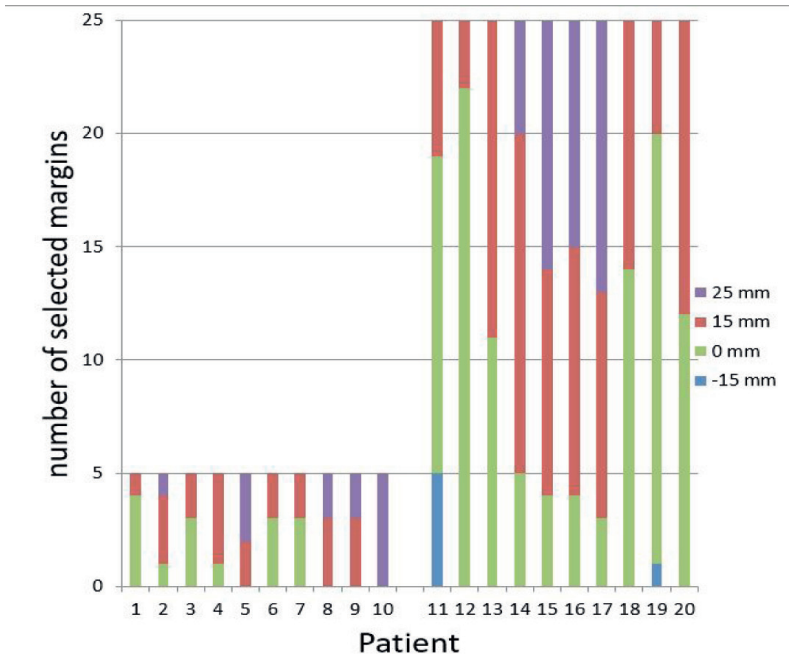

Figure 2. Distribution of selected margins per patient sorted on short (5 × 5Gy) and long (25x2Gy) treatment schedules

For each margin selected, the relative volume of the mesorectum differed significantly from the relative volume of the mesorectum of the other margins ($p < 0.001$). The graph shows that an increase in the selected margin was accompanied by an increase in relative volume (Fig. 3).

Our retrospective review of concordance with clinical selection guidelines showed that a smaller PTV could have been selected for 20% of fractions and a larger PTV should have been selected for 2%.

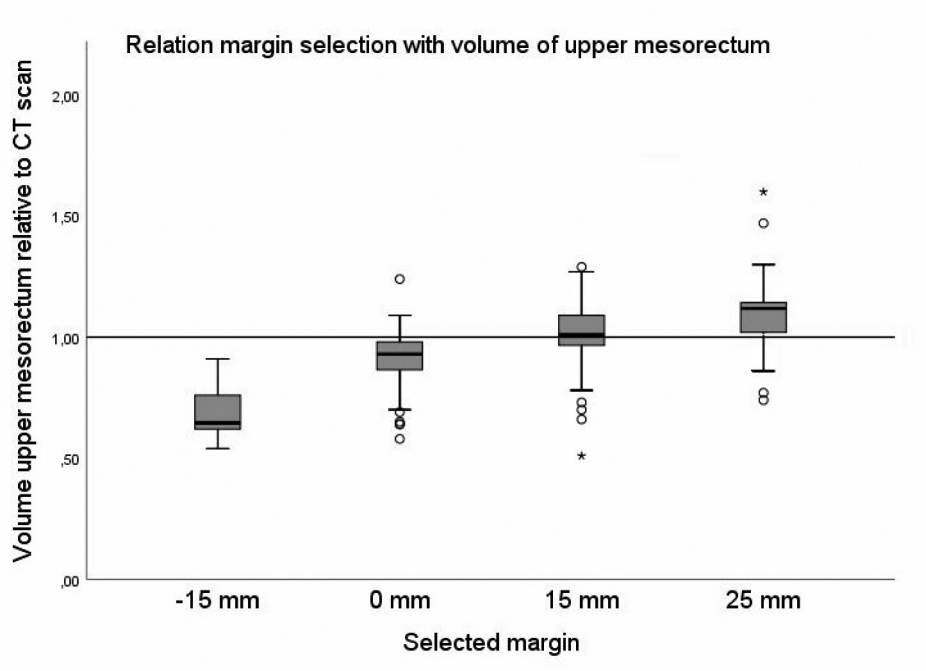

Figure 3. Boxplot shows the relationship between the upper mesorectum volume on CBCT relative to the planning CT scan with selected margin. It shows the interquartile range, with a horizontal line showing the group median. Whiskers indicate the 5th and 95th percentiles. Outliers are marked. One-way ANOVA testing with Bonferroni correction applied showed all margins to be significantly different (p < 0.001).

Target coverage

The average percentage of the mesorectum receiving at least 95% of the prescribed dose increased from 98.3 to 99.0%, for all patients and all fractions. This was not statistically significant (p = 0.878).

Dose to the organs at risk

The adaptive treatment for LCRT significantly reduced small bowel V15Gy, V40Gy, V45Gy and V95%, the average volume reduction being approximately 8 cm^3. V15Gy and V95% for SCRT were not significantly different (Table 2, Fig. 4). For both treatment schemes, the adaptive treatment significantly reduced all dose volume parameters in the bladder. The difference for V15Gy is very small but the average percentage reduction is approximately 7% (Table 2, Fig. 5).
In a subset of patients, the benefits were greater. In the bladder, for example, patient 7 (SCRT) had maximum average differences of up to 15% for V15Gy and of up to 12% for V95%. In the bowel, this patient had maximum average differences of up to 12 cm^3 for V15Gy and of up to 35 cm^3 for V95%. Similarly, for the bladder, patient 18 (LCRT) had maximum average differences of up to 11% for both V45Gy and V95%; and of up to 21 cm^3 for both V45Gy and V95% for small bowel.

Table 2

	Dose per fraction		Median values (range) ART	Median values (range) Non-ART	p-value
			LCRT (25x2 Gy)		
Bladder	V15Gy	(%)	99.8 (87.6-100.0)	100.0 (85.6-100.0)	< 0.001
	V30Gy	(%)	43.0 (12.6-99.3)	49.6 (19.1-96.8)	< 0.001
	V40Gy	(%)	22.8 (1.8-91.1)	29.0 (4.2-85.3)	< 0.001
	V45Gy	(%)	15.0 (0.2-87.0)	21.8 (0.4-77.6)	< 0.001
	V95%	(%)	10.8 (0.0-82.2)	17.8 (0.0-72.4)	< 0.001
	Dmean	(Gy)	1.2 (0.89-1.95)	1.3 (0.98-1.88)	< 0.001
Small Bowel	V15Gy	(cm^3)	847 (332-1447)	853 (294-1363)	0.001
	V30Gy	(cm^3)	309 (119-554)	309 (120-557)	0.542
	V40Gy	(cm^3)	205 (99-431)	214 (99-434)	< 0.001
	V45Gy	(cm^3)	179 (93-381)	187 (90-390)	< 0.001
	V95%	(cm^3)	160 (83-358)	170 (82-366)	< 0.001
			SCRT (5x5 Gy)		
Bladder	V15Gy	(%)	29.7 (5.7-58.6)	33.8 (9.9-60.5)	0.001
	V95%	(%)	4.4 (0.0-16.4)	7.1 (0.0-27.7)	0.013
	Dmean	(Gy)	2.7 (2.1-3.5)	2.8 (2.3-3.6)	0.001
Small Bowel	V15Gy	(cm^3)	329 (139-456)	317 (137-477)	0.237
	V95%	(cm^3)	176 (87-274)	191 (93-275)	0.135

Total dose V15Gy, V30Gy, V40Gy, V45Gy for LCRT corresponding to fraction dose V0.6Gy, V1.2Gy, V1.6Gy, V1.8Gy respectively and V15Gy total dose for SCRT corresponding to V3.0Gy fraction dose.

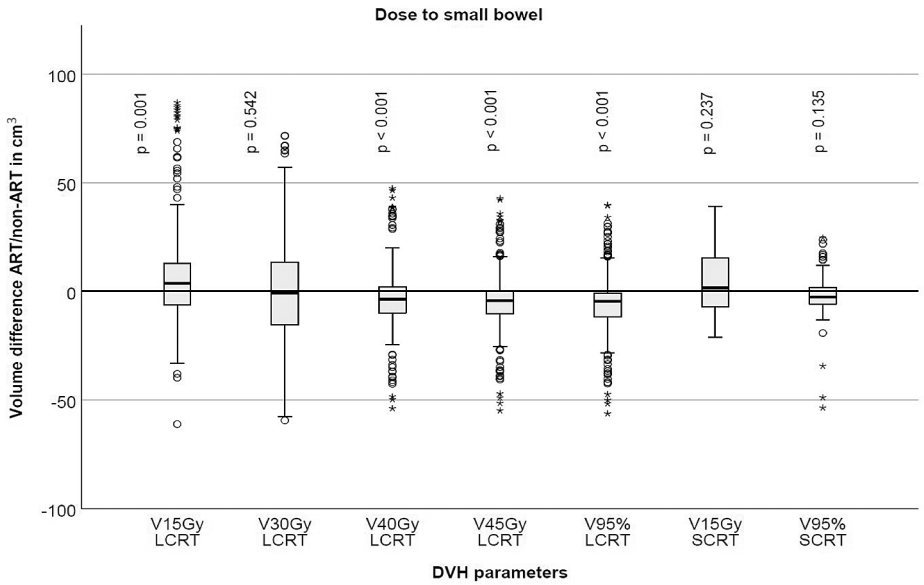

Figure 4. Boxplot showing difference in volume in cm³ for the small bowel for the different DVH parameters tested for long- and short-course radiation therapy. Negative volume favors the plan-selection strategy. The boxplot shows the interquartile range. Whiskers indicate the 5th and 95th percentiles. Outliers with values between 1.5 and 3.0 IQR (open circle) and extremes > 3.0 IQR (asterisk) are marked.

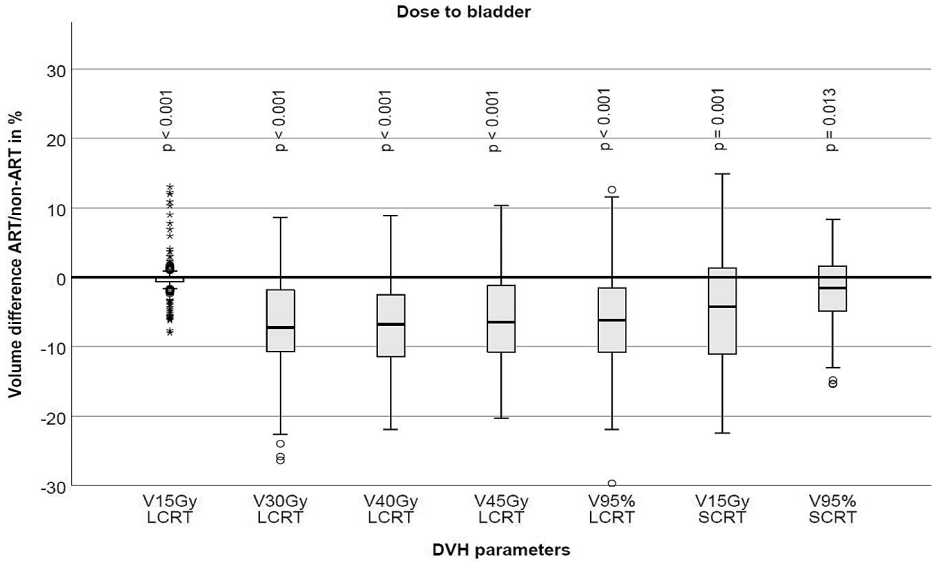

Figure 5. Boxplot showing difference in volume in percentage for bladder for the different DVH parameters tested for long and short-course radiation therapy. Negative volume favors the plan-selection strategy. The boxplot shows the interquartile range (IQR). Whiskers indicate the 5th and 95th percentiles. Outliers with values between 1.5 and 3.0 IQR (open circle) and extremes > 3.0 IQR (asterisk) are marked.

Discussion

This paper provides the first dosimetric comparison between a clinically implemented adaptive treatment and a non-adaptive treatment in external radiation therapy for rectal cancer. Based on a single CT scan, the plan-selection strategy used variable anterior margins to the upper mesorectum, and the margin was selected based on daily CBCT. This adaptive treatment maintained coverage of the target volume and reduced the dose to the small bowel and bladder.

The majority of the tested dose levels were significantly better but the absolute differences for the total cohort were small. However, for individual patients there can be substantial benefits and this raises the question about costs and potential benefit. For our department, where daily online CBCT imaging is standard and plan selection is also used for cervix and bladder, implementing plan selection for rectum was rather straightforward. Procedures, education and modifications of the technical infrastructure could be reused from the earlier implementations. However, plan adaptation for rectum may not be the first tumor type of choice when starting with a plan selection procedure from scratch.

A limitation of our study is the rather small sample size. Coincidentally, LCRT and SCRT were of equal size in this clinical cohort. Due to their different fraction doses, the two treatment schemes were analyzed separately. While Nijkamp et al. [3, 4, 6] describe different geometrical uncertainties for LCRT and SCRT, and also for male and female, prone and supine, the sample size in our cohort was too small to compare the two treatment schemes with respect to the benefit of plan selection. This cohort of 20 patients with a total of 300 fractions is sufficient to test the difference between ART and non-ART because data of different fractions within one patient can be considered independent due to large day-to-day variation of the mesorectum and OARs. The different DVH parameters that were considered, are not expected to be independent, but, because literature on IMRT/VMAT based dose volume predictors is sparse and inconclusive, we reported all tested DVH parameters anyway.

In this cohort, the dose to the small bowel (V15Gy, V95%) was not found to be significantly different for SCRT between ART and non-ART, whereas it was significantly different for LCRT (V15Gy, V40Gy, V45Gy and V95%). This difference may have been due to the time trend towards smaller rectum volumes described in the literature for long-course treatments in the prostate and rectum [6, 29]. It may also have been caused by the limited sample size of 10 patients, each of whom received only 5 fractions.

A second limitation of our study is the comparison of the dose levels per

fraction. The evaluation of dose levels per fraction was based on the corresponding total dose levels, such as V0.6Gy for V15Gy (LCRT). Evaluating the actual total dose for the entire treatment would require the accumulation of the fractional dose distribution, for which the deformable image registration algorithms available are not sufficiently accurate [23]. This explains our decision to test the difference doses to OARs between the adaptive and non-adaptive strategy per fraction.

In this study the initially planned dose in combination with the structures as delineated on CBCT were used to evaluate coverage of the target volume and dose to the OARs, because dose calculation based solely on CBCT scans has uncertainties since CBCT grey values were not calibrated. As a consequence, the dosimetric effect of anatomical changes (for example, air in rectum) was not taken into account. Alternatively, the planning CT could be deformably registered to the CBCT to use for dose calculation. Deformable image registration, especially in the presence or absence of air, has its limitations as well. Independent of the method used for recalculation of the dose, anatomical changes would affect the results for both ART and non-ART to some extent and not so much the difference between ART and non-ART.

Our results are similar to those in our study (see Lutkenhaus et al.) [19], which,

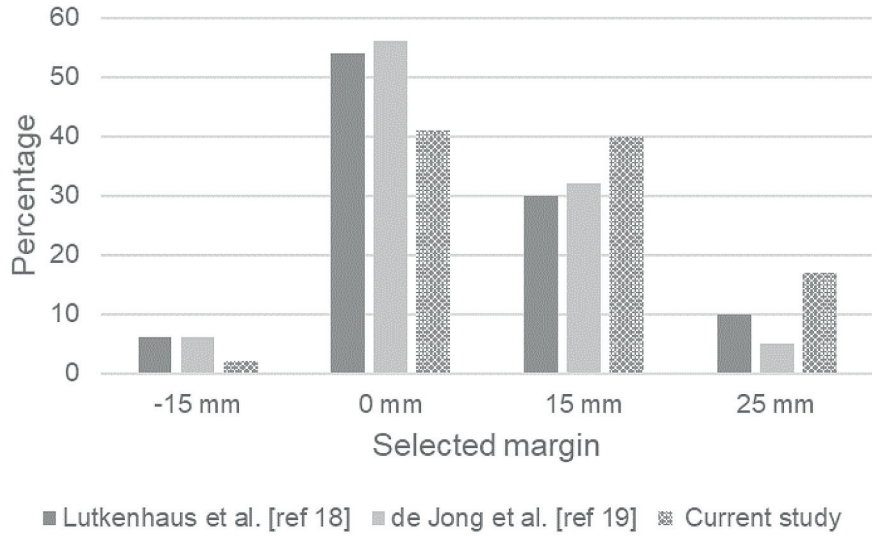

Figure 6. Bar chart showing the distribution of selected margins. Solid grays show two comparable retrospective studies; the dotted bar shows the current clinical study. The chart shows a shift towards larger plans under clinical conditions.

in SCRT only, describes the dosimetric benefit of plan selection in a simulation planning study conducted as part of our implementation strategy. Our current prospective study shows that the dosimetric benefit of the adaptive treatment remains in a clinical setting. What did change was the distribution of plans. In approximate terms, while selection of the 15 mm plan increased from approximately 30 to 40%, and selection of the 25 mm plan increased from 8 to 17%, selection of the 0 mm plan fell from 55 to 41% (Fig. 6) [19, 20]. As observers in a simulated study have more time to evaluate images and make hypothetical decisions than in clinical decision-making involving an actual patient, this may have resulted in a change of the distribution towards larger plans with more certainty about the target coverage in cases involving challenging image quality. This would be consistent with the retrospective review, which showed that a smaller plan could have been selected in 20% of fractions and a larger margin should have been selected in 2% of fractions. Even with this shift towards larger plans, the benefit of plan selection remains. Improving CBCT image quality might increase confidence, and also increase the benefits of plan selection.

In this study, the average extent to which the OARs were spared was limited. The re-planning strategy proposed by Nijkamp et al. [30] delivers more sparing to the OARs, as it does more than merely compensate the variability of the upper mesorectum. This strategy is based on 5 repeat CT scans and 5 repeat delineations followed by an new plan of an updated CTV structure, which deliver a 34 cm^3 reduction to the bowel area for V15Gy, and a 30 cm^3 reduction for V45Gy. Our study reports median reductions from 853 cm^3 to 847 cm^3 and 187 cm^3 to 179 cm^3 for V15Gy and V45Gy. For the bladder, Nijkamp et al. reported a reduction in mean dose to the bladder of 2.5Gy, compared to the median reduction of 2.8Gy to 2.7Gy we found in our study. While Nijkamp's initial anterior PTV margin to the upper mesorectum was 24 mm, our strategy compares to a 20 mm anterior PTV margin. The approach proposed by Nijkamp has a higher workload than the strategy proposed in this study, which is based on a single CT scan and single delineation. The extra workload in our adaptive strategy is incurred at treatment planning, thus adding 120 min to the total workflow.

Passoni et al. and Raso et al [31, 32] also reported on an adaptive procedure, but applied to the boost of the residual tumor during the last 6 fractions of LCRT. Byskov et al. [33] describe an adaptive approach to re-irradiation of rectal recurrence. As neither strategy is applied to the mesorectum, they cannot easily be compared.

A practical hurdle to the widespread adoption of plan selection is that if, in current commercial systems, a margin is selected that best fits the target on the CBCT, the corresponding plan in the delivery system has to be selected manually. Software support for an automatic plan delivery after selection of the plan would make the procedure less error-prone.
To exclude inter-observer variation, this study used the delineations of a single observer on CBCT. To minimize intra-observer variation, the clinical delineations on the CT scan were used as a guideline for the delineations on the CBCT. In their report on the intra-observer error of this observer (RdJ), Nijkamp et al. found maximum values of 3 mm SD for males and 2 mm for females [3].
We based plan selection on margin structures and not on the 95% isodose: in our department, this is clinical practice for image guidance for the other sites. However, perfect plan conformance will not always be possible, such as in situations with unfavorable edge-structure shapes. As a consequence, a larger margin may have been chosen than required for cases where the target volume on the CBCT lay inside the 95% isodose volume for one of the margin plans but outside the corresponding PTV.

Conclusion

6

A clinically implemented adaptive plan selection strategy for rectal cancer, based on a single CT scan with variable anterior margins to the upper meso-rectum, maintained coverage of the mesorectum and reduced the dose to the small bowel and bladder. For individual patients the benefit can be substantial.

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Chapter 7

Online adaptive radiotherapy compared to plan selection for rectal cancer: quantifying the benefit.

Radiation Oncology 15; Jul 8 (2020)

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Abstract

Background: To compare online adaptive radiation therapy (ART) to a clinically implemented plan selection strategy (PS) with respect to dose to the organs at risk (OAR) for rectal cancer.

Methods: The first 20 patients treated with PS between May-September 2016 were included. This resulted in 10 short (SCRT) and 10 long (LCRT) course radiotherapy treatment schedules with a total of 300 Conebeam CT scans (CBCT). New dual arc VMAT plans were generated using auto-planning for both the online ART and PS strategy.

For each fraction bowel bag, bladder and mesorectum were delineated on daily Conebeam CTs. The dose distribution planned was used to calculate daily DVHs. Coverage of the CTV was calculated, as defined by the dose received by 99% of the CTV volume (D99%). The volume of normal tissue irradiated with 95% of the prescribed fraction dose was calculated by calculating the volume receiving 95% of the prescribed fraction or more dose minus the volume of the CTV. For each fraction the difference between the plan selection and online adaptive strategy of each DVH parameter was calculated, as well as the average difference per patient.

Results: Target coverage remained the same for online ART. The median volume of the normal tissue irradiated with 95% of the prescribed dose dropped from 642 cm^3 (PS) to 237 cm^3 (online-ART)($p<0.001$). Online ART reduced dose to the OARs for all tested dose levels for SCRT and LCRT ($p<0.001$). For V15Gy of the bowel bag the median difference over all fractions of all patients was -126 cm^3 in LCRT, while the average difference per patient ranged from -206 cm^3 to -40 cm^3. For SCRT the median difference was -62 cm^3, while the range of the average difference per patient was -105 cm^3 to -51 cm^3.

For V15Gy of the bladder the median difference over all fractions of all patients was 26% in LCRT, while the average difference per patient ranged from -34% to 12%. For SCRT the median difference of V95% was -8%, while the range of the average difference per patient was -29 to 0%.

Conclusions: Online ART for rectal cancer reduces dose the OARs significantly compared to a clinically implemented plan selection strategy, without compromising target coverage.

Online adaptive radiotherapy compared to plan selection: quantifying the benefit

Background

Pre-operative external beam radiotherapy combined with chemotherapy and followed by surgery is standard of care for non-metastasized locally advanced rectal cancer [1]. For any treatment site in the pelvic region, radiotherapy is associated with toxicity due to the inevitable dose to the organs at risk (OAR) such as the bladder and small bowel [2]. Shaping the dose with steep dose gradients using Intensity Modulated Radiation therapy (IMRT) or Volumetric Modulated Arc Therapy (VMAT) has become common practice [3, 4], but to take optimal advantage of these treatment techniques, adequate PTV margins and visualization of the target volume prior to each treatment fraction to avoid misses is essential. Population-based margins are typically very large in the pelvic region due to large day-to-day variations of the target volume [5-9]. Online Conebeam CT (CBCT) image guidance at the treatment machine is widely applied and very effective in this patient group for verification of patient position and target coverage, while using the population-based (fixed) margins. Even with its limited soft-tissue contrast online CBCT image guidance can also be used for an adaptive procedure using plan selection. Plan selection using more individualized and therefore smaller margins enables reducing the dose to OARs and has proven its value in the treatment of bladder and cervix [10-14]. For rectal cancer we analyzed previously in a simulated study [15, 16] and prospective clinical study [17] such a plan selection strategy yields only a small advantage for the average population but has a benefit for individual patients and has been clinical practice in our department since 2016. Recent developments in improved image quality for treatment guidance, such as MRI-guided radiotherapy and CBCT guidance, as well as developments in fast and precise auto-contouring [18] and auto-planning ‘marks the beginning of a new era’ [19]. Online adaptive treatment, based on both MRI and CBCT guidance, is now a real possibility [19-22] and surely promising in reducing dose to the OARs even further.

Although the first step towards individualized margins using plan selection has been proven feasible and is clinically implemented for rectal cancer [16, 23], daily online adaptation is expected to be beneficial. To our knowledge the benefit of online adaptation for rectal cancer has not been reported yet, with a clinically implemented plan selection as the baseline.

The aim of this study is to assess the added value of online adaptive radiotherapy (online ART) for rectal cancer, by comparing the online adaptive treatment to a clinically implemented plan selection strategy by quantifying the

benefit with respect to dose to the OARs and coverage of the target volume.

Methods

In this study we used the same methodology and patient cohort [17] as in our previous study, a comparison between a fixed margin and a variable margin technique, e.g. plan selection, but applied to a clinical cohort of LCRT (25x2Gy) and SCRT (5x5Gy). For the plan selection distribution there is a brief summary (Supplement 1, 2) as the results are described in our previous article [17].

Patients

The first twenty consecutive patients that underwent plan selection between May and September 2016 were included in this study. This cohort included 20 patients of which 10 patients were treated with a short course treatment (5x5Gy)(SCRT) and 10 patients with a long course treatment (25x2Gy)(LCRT). Boost dose to the tumor is not part of the treatment regimen. Patient characteristics can be found in Supplement 3. The schedule regimen was determined by stage and resectability of the primary tumor. All fractions (N = 300) were used for analysis. All patients were positioned supine with a knee support and their arms raised over their heads (Posirest, CIVCO).

Planning CT and target volume

A planning CT was acquired with a full bladder, patients were instructed to empty the bladder 1.5 h before CT acquisition and to drink subsequently 0.5 l of fluid. No additional instructions have been given with respect to rectal filling and thus, spontaneous rectum filling was used.

Structures, based on the delineation guidelines by Roels et al. [24], were contoured using Advantage SIM (GE) or Velocity (Velocity, AI 3.2, Varian Medical Systems).

The GTV, defined as tumor and positive lymph nodes, was delineated. The tumor itself is indicated on the reference scan but no boost dose is applied to the tumor. For CTV, the mesorectum, presacral space, internal iliac lymph node regions and, when applicable, obturator lymph node regions, were delineated by a radiation oncologist. With the transition at the base of the bladder the mesorectum was divided into an upper and lower part to be able to differentiate margins between the upper and lower mesorectum based on the geometrical uncertainties reported by Nijkamp et al. [6, 7, 9]. Radiation Therapists (RTTs) contoured the OARs (i.e., the bladder, bowel bag for small bowel and femur heads) according to RTOG guidelines [25].

Plan selection margins

PTV margins for the clinically applied plan selection strategy around the CTV lymph node regions were created by expanding the volumes with 8 mm in all directions. The CTV pre sacral space was expanded with 10 mm in all directions. For the upper and lower mesorectum the volume was expanded with 10 mm in all directions, except for the ventral side. The ventral side of the lower mesorectum had an fixed anterior margin of 15 mm, whereas the ventral side of the upper mesorectum had variable anterior margins to use for plan selection. Two sets of margins were defined according to the anatomy captured on the planning CT scan: For an empty rectum (Supplement 4(a)) on planning CT we used PTV margins of 25 mm, 15 mm, 0 mm, as − 15 mm was unlikely to be needed. For a full rectum on planning CT (Supplement 4(b)), we used 15 mm, 0 mm and − 15 mm, as 25 mm was unlikely to be needed [15, 16].

Clinical procedure – registration, correction and plan selection

All CBCT scans were registered to the pelvic bony anatomy (XVI5.0, Elekta) using translations and rotations. If the rotation around one of the axes was larger than 4°, the patient was re-aligned. Remaining setup rotations under 4° were converted into a table correction (translations-only) by taken out the rotations using a rotation point at the center of gravity of the PTV. This means that rotational errors were still present during treatment delivery. Based on the anatomy of the day the smallest plan encompassing the target volume was selected to treat the patient.

Delineations

A graphic overview of the workflow can be found in Supplement 5. Each CBCT scan (N = 300) was resampled to the planning CT including the online table correction, which represented the anatomy of the patient at treatment, and exported to Velocity. For this study, delineations used in our previous study on these CBCT scans were available of upper and lower mesorectum as well as bladder and bowel bag. These structures were delineated by a single experienced observer (RdJ). The elective lymph nodes and pre sacral space were not re-delineated. Instead, the delineations were propagated from the planning CT to the CBCT using a bony anatomy match. The total CTV volume was uniformly expanded with 3 mm to create the PTV for the online adaptive

strategy. Using the identity transformation, these structures were then propagated to the planning CT scan.

Dose calculation and comparison between the online adaptive treatment and plan selection strategy

For the plan selection strategy a new plan library was created and for the online adaptive strategy a treatment plan was created for each fraction, in both cases using automated planning [26] with the same clinical goals with the same prioritization (Plan Explorer, RaySearch v6.99). The planning technique was VMAT dual arc with energy 10 MV using the planning CT for dose calculation. In order to avoid treatments plans with too much modulation, for each arc a maximum of 300 MU and 750 MU was allowed for plans with 2 Gy and 5 Gy prescribed fraction dose, respectively. All plans were checked for clinical acceptability. This resulted in 300 treatment plans for the online adaptive treatment and 60 plans for the plan selection strategy.

Evaluation

For both the plan selection strategy and the online adaptive strategy the DVHs for each fraction were calculated using the planned dose distribution on the planning CT together with the delineated structures from the registered CBCT. For the plan selection strategy only the selected plan for that fraction was used. Consequently only the anatomical changes to structures delineated on CBCT were taken into account. Literature on predictive dose volume parameters is relatively sparse, therefore a range of DVH parameters based on the parameters suggested in de QUANTEC papers [27, 28] as well as DVH parameters suggested by Mouttet-Audouard et al. [29] and Deville et al. [30, 31] were evaluated (i.e. the volume receiving at least 15 Gy (V15Gy), 30 Gy (V30Gy), 40 Gy (V40Gy), 45 Gy (V45Gy)). Deformable registration inevitably involves uncertainties [32], especially in the pelvic region with e.g. appearing and disappearing gas. For the comparison between the online adaptive and variable margin technique, e.g. plan selection, we chose to avoid dose accumulation by deformable registration for assessing the total dose to OARs. Instead the corresponding fractional dose levels were used and the difference of the dose to the OARs between the online adaptive treatment and plan selection strategy was tested per fraction.

The fractional dose levels analyzed for LCRT were V0.6Gy (equals V15Gy), V1.2Gy (equals V30Gy), V1.6Gy (equals V40Gy), V1.8Gy (equals V45Gy), V95%. The fractional dose levels analyzed for SCRT were V3.0Gy (equals V15Gy), V95%. Dose levels higher than the prescribed dose were skipped from evaluation. The mean dose (Dmean) for bladder was analyzed for both SCRT and LCRT.

For each fraction the difference between the plan selection and online adaptive strategy of each DVH parameter was calculated, as well as the average difference per patient.

We calculated target coverage as a percentage of the prescribed dose received by 99% of the CTV volume (D99%).

Statistical analysis

Wilcoxon signed-rank sum tests were used to test the difference between online adaptive strategy and plan selection for:

1) Volume of normal tissue irradiated with 95% of the prescribed fraction dose defined by the volume receiving 95% of the prescribed dose or more minus the volume of the CTV.
2) Difference of all DVH parameters for dose to the OARs per fraction.

Significance was set at $p < 0.05$. Statistical analysis was performed using SPSS25.

Results

Target coverage for the total cohort, expressed as D99%, the percentage of the prescribed dose received by 99% of the CTV volume, was on average 98.5% for plan selection and 98.7% for online adaptive strategy.

1) Volume of normal tissue irradiated with 95% of the prescribed dose

For the total cohort the median volume of the normal tissue irradiated with 95% of the prescribed dose dropped from 642 cm^3 using plan selection to 237 cm^3 using the online adaptive strategy, which was statistically significant ($p < 0.001$) (Fig. 1).

2) Dose to the organs at risk

Overall, compared to the plan selection strategy, the online adaptive strategy reduced dose to the bowel bag ($p < 0.001$) (Fig. 2) and bladder ($p < 0.001$) (Fig. 3) for all dose levels.

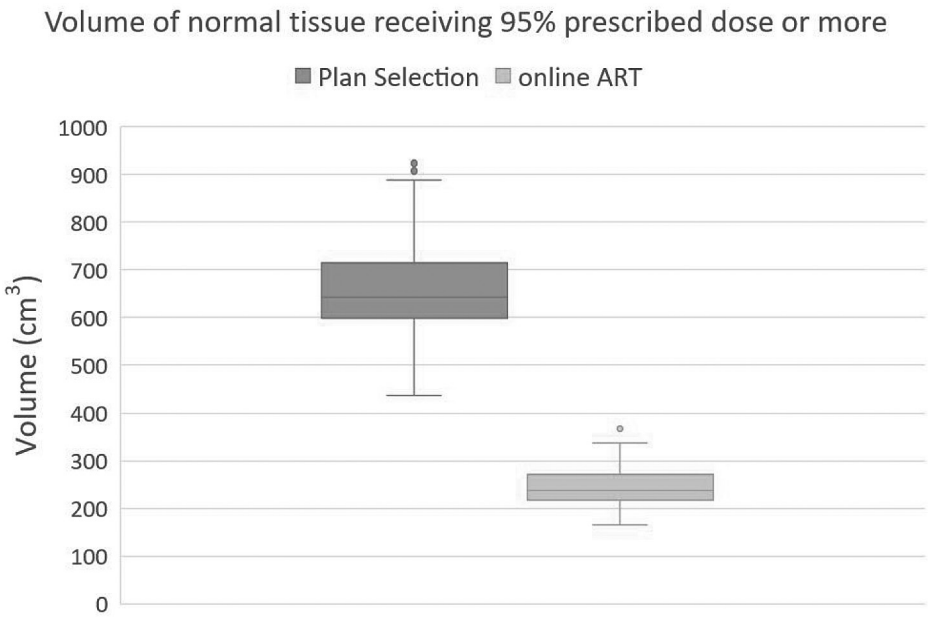

Figure 1. Boxplot showing difference in normal tissue irradiated between Plan selection and Online ART for the total cohort. The boxplot shows the interquartile range. Whiskers indicate the 5th and 95th percentiles. Outliers (°) are marked.

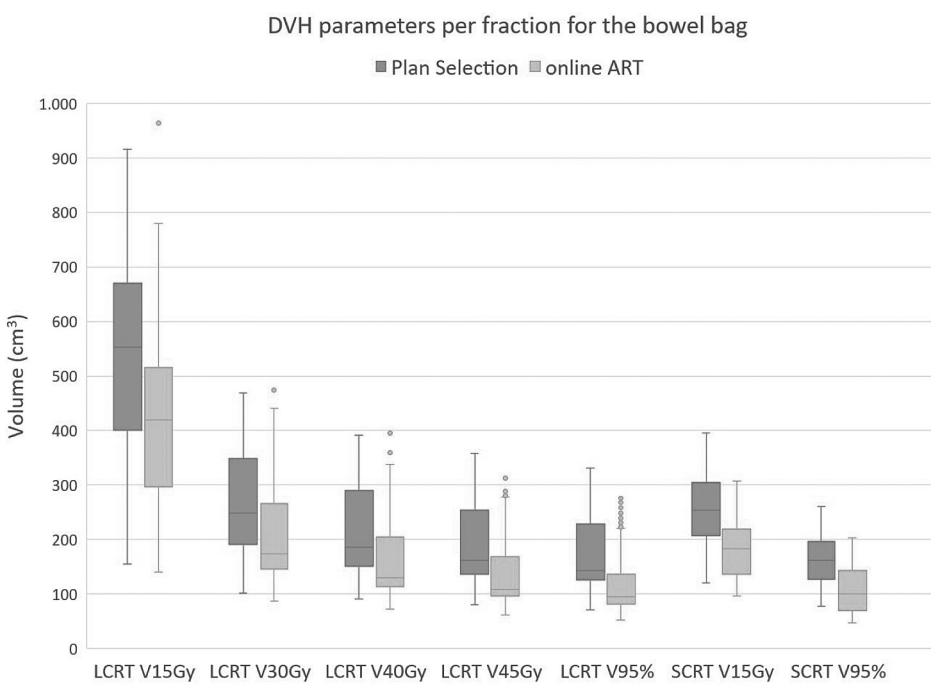

Figure 2. Boxplot showing the volume of small bowel receiving x Gy for different DVH parameters for both Plan selection and online ART. The boxplot shows the interquartile range. Whiskers indicate the 5th and 95th percentiles. Outliers (°) are marked.

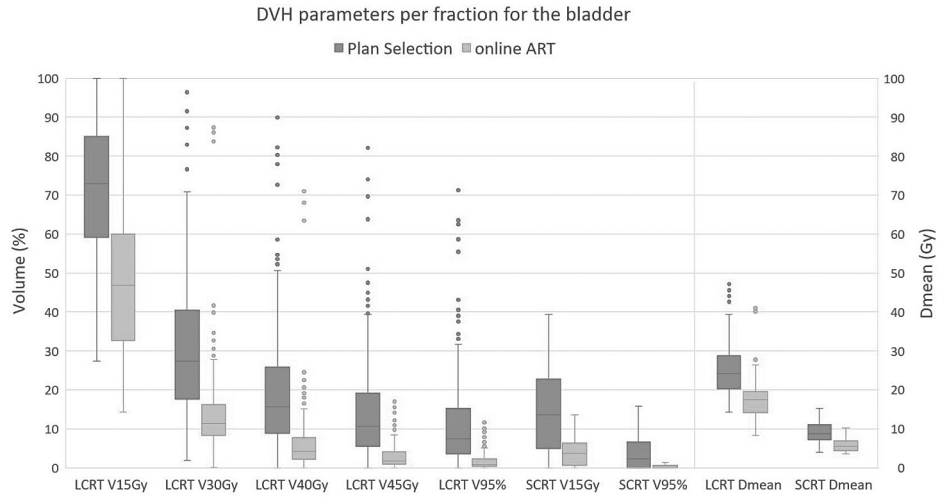

Figure 3. Boxplot showing the volume of bladder receiving x Gy for different DVH parameters for both Plan selection and online ART. The boxplot shows the interquartile range. Whiskers indicate the 5th and 95th percentiles. Outliers (°) are marked.

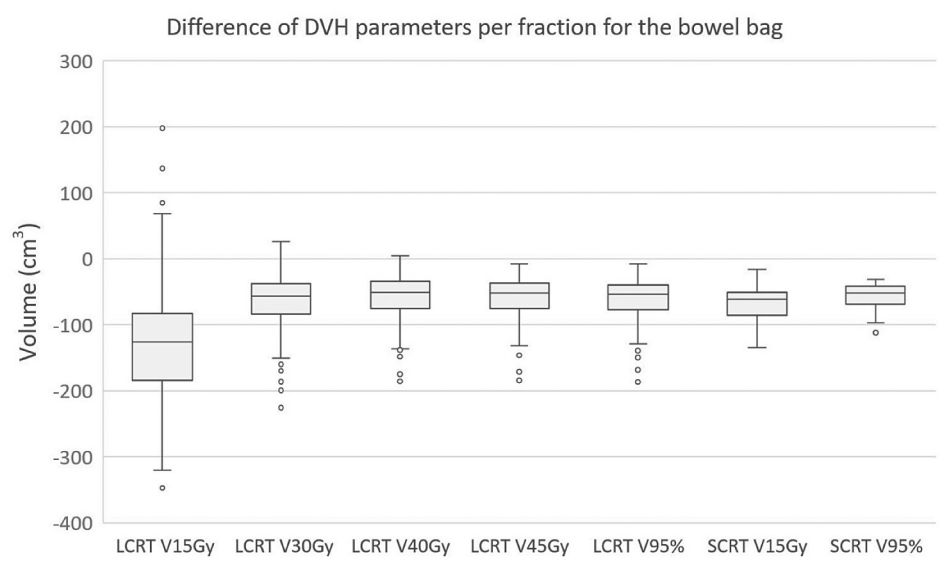

Figure 4. Boxplot showing the difference in volume of small bowel receiving x Gy for different DVH parameters. The boxplot shows the interquartile range. Whiskers indicate the 5th and 95th percentiles. Outliers (°) are marked.

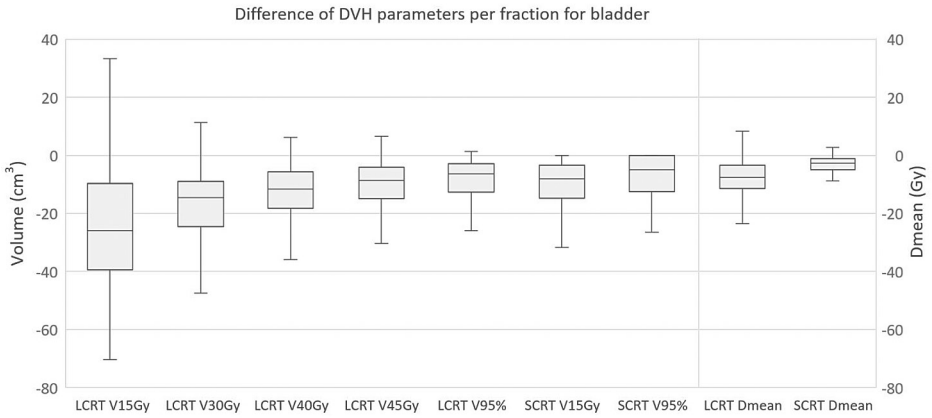

Figure 5. Boxplot showing the difference in volume of bladder receiving x Gy for different DVH parameters. The boxplot shows the interquartile range. Whiskers indicate the 5th and 95th percentiles. Outliers (°) are marked.

Table 1

				AVG	*min*	*max*
Bowel bag	LCRT	V15	(cm^3)	-127	-206	-40
	LCRT	V30	(cm^3)	-64	-117	-19
	LCRT	V40	(cm^3)	-58	-102	-25
	LCRT	V45	(cm^3)	-60	-101	-30
	LCRT	V95%	(cm^3)	-62	-101	-34
	SCRT	V15	(cm^3)	-69	-105	-51
	SCRT	V95%	(cm^3)	-57	-86	-42
Bladder	LCRT	V15	(%)	-24	-34	12
	LCRT	V30	(%)	-18	-39	-3
	LCRT	V40	(%)	-14	-39	-4
	LCRT	V45	(%)	-12	-36	-3
	LCRT	V95%	(%)	-10	-32	-2
	LCRT	Dmean	Gy	-8	-15	0
	SCRT	V15	(%)	-11	-29	0
	SCRT	V95%	(%)	-4	-12	0
	SCRT	Dmean	Gy	-3	-8	0

For V15Gy of the bowel bag the median difference over all fractions of all patients was − 126 cm^3 in LCRT, while the average difference per patient ranged from − 206 cm^3 to − 40 cm^3. For SCRT the median difference was − 62 cm^3, while the range of the average difference per patient was − 105 cm^3 to − 51 cm^3. Boxplots of the differences of all DVH parameters are shown in Fig. 4, while the range of the average differences per patient can be found in Table 1.

For V15Gy of the bladder the median difference over all fractions of all patients was 26% in LCRT, while the average difference per patient ranged from − 34 to 12%. For SCRT the median difference of V95% was − 8%, while the range of the average difference per patient was − 29 to 0%. Boxplots of the differences of all DVH parameters are shown in Fig. 5, while the range of the average differences per patient can be found in Table 1.

Discussion

This study is the next step in our research to improve radiotherapy treatment for rectal cancer. After reporting on the possible benefit with a simulated plan selection strategy for SCRT [15, 16] and a prospective comparison for both SCRT and LCRT [17] we now present the results of the comparison between a simulated online adaptive treatment to a clinically implemented CBCT-based plan selection strategy for SCRT and LCRT. The results when comparing plan selection to the online strategy show large and significant reductions for both bowel bag and bladder for all DVH parameters analyzed.

The online strategy results in much less dose to the normal tissue because of smaller margins used. It is likely that this translates into a clinically relevant reduction of toxicity. Toxicity has been mostly reported in prostate patients that are treated with higher doses than rectal cancer. Holyoake et al. [33] conducted a meta-analysis looking at the mean difference in volume for small bowel for different dose levels between grades 0–2 and grade 3 toxicity and a toxicity risk for V10Gy and V40Gy received by normal fractionated radiotherapy. In all included studies the patients were treated with chemotherapy concomitantly. They found evidence for a significant dose-volume-toxicity response effect for a wide range of clinically-relevant doses in the treatment of rectal cancer. Comparison with our results is hampered by the different delineation of small bowel (bowel loops versus bowel bag). For late toxicity for bladder the

significance of reduced dose is much less evident. Fiorini et al. [34] summarizes that only high doses (> 60-65Gy) to small volumes and 50-60Gy to whole bladder increases the risk of moderate to high toxicity, analyzed for different treatment sites. These dose-volume-toxicity response fall outside of the clinically-relevant doses for rectal cancer. Harsolia et al. [35] however suggest to limit the bladder wall V30Gy to < 30 cm^3 (if wall information is not available to use solid V30Gy) based on a large prospective study on prostate patients assessing predictors for grade 2 and 3 chronic urinary toxicity. For acute toxicity for bladder in rectal patients Appelt et al. [36] report a dose-cut-off model of V35Gy and later suggest constraints [37] for bladder of V21Gy < 15% and V25Gy < 5% (SCRT) and V35GY < 22% and V50Gy < 7% (LCRT) in early stage rectal cancer.

This study used a 3 mm margin around the entire CTV volume for the online adaptive treatment. This 3 mm margin is often suggested in the literature for different sites [38-41] when using online MRI image guidance. Even though in principle all shape variations and rotations are corrected with the online strategy, some uncertainties will remain [42, 43]. Intra fraction motion, i.e. shape change of the rectum during treatment, is not accounted for. This has been assessed by Kleijnen et al. [44]. They observed that 90% of the time motion is below 3.6 mm for the CTV when looking at 1 min time intervals. Their results cannot be translated into margins but they state “plan of the day’ approaches [are] only meaningful if imaging, planning, and delivery can be done in under 18 min. Also, delineation uncertainty has always been a prominent factor contributing to the margin [43, 45, 46]. Conventionally, when designing a plan on a single pre-treatment CT scan this uncertainty is systematic in nature. However, for an adaptive procedure with multiple fractions, with a daily (re-) delineation is repeated (or adjustment), that error can be characterized as random [42]. Data on this random uncertainty, obtained under realistic clinical time constraints, is currently lacking and should be quantified. Previously there have been reports on overestimating accuracy with detrimental effects on local control [47].

A limitation of our study is the use of the original delineation of the lymph node region. An online adaptive workflow will be a balance between complexity and speed. Keeping the original lymph node delineation will speed up the adaptive process. Gwynne reports in a review that pelvic vessels have a relatively stable position in relation to the bony pelvis and a 3 mm margin would be sufficient [48-50]. Although the vessels and with that the lymph nodes are stable Nijkamp et al. [6, 7, 9] suggest to use non uniform margins of a 5–13 mm for presacral space for an offline adaptive workflow. This is not due to variety in lymph node position but because of bowel loops moving in and out of the pre sacral volume. Adapting the lymph node region as well might be necessary when using a 3 mm margin, ands need further research.

A limitation of this study is the moderate number of patients (20) and fractions (300) used for analyses. The significance and large difference between the online strategy and plan selection for all dose levels and for both SCRT and LCRT is, however, convincing. The quantification of the added value of online adaptation could benefit from larger patient numbers.

In our study the initially planned dose was used to evaluate coverage of the target volume and dose to the OARs per fraction instead of dose accumulation. Preferably the dose would be accumulated but deformable image registration, especially in the presence or absence of air, has large limitations [32]. By analyzing the dose per fraction we avoided additional uncertainties that would be introduced by deformable image registration and subsequent dose accumulation. However, an accurate deformable image registration algorithm, taking the complexities of the pelvic region into account, should be preferred whenever that becomes available.

To compare de DVHs per fraction a different option could have been to deform the planning CT to the CBCT and thus account for difference in densities due to anatomical changes (for example, air in rectum). However this method introduces an uncertainty as well. If anything, dose calculation on CBCT would favor the online adaptive treatment, because density changes would be accounted for with daily plan creation. For both approaches the uncertainty applies to both the plan selection and online adaptive treatment with the same magnitude and therefore does not affect our results. Nevertheless, we expect that the effect will be small as compared to the dosimetric effect of using much smaller PTV margins.

Online adaptive strategies require not only accurate and fast contouring and treatment planning but also a reconfiguration of workflows and responsibilities. It may very well result in the need of the presence of radiation oncologist, medical physicist and/or dosimetrist at the treatment machines. Also, timeslots may need to be adjusted as adaptation will take additional time [51, 52].

The margin choice (3 mm) is important for the conclusion of this paper. Moving towards online adaptive treatment for rectal cancer the practicality, accuracy and quality needs to be investigated to be able to calculate appropriate margins. This paper however, gives a first estimate of the potential benefit of online adaptation for rectum and helps in the process of prioritizing treatment sites.

Conclusion

Radiotherapy with online adaptive re-planning of locally advanced rectal cancer reduces dose to the bladder and small bowel significantly, compared to a clinically implemented plan selection strategy.

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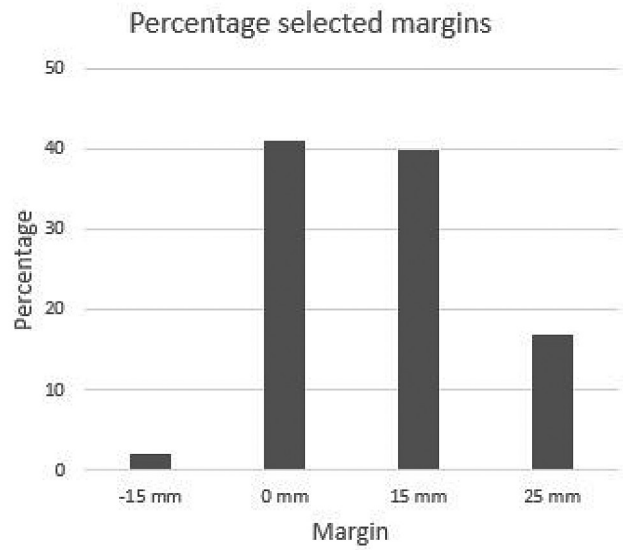
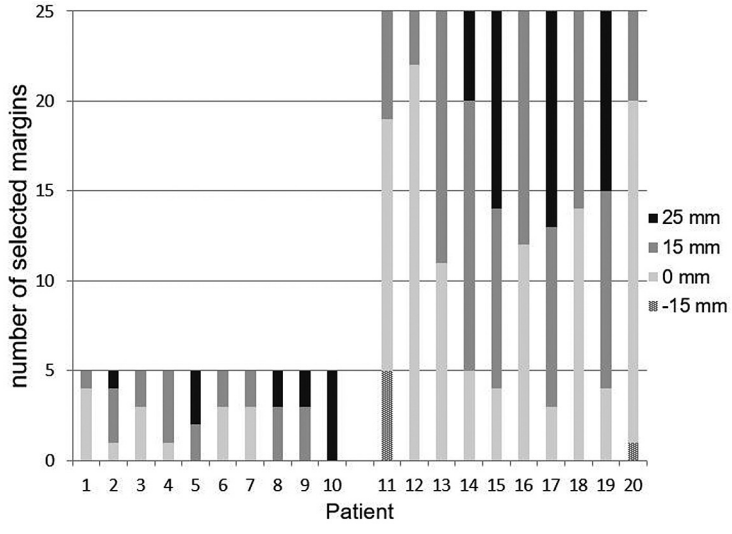
Supplementary Material



Supplement 1. Distribution of selected margins for all patients and all fractions.



Supplement 2. Distribution of selected margins per patient sorted on short (5x5Gy) and long (25x2Gy) treatment schedules.

Supplement 3. Patient characteristics.

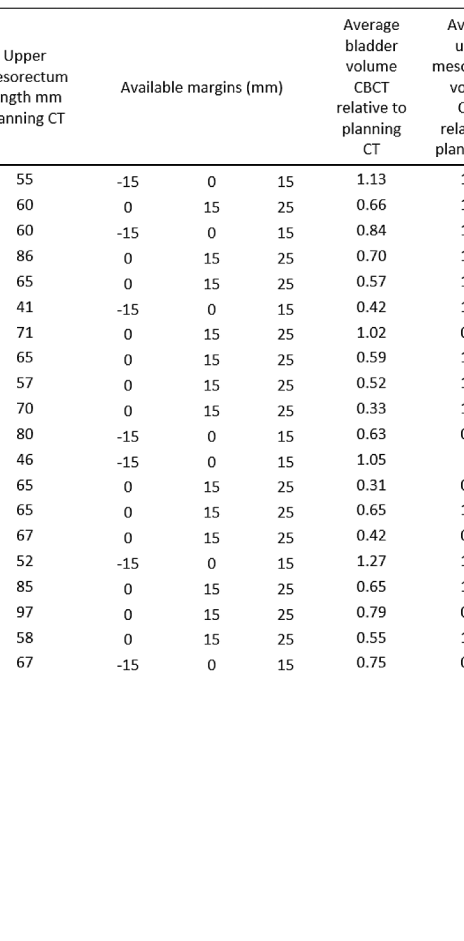
Table 1: *Patient characteristics*

X	Age	Sex	Tumor stage	Treatment scheme	Chemo	GTV location	Surgery	Bladder volume cm³ planning CT	Upper mesorectum volume cm³ planning CT	Upper mesorectum length mm planning CT	Available margins (mm)			Average bladder volume CBCT relative to planning CT	Average upper mesorectum volume CBCT relative to planning CT
1	65	M	cT3N1M0	5x5 Gy	N	proximal	LAR	185	259	55	-15	0	15	1.13	1.03
2	70	F	cT3N0M0	5x5 Gy	N	mid	LAR	558	143	60	0	15	25	0.66	1.05
3	63	M	cT4N1M0	5x5 Gy	Y	distal	ns	203	269	60	-15	0	15	0.84	1.06
4	71	M	cT3N1M0	5x5 Gy	N	mid	LAR	622	184	86	0	15	25	0.70	1.14
5	74	M	cT3N0M0	5x5 Gy	N	proximal	LAR	557	226	65	0	15	25	0.57	1.06
6	56	F	cT3N1M0	5x5 Gy	N	mid	LAR	135	156	41	-15	0	15	0.42	1.02
7	73	M	cT3N2M1	5x5 Gy	Y	proximal	LAR	160	357	71	0	15	25	1.02	0.97
8	70	M	cT3N2M0	5x5 Gy	N	distal	APR	295	244	65	0	15	25	0.59	1.03
9	40	F	cT3N1M0	5x5 Gy	N	mid	LAR	941	131	57	0	15	25	0.52	1.25
10	78	M	cT4N1M0	5x5 Gy	N	rectosigmoid	LAR	613	289	70	0	15	25	0.33	1.06
11	71	F	cT3N1M0	25x2 Gy	Y	proximal	LAR	791	393	80	-15	0	15	0.63	0.71
12	66	M	cT3N2M0	25x2 Gy	Y	mid	LAR	150	185	46	-15	0	15	1.05	0.9
13	64	F	cT3N2M0	25x2 Gy	Y	distal	APR	403	223	65	0	15	25	0.31	0.95
14	65	M	cT3N2M0	25x2 Gy	Y	proximal	LAR	446	309	65	0	15	25	0.65	1.09
15	55	F	cT4N0M0	25x2 Gy	Y	distal	LAR	595	186	67	0	15	25	0.42	0.91
16	59	M	cT3N0M0	25x2 Gy	Y	mid	LAR	166	170	52	-15	0	15	1.27	1.00
17	72	M	cT3N2M0	25x2 Gy	Y	proximal	LAR	420	373	85	0	15	25	0.65	1.05
18	69	F	cT4N1M0	25x2 Gy	Y	mid	LAR	511	442	97	0	15	25	0.79	0.99
19	77	M	cT3N2M0	25x2 Gy	Y	distal	ns	456	128	58	0	15	25	0.55	1.10
20	60	M	cT3N2M0	25x2 Gy	Y	distal	ns	392	261	67	-15	0	15	0.75	0.92

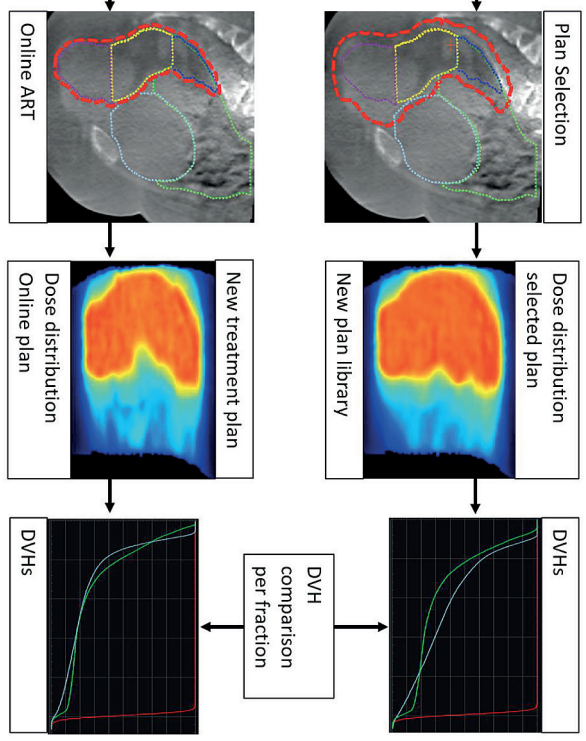
ns: not specified

LAR: low anterior resection

APR: abdominal perineal resection



Supplement 4. Margin sets based on anatomy as captured on planning CT. (1a) shows an empty rectum with a set of 25 mm, 15 mm, and 0 mm margins (red) for the upper mesorectum (blue). (1b) shows a full rectum with a set of 15 mm, 0 mm, and – 15 mm anterior margins (red) for the upper mesorectum (blue). Yellow is the lower mesorectum.



Supplement 5. Flowchart of study comparing target coverage and dose to the organs at risk (OAR). Structures of upper mesorectum (yellow), lower mesorectum (purple), bladder (light blue) and bowel bag (green) were delineated on Conebeam CT. Elective lymph nodes (blue) and presacral space were rigidly propagated from planning CT to Conebeam CT. PTV in red.

Chapter 8

Feasibility of Conebeam CT-based online adaptive radiotherapy for neoadjuvant treatment of rectal cancer.

Radiation Oncology 16; Jul 23 (2021)

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Abstract

Background: Online adaptive radiotherapy has the potential to reduce toxicity for patients treated for rectal cancer because smaller planning target volumes (PTV) margins around the entire clinical target volume (CTV) are required. The aim of this study is to describe the first clinical experience of a Conebeam CT(CBCT)-based online adaptive workflow for rectal cancer, evaluating timing of different steps in the workflow, plan quality, target coverage and patient compliance.

Methods: Twelve consecutive patients eligible for 5 x 5 Gy pre-operative radiotherapy were treated on a ring-based linear accelerator with a multidisciplinary team present at the treatment machine for each fraction. The accelerator is operated using an integrated software platform for both treatment planning and delivery. In all directions for all CTVs a PTV margin of 5 mm was used, except for the cranial/caudal borders of the total CTV where a margin of 8mm was applied. A reference plan was generated based on a single planning CT. After aligning the patient the online adaptive procedure started with acquisition of a CBCT. The planning CT scan was registered to the CBCT using deformable registration and a synthetic CT scan was generated. With the support of artificial intelligence, structure guided deformation and the synthetic CT scan contours were adapted by the system to match the anatomy on the CBCT. If necessary, these contours were adjusted before a new plan was generated. A second and third CBCT were acquired to validate the new plan with respect to CTV coverage just before and after treatment delivery, respectively. Treatment was delivered using volumetric modulated arc treatment (VMAT). All steps in this process were defined and timed.

Results: On average the timeslot needed at the treatment machine was 34 minutes. The process of acquiring a CBCT, evaluating and adjusting the contours, creating the new plan and verifying the CTV on the CBCT scan took on average 20 minutes. Including delivery and post treatment verification this was 26 minutes. Manual adjustments of the target volumes were necessary in 50% of fractions. Plan quality, target coverage and patient compliance were excellent.

Conclusions: First clinical experience with CBCT-based online adaptive radiotherapy shows it is feasible for rectal cancer.

Feasibility study for online conebeam based online adaptive radiation therapy for locally advanced rectal cancer

Background

Radiotherapy is standard of care in neoadjuvant treatment of intermediate and locally advanced rectal cancer, generally followed by Total Mesorectal Excision (TME) surgery [1]. In intermediate risk tumors radiotherapy is applied with a prescribed dose of 5 x 5 Gy in order to sterilize surgery planes. For locally advanced rectal cancer a dose of 25 x 2 Gy is given for downstaging to improve rates of complete resection. Radiotherapy comes inevitably at the cost of toxicity as a result of dose to healthy tissue, in case of rectal cancer mostly due to dose to bladder and small bowel [2, 3].

To ensure target coverage during treatment the radiotherapy target volume as defined on a single reference CT is enlarged with a PTV margin. The margin size is based on all uncertainties in the treatment chain of radiotherapy [4]. For rectal cancer the daily change in volume and shape is the main contributor to the PTV margin. It results in a required margin of up to 25 mm at the ventral side of the upper mesorectum [5-7] in order for the CTV to receive at least 95% of the prescribed dose for 90% of the patients.

Multiple steps have been taken in the last two decades to minimize toxicity of radiotherapy treatment by reducing dose to the healthy tissue without compromising coverage of the target volume. First, treatment delivery and planning technique evolved to intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT), which enabled tightly shaped dose distribution around the PTV with a steep dose gradient [8-10]. Secondly, integrated in-room 3D-kV imaging (Conebeam CT (CBCT)) made it possible to position the patient and assess target coverage on a daily basis [11]. In case of insufficient target coverage due to systematic local anatomical changes or more global anatomical changes that would result in a suboptimal dose distribution, the plan could be adapted in an offline setting using repeat CT scan [12]. Online CBCT also allows a plan selection strategy where a-priori generated plans are available and the plan that best fits the anatomy of the day is selected [13-15]. We previously demonstrated that this plan selection strategy can reduce dose to the organs at risk (OAR) significantly for individual patients for whom the population based margins (PTV=20 to 25mm) are too large. For the group of patients as a whole the benefit of plan selection is limited [16].

Recently, technologies have become available that enable online adaptive radiotherapy (ART) such as in-room online MRI guidance. It combines improved image quality (with respect to CBCT) with software programs that allow automatic identification of the target volume and organs at risk and

automatic re-planning [17, 18]. In a previous study we showed that there is a large dosimetric advantage of online ART for rectal cancer [19].
Currently, also a more economic online adaptive system has become commercially available that uses not MRI imaging but CBCT scans for the online workflow and combines it with artificial intelligence to support the online workflow. The goal of this study was to describe and evaluate the feasibility of such a CBCT-based online ART procedure. We selected rectal cancer (in the neoadjuvant setting) as it has large interfractional shape changes making it a perfect candidate for online ART.
This study describes and evaluates our first experience with a CBCT-based online adaptive workflow with respect to timing of different steps in the process, plan quality, target coverage and patient compliance.

Methods

Patients

Twelve consecutive rectal cancer patients eligible for a prescribed dose of 5 x 5 Gy according to Dutch guidelines [20] were scheduled for external beam radiotherapy (Ethos, Varian Medical Systems, Palo Alto, USA) between June 2020 and February 2021. Exclusion criteria were hip prosthesis on both sides and an inability to lie still at the treatment table for a period of 30 minutes. Patient compliance with respect to bladder filling and total treatment time were monitored.

Reference CT and target volumes

A reference CT was acquired with a drinking instruction aiming at a comfortably filled bladder. To achieve this, patients were asked to void the bladder 1.5 hours before the scheduled CT appointment and subsequently drink 0.5 liter of fluid. All patients were positioned supine using a knee support and with arms raised over the head using a thorax support (Thorax support, MacroMedics). All patients received intra venous contrast and female patients with distal tumors vaginal contrast as well.
Clinical target volumes were delineated (Velocity 4.1, Varian Medical Systems) using the national delineation guidelines following Valentini et al. (Fig. 1) [21]. Next to the GTV (tumor and positive lymph nodes) the radiation oncologist separately delineated the CTV upper and lower mesorectum (divided at the base of bladder), presacral space and left and right elective lymph node

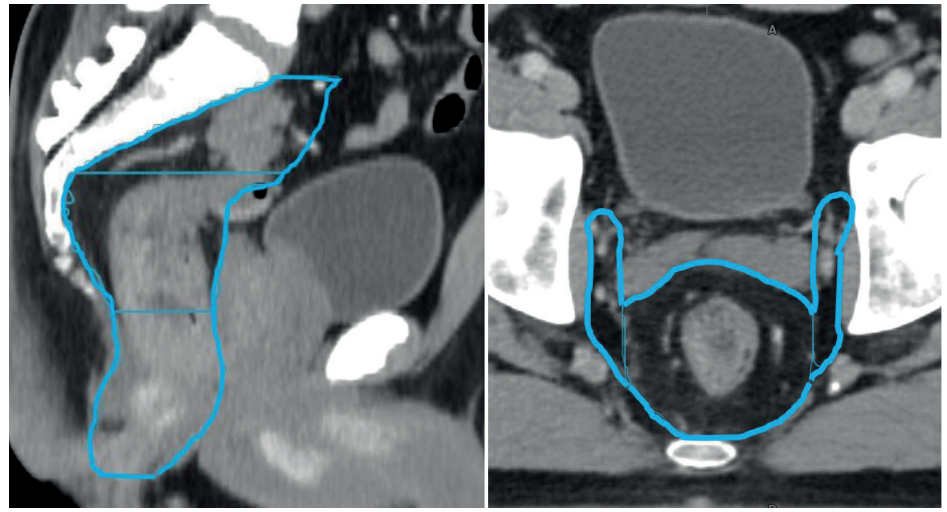

Figure 1. Illustration of planning CT with target definition in blue. On the right, the axial slice shows the CTV of the upper mesorectum and lymph node region left and right, while on the left the sagittal slice shows the lower mesorectum, upper mesorectum and presacral space (bottom to top).

regions. Organs at risks (OAR) were delineated by Radiation Therapists (RTTs) according to RTOG guidelines as well as the rectum. Target volumes were reviewed by a second expert radiation oncologist.

Margins

In all directions for all CTVs a PTV margin of 5 mm was used, with the exception in the cranial direction of the presacral, mesorectum upper and lymph node CTV and for the caudal direction of the mesorectum lower CTV. Because it was expected to be difficult to discern the cranial and caudal borders of the target volumes on CBCT it was decided to use a PTV margin of 8 mm in these cases.

Treatment planning

The planning CT and delineations were exported from Velocity to Aria (Varian Medical System, version 16.00.00). In Ethos Treatment Management (Varian Medical Systems, version 02.00.10) a template was loaded with a departmental prioritized list of clinical goals. These clinical goals consisted of the evaluation objectives that were used for plan evaluation, as specified in the clinical protocol. Additionally, in order to achieve a more desirable dose distribution than achieved by only supplying the evaluation objectives, also optimization objectives were added as clinical goals in the template. The CT was imported

into Ethos from Aria, after which the body contour was automatically delineated as well as the bony structures. If present, gas pockets and regions with contrast fluid were delineated and a material assignment was applied, where water was used as material. Next a preview of the dose distribution was automatically generated by the system. This dose preview was generated using a fluence optimized nine beams IMRT plan (system assigned) with the provided clinical goals as input. Based on the dose preview the clinical goals that were used as optimization objectives were adjusted to further improve the plan as routine practice for all patients. Subsequently, the final clinical goals and material assignments were used by the system to generate multiple deliverable IMRT and VMAT plans with fixed beam setup. From these plans the best plan deemed by the radiation oncologist was selected as reference plan and approved. As part of the QA protocol, an independent dose calculation was performed (Mobius3D 3.1, Varian Medical Systems) on the reference plan. The pass rate was required to be larger than 90%, which indicated the percentage of voxels with gamma < 1 (3%/3mm, where the percentage was relative to the maximum dose and only voxels with a dose of more than 10% of the maximum dose were taken into account). In addition, the reference plan was delivered to a phantom (Octavius 4D, PTW, Germany) and a pass rate of at least 90% was required (gamma 3%/3 mm, where the percentage was relative to the local dose and only voxels with more than 10% of the maximum dose were taken into account).

Adaptive Workflow

For all patients and all fractions one physicist, one radiation oncologist and two RTTs were present at the treatment machine. RTTs were in charge of running the software and adjusted structures under supervision of the radiation oncologist. For every patient, prior to the first treatment session, a 30-minute timeslot was scheduled to discuss patient specific clinical target volumes and reference plan to avoid discussions during the online adaptive workflow. Because both radiation oncologist and two RTTs were evaluating contours on a single monitor a checklist was developed to streamline and order this process (Supplement 1). A flowchart of the standard adaptive workflow as provided by the system on the treatment machine is shown in Figure 2.

After patient setup the first CBCT was acquired (scatter grid, 125 kV, 1080 mAs, iterative reconstruction, extended FOV if the CTV in CC direction exceeds 24 cm with a maximum of 36 cm, matrix 512x512).

The system generated a synthetic CT by deforming the pretreatment planning

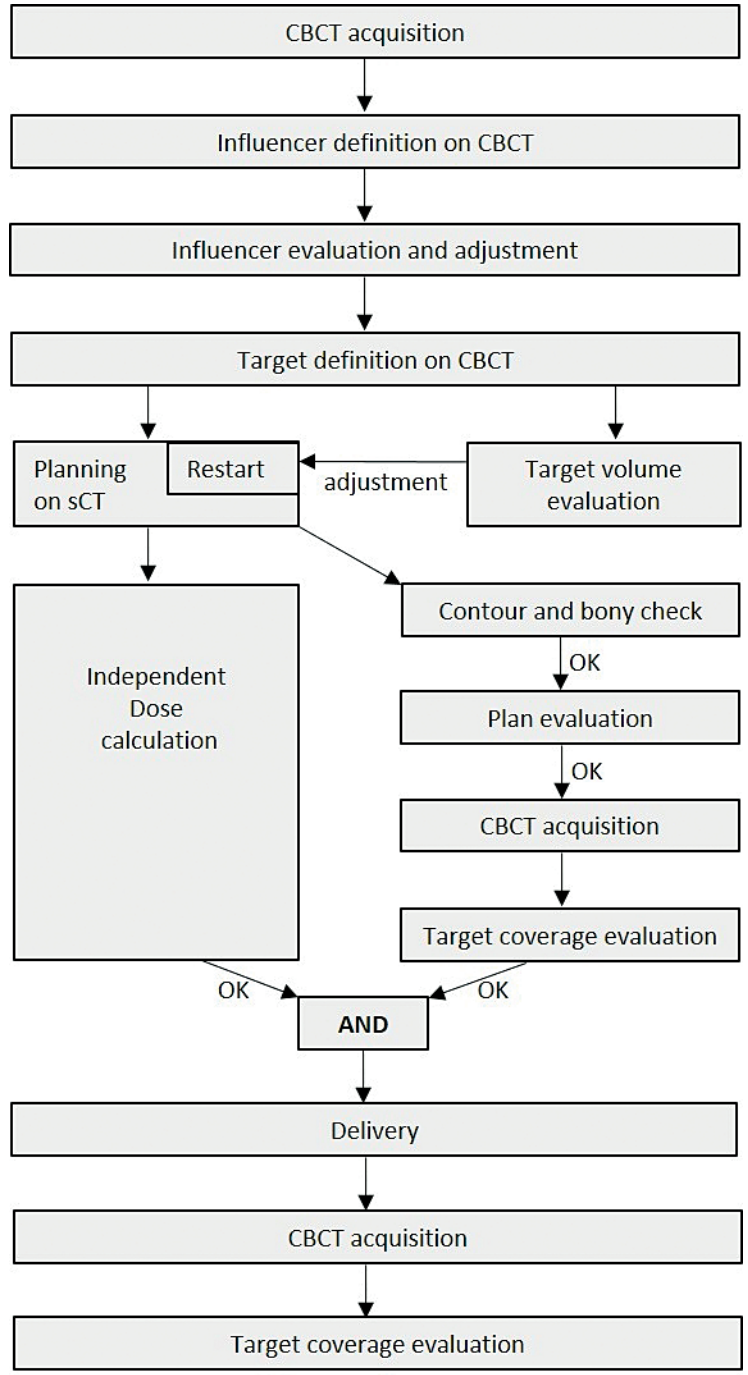

Figure 2. Flowchart of the standard online adaptive workflow.

CT to the CBCT using mutual information. The resulting vector field was used by the system to propagate the body contour, bony structures, and material override structures from the pretreatment planning CT to the synthetic CT.
Subsequently, the system generated delineations using Artificial Intelligence of the following pelvic organs: rectum and bladder. In this system these structures are called 'influencer structures' as they influence the deformation of the target volumes using structure-guided deformable registration. If necessary, these delineations were adjusted by the RTT.
In the following step the system combined the deformation vector field and the influencer structures to automatically propagate the target volumes from the pretreatment planning CT to the CBCT. At the moment the system determined the target volumes of the patients current anatomy it presented these target structures to the users and at the same time started 1) generating a newly optimized treatment plan using the beam setup and clinical goals of the reference plan and 2) calculating the dose distribution of the unaltered reference plan but using a isocenter translation aligning the target volumes on pretreatment planning CT and those propagated to the CBCT. In both calculations the system used the patients anatomy as represented by the synthetic CT including body contour and material assignments. The newly created plan was called the adapted plan, whereas the reference plan recalculated on current anatomy was referred to as the scheduled plan.
The RTT and radiation oncologist review the propagated contours and if necessary the RTT applies adjustments. Making adjustments yields a restart of 1) and 2) described above, at the moment the adjusted target volumes were approved.
RTTs, together with the radiation oncologist and physicist, evaluated both plans by comparing the clinical goals and the dose distribution, after which the best plan was selected. After approval of the selected treatment plan a second CBCT scan (same variables as first CBCT except for 540 mAs) was acquired to verify if the target volumes were still within the PTV. The second CBCT scan was registered to the first CBCT scan using bony anatomy. If the correction was more than 1 mm in any direction a table displacement was applied. For the visual assessment if the target volume was still within PTV the system propagated the PTV structure of the adapted treatment plan on to the CBCT.
Concurrently, an independent calculation of the dose distribution was done as part of our QA protocol (Mobius, Varian Medical Systems), where a pass rate of 90% was required (gamma 3%/3mm). Additionally, as a sanity check, the number of monitor units (MU) of the selected plan was compared to the number of MU of the reference plan.
After treatment delivery a third, post RT CBCT scan was acquired to again check if the target volume, as visible on the post treatment CBCT scan was inside the PTV of the plan used for treatment.
Timing of each step was captured to provide an overview as well as the number of fractions the target volumes needed to be adjusted by the users. Since this was a novel procedure for our department with no extensive clinical experience, unplanned events were recorded.

Results

An overview of the twelve patients included in this study can be found in Table 1, a summary of the timing of all steps of the online adaptive workflow can be found in Table 2.

In-room time, on-table time and patient compliance

The average total treatment time defined as the patient entering and exiting the treatment room was 34 minutes.
The complete online adaptive workflow including all CBCT imaging, adjustments of contours, plan calculation and treatment delivery (excluding patient alignment) took on average 26 minutes.
No fractions were interrupted as all patients tolerated the time needed for the procedure.

Contour adjustments

The average time spent to evaluate and adjust the system generated contours of bladder and rectum (influencers) needed for contour propagation of the target volumes was 4 minutes.
Subsequently, the time spent evaluating the target volumes when adjustments were not applied was on average 4 minutes. If the target volumes were adjusted the average time increased to 9 minutes. In 30 out of 60 fractions (50%) the target volumes were adjusted after visual inspection.

Plan calculation, plan quality and independent dose calculation

When selecting the most suitable reference plan a VMAT delivery technique was preferred to limit delivery time to minimize the possibility of intra fraction motion. Calculating the scheduled and adapted plan during the online

Table 1: Patient characteristics

	Age	Sex	Tumor stage	GTV location	Chemo	Surgery	Remarks
1	66	F	cT3bN1M0 MRF-	mid	no	yes	
2	82	M	T4N0M0 MRF+ EMVI+	mid	no	yes	
3	39	M	T3N2M1	distal	yes	no	Reirradiation
4	62	M	cT3cN2M1 MRF+	distal	yes	yes	
5	49	M	cT4bN2M1 MRF+	distal	yes	yes	
6	46	F	cT4aN2bM1 MRF+	distal	yes	no	
7	50	M	cT3c-T4M1 MRF+ EMVI+	distal	yes		Surgery pending chemo
8	81	M	iT3aN0Mx MRF- EMVI-	distal	yes		+ Oesophagus tumor, Surgery pending chemo
9	75	F	cT4N1M0 MRF+	distal	yes	yes	+ Sigmoid tumor
10	47	M	cT3bN2M0 MRF-	distal	yes	yes	
11	69	M	cT3N1M0 MRF- EMVI+	proximal	no	yes	
12	62	M	cT3bN1M0 MRF-EMVI-	distal	no	yes	

Table 2: Overview of steps and duration

Time (Minutes) needed for:		*AVG*	*min*	*max*
1	Evaluation and adjustment system generated contours (Influencers)	4	1	11
2	Evaluation target volume without adjustments	4	2	11
3	Evaluation and adjustment target volume	9	4	21
4	Adaptive procedure before delivery (CBCT2 - CBCT1)	20	11	40
5	Plan calculation	8	6	11
6	Treatment delivery	4	3	6
7	On table (CBCT3 - CBCT1)	26	16	46
8	Patient entering and leaving treatment room	34	20	54

procedure took on average 8 minutes (synchronous calculation).
To assess the quality of the scheduled and the adapted plans, the volume of the PTV receiving 95% of the prescribed dose or more (V95%) and the conformity of the 95% isodose to the PTV were checked and used as criteria for selecting the best plan. For all fractions the adapted plan was selected. For 55 out of 60 fractions V95% of PTV was less than the required 99% for the scheduled plan, while for the adapted plan this was the case for 3 fractions (Fig. 3). For fractions where the bladder V440cGy was lower for the scheduled plan than for the adapted plan, the PTV coverage of the scheduled plan was insufficient, except for two fractions.
The number of MU of the selected plan never deviated more than 15% from the number of MU of the reference plan.
All plans passed the independent dose calculation.

Online procedure

Completing the online adaptive procedure, i.e. from the first CBCT followed by contour adjustments (influencers and target volumes), plan calculation up to and including the second CBCT for verification took on average 20 minutes.

Treatment delivery and intra fraction motion

Treatment delivery took on average 4 minutes.
For all post RT CBCTs the visual check showed no target volume outside the PTV.

Unplanned events

For a few fractions the adaptive procedure did not go according to plan as a result of the following:
1) the workflow was interrupted after first CBCT due to a very full bladder in one fraction, because it was expected that the patient required voiding the bladder before the end of the fraction. (Fig. 5a).
2) the workflow was completely restarted after the second CBCT because of insufficient target coverage due to intra fraction motion of a large gas pocket in one fraction.
3) after the second CBCT there was insufficient target coverage due to limited intra fraction motion of a gas pocket. Coverage was restored with a table shift in one fraction.
4) for one patient the synthetic CT had a small error in 3 out of 5 fractions with respect to bony anatomy registration that resulted in a need to extensively

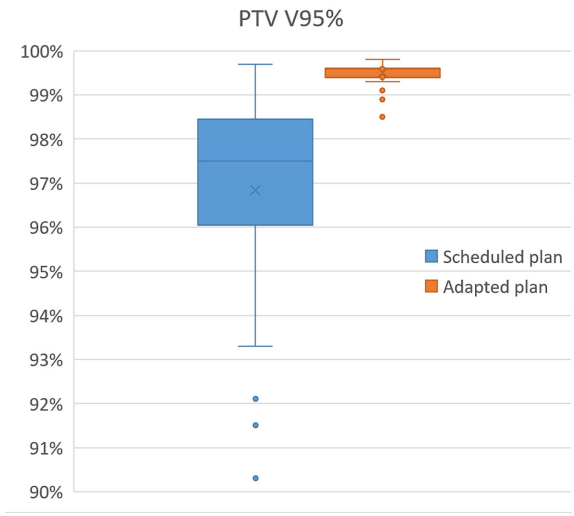

Figure 3. Boxplot showing PTV V95% of the scheduled and the adapted plan.

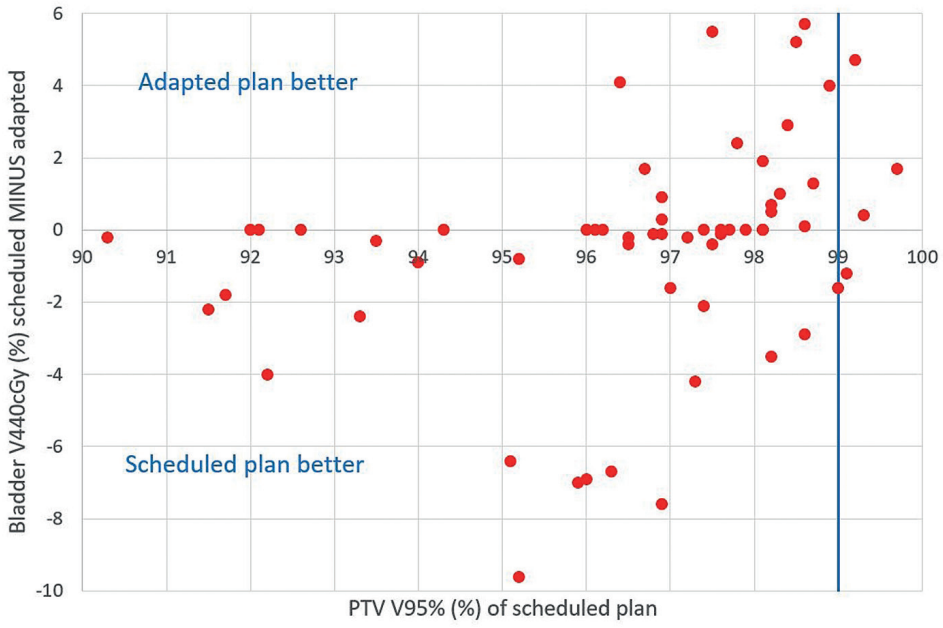

Figure 4. Difference between the bladder V440cGy of the scheduled and adapted plan in relation to the PTV V95% of the scheduled plan for all fractions of all patients patients (one dot corresponds to one fraction). The required value of 99% for the PTV V95% is indicated by the vertical blue line.

adapt the presacral delineation in that region (Fig. 5b).
5) for one patient the synthetic CT had an error in all fractions with respect to body contour definition (Fig. 5c). This error was ignored because limited impact on the dose distribution was expected.

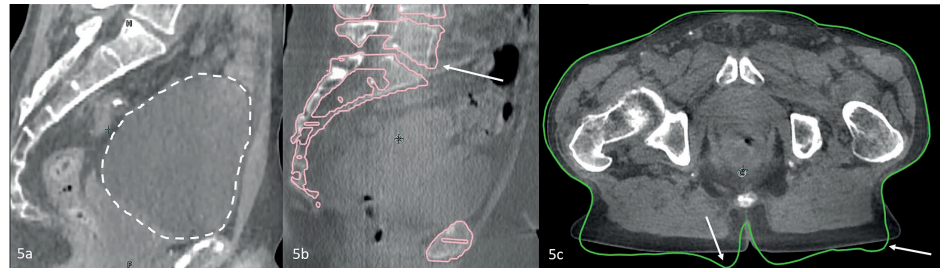

Figure 5. CBCT with a too full bladder at start of treatment (5a). A small error with respect to deformable bony anatomy registration of CT to CBCT. In pink the representation of the bony anatomy of the sCT with overlay on the CBCT(5b). A small error with respect to deformed body contour of CT to CBCT. In green the representation of the body contour of the sCT with overlay on the CBCT(5c).

Discussion

To our knowledge, this is the first study that describes an online CBCT-based adaptive radiotherapy workflow for rectal cancer in the neoadjuvant setting and reports the first clinical experience. All scheduled patients were treated as intended. The workflow worked well but was labor intensive as it required a multi-disciplinary team at the treatment machine and compared to our previously used plan selection protocol [14, 16] time slots at the treatment machine are prolonged (15 minutes versus 35 minutes). Patient compliance was not affected.

Treatment times

Intven et al. [22] was the first to report daily adaptive radiotherapy for rectal cancer patients treated with 5 x 5 Gy and similar target volumes and showed it was a feasible strategy for MR guided radiotherapy.
Overall, the online adaptive workflow they described took longer in comparison to our workflow. Median of the total treatment time defined as the time between first MR scan and end of treatment delivery was longer with

a median of 43 minutes (IQR 9 minutes), as compared to 26 minutes (range 16 – 46) in our study. They report contouring time with a median of 13 minutes (IQR 11). In our workflow contours can be evaluated and adapted in two steps: 1) the system generated structures of the pelvic organs (the influencers), i.e. rectum and bladder, and 2) the target volumes. This first step is not part of the MR guided workflow. When only the system generated delineations of bladder and rectum were evaluated and/or adjusted it took on average 4 minutes. If on top of that the target volumes needed to be adapted this increased to an average of 9 minutes.
When selecting a reference plan for our online workflow the VMAT technique was favored for its fast delivery over IMRT. The 5-field IMRT technique used for delivery by Intven et al. [22] resulted in a median of 7 minutes (IQR 1) treatment delivery time compared to an average of 4 minutes (range 3 - 6) in our study.

Imaging

The system provided the possibility of iterative reconstructed CBCT scans and produced sufficient image quality for the evaluation and adjustment of the influencer structures and target volumes. Incidental unfavorable patient anatomy, causing a lot of streak artefacts (moving gas in small bowel), increased the time needed to evaluate and adapt contours.
Online adaptive radiotherapy is to date commonly reported using an MR-Linac. MR guided radiotherapy has the potential benefit of better soft tissue contrast compared to CBCT scans [22]. Possibly, the MRI image quality could result in more accurate re-delineation of contours which needs to be investigated. MRI guided imaging could also enable the visualization of the GTV and treatment response which is not possible using CBCT-based online adaptive radiotherapy.

Margins and intra fraction motion

We previously compared plan selection and online ART with respect to dose to the healthy tissue [19]. In that study a 3 mm PTV margin around the total target volume was used. As this was our first clinically implemented online adaptive workflow with the Ethos system we decided to start with a slightly larger margin: 5 mm in all directions with the exception of 8 mm in cranial direction for upper mesorectum, presacral space and elective lymph node regions and 8 mm in caudal direction for lower mesorectum because it was expected to be difficult to discern the cranial and caudal border of the target volume on CBCT. In this decision it was also taken into account that when using smaller margins possibly more adjustments of small deviations would be needed, consequently increasing the time needed for the online ART process. Conversely, larger margins would possibly mean less adjustments are needed of small deviations, but this would yield less advantage of the online ART process with respect to dose to the OARs. Due to the different margins, the results in terms of dosimetric effect of online adaptive ART of the present paper are not directly comparable with e.g. the procedure with the plan-of-the-day [16].
To assess target coverage in the context of intra fraction motion, we also acquired a pretreatment and post treatment CBCT scan. As stated, the adapted plan needed to be shifted in one fraction and workflow was interrupted in one fraction because of insufficient target coverage. Post treatment CBCT scans showed the target volume was within PTV for all performed adapted treatments. Whether margins can be reduced further needs to be investigated. Intven et al. [22] started using 10 mm PTV margin around the mesorectum in all directions and 8 mm PTV margin around lymph node regions. After 25 patients they reduced margins to the mesorectum to 4 mm in all directions except for 6 mm in CC and ventral direction. For the lymph node regions the margins were reduced to 4 mm in all directions except for 6 mm in CC direction. These PTV margin reductions were based on an evaluation of adequate coverage to the target on the post treatment MRI scans.

Resources

When designing the adaptive protocol we aimed for an RTT led workflow from the start. Therefore, we protocolized that RTTs would drive the software under supervision of the radiation oncologist and the medical physicist for the first 12 patients. RTTs were already experienced in CBCT-based online IGRT and plan selection for rectal cancer. For the adaptive workflow, additional training for the RTTs was provided in the form of the ESTRO Falcon delineation course followed by a target definition workshop for departmental specific criteria. This was combined with 40 hours of individual training on a research version of the clinical software after individual instructions. A total of 5 RTTs were trained. To streamline and order the process of evaluation and adaptation of contours we developed a checklist, see Supplement 1. An offline QA protocol would help and is currently under investigation as well as the possibility to remotely view the screens to support a workflow without the physician and/or physicist physically present at the treatment machine.
Intven et al. [22] report that their workflow started with recontouring performed by radiation oncologists for the first 12 patients. As of patient 13 RTTs were

trained followed by a gradual shift in the responsibility of the recontouring to RTTs. This shift towards an RTT led online adaptive procedure is in line with the results of an international survey published by McNair et al. [23].
In our workflow also the medical physicist was present at the treatment machine to approve the adapted plan and to evaluate the independent dose calculation. A traffic light protocol would further enable an autonomous RTT led workflow in the future as is described by Betgen et al. [24].
The time slots at the treatment machine were 40 minutes. The difference between the on table time (26 minutes) and the total treatment time as defined by patient entering and leaving the treatment room (34 minutes) is large. This is most likely the result of a not fully booked patient schedule, leaving extra time for social interaction between RTTs and the patients.

Patient compliance

In general, rectal cancer patients receive a bladder filling instruction that aims at comfortable full bladders during treatment. We estimated the treatment time for online ART to be about 30 minutes and did not change drinking instructions as a (comfortable) full bladder is beneficial for dose to the bladder and it improves CBCT image quality. The average in-room time as defined by patient entering and leaving the treatment room was on average 34 minutes but with outliers up to 54 minutes. All patients were compliant with these treatment times, although for one fraction the workflow was interrupted based on an extremely full bladder on the first CBCT scan.
Prolonged treatment times (compared to previous plan selection time slots) can affect patient comfort as they are immobilized with the arms elevated. As a result we needed to alter arm position to arms crossed on the chest for one patient after the first treatment fraction.

Scheduled and adapted plan

The system automatically provides a scheduled plan next to the adapted plan. The user is able to compare both plans with respect to clinical goals and dose distribution. In this study the scheduled plan was never selected (Figure 4).

Future directions

With a feasible CBCT-based online adaptive workflow a new resource has become available for radiotherapy departments to improve treatment. Whether the CBCT image quality suffices for other treatment sites than rectal cancer needs to be investigated.

To improve CBCT-based online ART for rectal cancer effort has to be made to assess remaining and new uncertainties to calculate optimal margins and evaluate whether using online adaptive radiotherapy will translate into a clinically relevant reduction of toxicity and improvement of patient's quality of life.
Also the supporting software tools in this process needs to be optimized to reduce time per fraction.

Conclusion

CBCT-based online adaptive radiotherapy in the neo adjuvant treatment of intermediate and locally advanced rectal cancer is feasible and appears to be a promising strategy to reduce PTV margins and thus toxicity.

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Feasibility study for online conebeam based online adaptive radiation therapy for locally advanced rectal cancer

Supplementary Material

Influencer Review: RTT 1/2

- ◯ Bladder
- ◯ Rectum

Target Review: RTT 1/2 + RO

Sagital viewer:
- ◯ Caudal border lower mesorectum
- ◯ Cranial border upper mesorectum
- ◯ Cranial border presacral space

Axial viewer:

Cranial to caudal
- ◯ Lateral and dorsal borders

Caudal to cranial
- ◯ Ventral borders

Plan Review: RTT + RO + Physicist

- ◯ Body & bones (sCT)
- ◯ Isodose 95%-105%
- ◯ Goals
- ◯ MU check

- ◯ CB2: target coverage

Mobius: Physicist

- ◯ Approvals
- ◯ Details gamma
- ◯ Orthogonal images sCT

- ◯ CB3: target coverage

Supplement 1. Check list online adaptive radiotherapy used to manage and order the steps in the workflow.

Chapter 9

Discussion

Introduction

Radiotherapy in the neo adjuvant treatment of rectal cancer is associated with toxicity [1-5]. This thesis describes the process of reducing irradiated volumes without compromising target coverage to possible reduce this toxicity. The introduction of pretreatment CT and integrated in-room 3D imaging into the radiotherapy workflow enabled us to visualize the patients' anatomy over the course of treatment and allowed us to evaluate and quantify anatomical changes. This resulted in the calculation of population based margins (Chapter 2 and 3). For rectal cancer this margin was especially large in the upper ventral direction of the mesorectum, which is adjacent to small bowel and bladder, both organs that are sensitive to radiation.

To reduce these large margins we investigated, developed and implemented a plan selection strategy. In this strategy a-priori plans were created and based on daily conebeam CT (CBCT) images at the treatment machine (Chapter 4, 5 and 6). One plan per day was selected for treatment. With this strategy, we were able to individualize the margin used locally at the upper ventral side of the target volume benefitting the patients for whom the population based margin was too large.

Ten years after the quantification of population based fixed margins, in which supporting software tools have been developed like auto-segmentation of structures and auto-planning, we were able to take adaptive radiotherapy to the next level. We investigated, developed and implemented an online adaptive radiotherapy strategy that incorporated patient individualized margins to the entire target volume and reported the very first clinical experience of online adaptive radiotherapy based on CBCT images (Chapter 7 and 8). Online adaptive radiotherapy dramatically reduced irradiated volumes further.

PTV margins

Delineation uncertainty of the CTV

Target definition is the first step in the treatment chain of radiation therapy. Important steps have been taken in the definition of the target volumes for rectal cancer that substantially decreased population based PTV margins and is well described in literature. Because target volume delineation is performed only once for every patient, any error in its definition will propagate over

all treatment fractions and is therefore considered a systematic error with major impact on the size of the PTV [6]. In radiotherapy consistent and standardized delineations of the target volume with small observer variations can be achieved if the definition of that target volume is well described and/or visualized in detail. Roels et al. [7] published a delineation guideline that aims at achieving exactly that for rectal cancer and was based on a review of literature on local recurrences. Inter-observer variation for rectal cancer since then has been studied and quantified [8-10] as well as the effect of using standardized delineation guidelines [8, 9, 11]. Nijkamp et al. describe a reduction in observer delineation variation of 0.3 – 0.8 cm [8]. Since then, in 2014 Roels' delineation guideline has been updated [12] based on new recurrence data in the literature, with an adjustment with respect to the cranial and caudal border. In 2016 additional guidelines have been published by Valentini [13].

Inter fraction motion of the CTV

In chapter 2 and 3, we calculated population based margins using delineations on CBCT scans used for patient positioning and/or additional CT scans. The patient characteristics included prone and supine positions, of male and female patients, treated with short and long course radiotherapy schemes. Although the number of patients was moderate the dataset was large enough to conclude that there were large geometrical uncertainties that were non-uniformly distributed over the boundaries of the clinical target volume. The largest uncertainty was found at the anterior cranial border and required a margin of 25 mm, based on the classical margin recipe [6], i.e. $2.5\ \Sigma + 0.7\ \sigma$.
In chapter 2 and 3 we stated that this margin recipe ($2.5\ \Sigma + 0.7\ \sigma$) would probably over-estimate the margins needed for geometrical uncertainties as this margin recipe assumes translations of spherical and rigid bodies. In our opinion there were two arguments that the margin would be an over-estimation: 1) The CTV of locally advanced rectal cancer is cylindrical instead of spherical, and therefore the multiply factor is smaller, 2) the CTV is much more a deforming volume instead of a rigid body, where only outward movement deformation will lead to a reduction of dose to the CTV. Hence, we assumed the classical margin recipe was likely to overestimate the margin needed to cover 90% of patient with 95% of the prescribed dose.
However, later in a sequel paper we proved our assumptions incorrect and that the opposite was true, when we investigated using a pragmatic approach to define a margin recipe that is applicable for deformation of the CTV using target coverage [14] (not in this thesis). In this work we proposed a margin recipe for the clinical target volume based on scoring what margin is needed to cover 90% of patients with 95% of the prescribed dose. We concluded that this result was achieved by using a larger multiply factor for the systematic error (Σ): $3.2\ \Sigma + 0.7\ \sigma$.
In retrospect, the explanation is that the deformations of different parts of the target volume are not fully correlated, something we did not take into account in chapter 2 and 3. The larger weight of the systematic error in this margin recipe can be understood by considering two target volumes (or more) that move independently. With the classic margin recipe for rigid bodies (i.e. $2.5\ \Sigma + 0.7\ \sigma$), the probability of sufficient target coverage for each of these volumes independently is 90%, but for both volumes together to receive sufficient dose this probability is lower, as multiplication of probabilities will lead to a smaller number, only 81% (90% times 90%). Therefore, the weight of the systematic error in the margin recipe must be larger for this probability to become 90% again. It is important to note that this margin recipe is pragmatically derived based on coverage of this specific target definition. Changes in how the target volume is defined, or application to other tumor sites demands new research to derive appropriate margin recipes to account for deformation of targets.
A different approach to margins is robust and probabilistic optimization [15, 16]. This approach balances tumor control probability with normal tissue complication probability and is able to incorporate the knowledge as well as the lack of knowledge of dose response relationships. However, current models are not robust enough yet and should be improved by using not only geometrical uncertainties but also include medical and biological parameters and its uncertainties [17].

Reducing PTV margins - Offline adaptive radiotherapy

Triggered and scheduled adaptation

With the calculation of the population based fixed margins (Chapter 2 and 3) around the standardized target volume 90% of patients receive 95% of dose. This means that the margin is too small for 10% of patients and too large for 89% of patients.
When applying online kV CBCT for patient positioning it is possible to identify the patients for whom the margin appears to be too small during the course

of treatment and take action to ensure a proper coverage for those patients. This is often referred to as triggered adaptation. Underdosage of the target volume could be a result of changing contour/surface (dosimetry changes) or large deformations of the target volume outside the PTV margin because of large differences compared to the reference CT. A useful tool at the treatment machine is a management system for anatomical changes [18-20]. Such a management system defines action levels as a decision support system when evaluating images and is often referred to as 'traffic light protocol'. Such a system allows RTT to autonomously evaluate the daily images within the department specific boundaries and flag differences that subsequently can be recalculated on the treatment image to evaluate its effect. Every individual department can shape such a management system to fit departmental specific variables like treatment planning technique and margins used. This (trigged rescanning and) replanning has the disadvantage that resources are needed ad hoc and can heavily impact workload.

To identify patients where the margin is too large is more complex. One way to ensure that the margin is not too large for patients when using a fixed population based margin is scheduled adaptation. In this way the individual patient starts with a population based margin that consequently can be reduced after a certain number of fractions by assessing the patient-individual uncertainties and recalculate necessary margins [21, 22]. In case the PTV margin is too large because the target volume is regressing as a result of treatment response the target volume can be adapted after reaching a certain threshold as seen on CBCT, a form of triggered adaptation just as described above for margins that are too small. It can also be scheduled at a fixed time point in treatment [23, 24]. Again, the triggered adaptation has the disadvantage of ad hoc allocation of resources, whereas the scheduled adaption has the disadvantage that in case of limited regression resources have been allocated that are not necessary or do not improve patient treatment.

A-priori adaptation

Our department has a management system for anatomical changes for all treatment sites. For the first step towards individualized margins for rectal cancer we developed an offline adaptive approach by means of plan selection and this is described in chapters 4, 5 and 6. With this approach we were able to account for expected shape changes as a result of changing rectal and/or (to a lesser extent) bladder filling using a-priori designed plans. This approach is especially suited for tumors with predictable, potentially large and frequent inter fractional geometrical uncertainties and relatively small intra fraction motion. Plan selection has been described earlier in the treatment for cervix and bladder cancer and uses different a-priori designed plans that are based on full and empty bladder CT scan in combination with deformable registration tools to generate intermediate and/or extrapolated structures [25-27]. For rectal cancer, due to its limited correlation with bladder filling we decided to base the a-priori plans on a single CT and to use multiple margins for the most variable part of the target volume: the upper anterior side of the mesorectum. At the treatment machine the best fitting plan is selected based on online CBCT scans.

In preparation of the clinical application of plan selection we retrospectively analyzed (Chapter 4) the potential efficacy of our plan selection strategy with respect to dose to the OARs (bladder and small bowel). We found that using plan section resulted in significantly less dose to the bladder and small bowel but the differences in absolute volume were small. Clinical benefit was therefore unsure. Because in this dataset a subset of patients did show a large difference and an infrastructure that supported plan selection was already in place for the treatment of bladder and cervix cancer we proceeded with a clinical implementation of plan selection for rectal cancer. In chapter 5 we describe our implementation process and the feasibility of our RTT-led plan selection. In chapter 6 we prospectively analyzed the actual benefit in terms of dose to the OARs and confirmed the previous data as described in chapter 4; The benefit of plan selection was limited when averaged over the population but it was beneficial to a subset of patients that can be treated with smaller margins for a majority of treatment days.

Plan selection for rectal cancer using variable margins has proven to foresee most anatomical changes over the course of treatment even though it is based on only a single CT scan. In that sense plan selection for rectum is more robust than plan selection for cervix and bladder where multiple target volumes are based on interpolated structures between full and empty bladder CT scan. Plan selection for bladder and cervix regularly requires the a-priori plans to be adapted. Reasons for those adaptations are that not all motion is captured on the full and empty bladder CT scans; they are acquired directly after each other and only represents motion based on the bladder difference of that day. It does therefore not take other motion into account like day to day changes in surrounding tissue and/or changes as a result of treatment response. If such motion presents on the daily scans the a-priori plans are

no longer valid. At Amsterdam UMC this has resulted in repeat scanning and planning in around 25% (16 out of 60) of cervix and 10% (5 out of 45) of bladder patients (internal analysis, not published 2013-2018). The variable margins for plan selection for rectal cancer proves to be the most robust approach: only in 1 patient (out of 150) reference scan and planning of ART needed to be repeated. Combined with the relatively straightforward approach of variable margins of the PTV this plan selection approach is (technically) feasible for every department able to acquire daily CBCT scans.

A slightly different approach to plan selection has been proposed and clinically implemented by Beekman et al. [28]. Their approach is also based on a single reference CT scan but generates multiple CTV structures based on population statistics of geometrical uncertainties instead of multiple PTV margins. An algorithm creates 5 smooth CTV structures with increasing size from the caudal to cranial part of the mesorectum at the ventral side. This approach resulted in 127 cc average PTV volume reduction compared to a median PTV reduction of 30 cc in our preparation study [29]. The large difference in PTV reduction could be explained by the fact that in our approach the margin is only variable at the upper anterior side of the mesorectum. The downside of the design by Beekman et al [28] is that this approach depends on correlation of size and direction of anatomical changes globally which is not always true, as above discussed, and it depends on a not commercially available algorithm. The strong point of their approach is that it is in line with the conceptual use of a PTV margin that is lost in our approach, e.g. no margin for delineation error and intra fraction error. Our approach to plan selection to select the smallest PTV encompassing the CTV as delineated on de reference CT scan matched our departmental management protocol for anatomical changes when treating with a fixed margin plan. It is also in line with plan selection described for cervix [30, 31] and bladder [25, 32] where the smallest plan is selected that encompasses the target volume either based on the PTV or 95% isodose line. The UK bladder plan selection protocol is slightly different. It uses variable PTV margins based on a single CT scan and it decided on a different selection criteria: they instruct not to select the smallest PTV that encompasses the bladder but the PTV that ensures a 3mm gap between the CTV and PTV [33]. Thus allowing for some intra fraction motion. The dosimetric consequences of the different selection criteria are not investigated.

A similarity between Beekman et al. [28] and our study is the number of plans used for plan selection, the method of implementation and training for the RTT-led workflow and the results with respect to inter observer consistency in plan selection.

An alternative adaptation strategy to plan selection was described by Nijkamp et al. [34]. In their proposed method an adapted target volume is derived after 5 days by creating an average of the target volumes based on CBCT scan or repeat CT scans. Although this method involves a higher workload it results in a better sparing of bladder and small bowel than our plan selection as a reduced PTV margin is applied for the entire CTV.

Reducing PTV margins - Online adaptive radiotherapy

Online adaptive radiotherapy (ART) is a daily workflow that reoptimizes an initial plan and takes daily variation of the target volume and OARs into account [35, 36]. This would resolve the problems not tackled by plan selection approaches such as unexpected changes and changes as a result of treatment response. It can also be more efficient in reducing PTV margins especially for highly deformable target volumes where day to day variation is much larger than intra fraction motion. Online ART requires fast, semi-automatic and accurate 3D soft tissue imaging, definition of the target volume (and OARs), and re-planning [36]. Not too long ago online ART became achievable based on MRI images [37-41] and recently CBCT-based adaptation has become a reality as well.

In chapter 6 we compared the dosimetric benefit of online ART over plan selection for rectal cancer patients and we found a substantial reduction in dose to the healthy tissue, bladder and small bowel. Although it is likely that this reduction will translate into a clinically relevant reduction of toxicity this needs to be investigated. The downside is that it requires the dedicated (and more expensive) machines and software and that time slots are usually larger increasing the burden of departmental resources [38-40].

Chapter 7 describes the CBCT based online adaptive protocol for rectal cancer we developed as well as our first clinical experience. The ring-based accelerator on which the patients were treated (Varian Medical Systems, version 02.00.10) was operated using one software platform for both treatment planning and delivery. First, a reference plan was generated using a single planning CT. After patient set-up the adaptive workflow started with a CBCT. The reference CT scan was registered to the CBCT using deformable registration. Using artificial intelligence and contour guided deformation reference contours were adapted by the system to match the anatomy on the CBCT. A second pretreatment and post treatment CBCT were acquired to validate the new plan with respect to CTV coverage just before and after treatment delivery, respectively.

Due to potential intra fraction motion the time needed to complete the adaptation and delivery is crucial to keep the margins to a minimum. Currently three steps in the process are time consuming: 1) user evaluation and manual adjustments of the system generated structures for contour guided deformation, 2) user evaluation and manual adjustments of the target volumes and 3) calculation of the adapted plans. For rectal cancer, which is usually a relatively large volume this resulted in a total adaptive workflow that will take 25 minutes at best. In clinical practice it is possible to acquire a second CBCT scan just prior to treatment to check target coverage just before treatment delivery. Workflow is usually interrupted if this check fails resulting in a delayed treatment. Intven et al. [37] report on an MRI guided online ART workflow that takes longer from first pretreatment to post treatment scan with a median of 43 minutes versus an average of 26 minutes respectively. It will be interesting to see if developments in advanced segmentation algorithms will be able to take advantage of the better image quality of MRI images [42].
Once a new plan is ready treatment delivery in our workflow is in the order of 4 minutes. Momentarily data on intra fraction motion for the total CTV is scarce but Intven et al. [37] proposed margins of 4 mm in all directions except for 6 mm in CC and ventral direction for the mesorectum based on their post treatment MRI images for their MRguided RT for rectal cancer to compensate for intra fraction motion. This incorporated changes during the adaptation as well. Their results are in line with the margin we selected; 5 mm in all directions except for 8 mm for the cranial and caudal borders of mesorectum and elective lymph node regions.

Requirements for RTT-led adaptive radiotherapy

When adaptive therapy was first proposed in 1997 it came with the statement that adaptive therapy would become the new standard [35]. To this date however, online image guidance and adaptive radiotherapy is not widely adopted yet. The POP-ART study demonstrates after a survey completed by 177 centers from 40 countries that the main barriers were human and material resources as well as technical implementations [43]. Challenges identified were the added workload, longer daily treatment times, limited image quality, uncertainty in dose accumulation, and (RTT-) training. In the Netherlands, and our department at Amsterdam UMC, it is a generally accepted and an efficient and effective strategy to have RTT-led IGRT and ART. The level of autonomy for RTTs with respect to IGRT and ART greatly varies in the world. In chapter 5 and 8 we described an RTT-led strategy for both plan selection and online adaptive radiotherapy for rectal cancer although the latter needs to shape further in the future.

Triggered adaptation

Considering daily image guidance as a QA tool to deliver the right dose at the right spot at the treatment machine triggered adaptation is likely to be the RTTs responsibility. Key tools for RTTs to support this responsibility are 1) software tools that can be used for (automatic) image registration and image evaluation in a standardized manner [44], 2) comprehensive knowledge of anatomy, 3) a management system to flag anatomical differences that could compromise the delivering of the correct dose at the right spot [18, 19], and foremost important 4) training to acquire competence and confidence for all 3 above-mentioned elements [45, 46].
For rectal cancer specific online imaging with daily evaluation is especially important for short course radiotherapy (5 x 5Gy) giving only the few fractions.

Plan selection

Plan selection as a strategy is to this date not widely implemented, but implementation strategies and maintaining competence and confidence are well described in literature. Most of them are based on RTT-led plan selection and a difference in multidisciplinary participation between start and routine use of plan selection [45-47]. In chapter 5 we describe our implementation strategy for rectal cancer that we previously used for implementing cervix and bladder cancer and later for gastric cancer [47]. At the bases of this strategy is a team of RTTs that have experience with CB acquisition, automatic registration and daily image evaluation with respect to target coverage and dose to the target and/or OARs using a management system for anatomical changes. Plan selection training then starts with a recap of target volume definition followed by an observer study. In this observer study RTTs need to individually select the best fitting plan based on CBCT without the means to discuss with peers. This is quickly followed by a multi-disciplinary meeting to assess all plan selection choices and create a set of criteria for selection. Subsequently, a second round of plan selections takes place where the RTTs select the plans individually. To appreciate different views and knowledge and to gain understanding of the plan selection workflow physicists and radiation oncologist also participate in the observer study.
A similar implementation and training strategy is described by van Beek et al. [48]. Although the technical approach is different the outcome of the observer

variability is comparable, concluding that although image quality of CBCT in the pelvic region is not always optimal, RTT-led plan selection is consistent and feasible. They also recognize that developing competencies for plan selection workflows has a large workload and that does not even take into account maintaining competence and confidence.
Although the first papers describing plan selection are written 10 years ago, commercial vendors have not (yet) set up their software for plan selection. A major hurdle is that there is no connection between the imaging system and the delivery system making this workflow prone to human error.

Online ART

So far for the workflow of online ART the general consensus to a design seems to be a multi-disciplinary approach, where all the disciplines are present at the treatment machine not only for the startup period but also in routine use. This logically originates from the fact that for decades the approval of target volume delineations and subsequent treatment plan was the responsibility of the radiation oncologist. However, in the online ART workflow 'delineations and plans are often adjusted in order to realize the dose distributions of the initial plan in the continuously-changing patient. Consequently, such adaptations do not alter the physician's treatment intent.' [36]. This opens up the possibility of a shift in responsibilities from the radiation oncologist to the RTTs, especially if you take into account that the target volume is not generated once by one observer but daily by different observers, giving it a more random component. But not only the target volumes need to be approved also the re-optimized plans need to be evaluated in an online and swift workflow. Again, conventionally that has been the responsibility of the radiation oncologist, together with a physicist. In that context Betgen et al. [49] proposes a management system to check adapted plans very similar to a management system used for anatomical changes. Such a tool supports autonomous decision making within clear boundaries of tolerances for RTTs. McNair et al. [50] confirms this change towards a more autonomous RTT-led workflow.

Human Resources

With the proper requirements RTT-led online imaging and adaptation is very well achievable and could be the solution to clinically implement more advanced strategies at the treatment machine [43]. However, in the Netherlands there is momentarily a shortage of RTTs. Making the job more appealing to a larger public should be explored. One aspect, next to cost perspective, is job satisfaction which can be improved by 1) extension; because of the increasingly more complex protocols of radiation therapy [51-53], and 2) Expansion; where the role of the RTT is diversified outside the traditional scope of the treatment chain [51-53] and 3) Advanced practice roles [54-56].
Role extension as a result of more complex and sophisticated treatment protocols, has been extensively described in this thesis, specifically with respect to skill, competencies and responsibilities for image guidance and adaptation at the treatment machine [51-53].
Role expansion was traditionally limited to education and management but has been changing. Nowadays there is a variety of functions available that RTTs could qualify for that start with their expertise in radiotherapy [51-53]. In the Netherlands there are now post graduate courses available to pursue a career as physician assistant, or in case-management, trial-management and research. Sometimes these changes in role are challenging as they touch on (shared or shifted) responsibilities and decision making with other disciplines and addresses issues as to who is best equipped/experienced to do certain tasks. However, it can be quite rewarding in many ways both for the department as well as for individuals.
As in nursing, physiotherapy and radiology advanced practioner roles are more introduced into radiotherapy with the general distinctive aspect being a higher level practice and formal education. Sometimes these roles are a logical sequel to role extension and/or expansion. While no one single definition of advanced practice exists literature suggests advanced practioner role incorporates 4 core functions [54-56]: innovation, education, research and clinical leadership. Titles, scope of practice, levels of autonomy, registration or licensing and education differ greatly.

Alternatives to reducing toxicity

This thesis describes our journey to minimize toxicity for patients treated for rectal cancer with external beam photon radiotherapy by reducing dose to the OARs by reducing PTV margins.

Organ preservation

TME surgery impacts quality of life in rectal cancer patients [57, 58], therefore there is a growing interest in organ preservation with a non-operative approach. Surgery in the multi-modality treatment is then delayed to improve chances of complete response and subsequently omitted if this complete

response is achieved for both early, intermediate and locally advanced rectal cancers [59-62]. These patients continue in a strict surveilled watchful waiting program [63]. The delayed surgery in the watchful wait program compared to immediate surgery resulted in an increased hospitalization as a result of acute radiotherapy toxicity (grade 3 and 4) but a decreased number of post-operative complications. There is limited evidence that for this patient group there is no significant difference with respect to overall survival and disease free survival [64-66]. Patients in the watchful waiting program report better quality of life as well as better anorectal and urogenital function [5, 67-69]. Methods to improve complete response rates are currently investigated, but intensification of (chemo)therapy often results in higher and unacceptable toxicity rates toxicities [70-73].

Proton therapy

The physical properties of proton beams have the advantage that dose is deposited in only a small range of tissue resulting in less dose in the entry of the beam and stops at a predefined depth [74]. This results in very sharp dose gradients in the direction of the beam with close to zero exit dose resulting in lower integral doses. Potentially this could be beneficial for the treatment of rectal cancer with organs at risk like bladder and small bowel directly adjacent to the target volume. If the direction of the treatment beams would be mainly posterior this could avoid dose to those OARs almost completely. A disadvantage of protons is the dependency of dose deposit on tissue density along the beam direction. Unexpected gas pockets could possible result in underdosing the target and overdosing the OARs even if the outer contour of the target volume has not changed at all. Robust planning methods can help to some degree but to optimal take advantage of protons the large interfraction motion and changes in density should be counteracted by using online ART. This is currently under investigation but should be possible in the near future [74]. Then, the possible reduction in dose to OARs using protons compared to photons needs to be investigated giving the economic aspects of proton therapy.

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Summary

Individualized neo adjuvant external beam radiotherapy for rectal cancer: From concept to clinical implementation

Introduction

The standard of care for intermediate and locally advanced rectal cancer is a multimodality treatment of chemotherapy, surgery and radiotherapy. Radiotherapy improves local control and/or improves chances of a complete resection but comes at the cost of increased toxicity.

This thesis starts with defining appropriate population based planning target volume (PTV) margins for a single fixed treatment plan for rectal cancer. It subsequently explores more flexible concepts than a single fixed treatment plan in the form of multiple a-priori designed treatment plans to reduce the PTV margins and it describes the translation of this concept into clinical practice. This thesis concludes with the design and clinical implementation of online adaptive radiotherapy, a technique to adapt the treatment plan to the daily anatomy. In short, this thesis describes the road from 3D conformal radiotherapy to online adaptive radiotherapy for the treatment of rectal cancer.

Chapter 1 is a general introduction into rectal cancer and image guided radiotherapy.

When intensity modulated (IMRT) and volumetric modulated arc (VMAT) treatment were introduced as a treatment planning and delivery technique it became possible to deliver highly conformal dose distributions with steep dose gradients around the planning target volume. To take optimal advantage of these techniques the definition of appropriate PTV margins became very important. In ***chapter 2 and 3*** we described the quantification of the anatomical changes of the target volume in short course radiotherapy treatment (SCRT), delivered in 5 x 5Gy for prone (chapter 2) and supine position (chapter 3). With this data the influence of geometrical uncertainties on the PTV margin could be calculated. For a total of 55 patients we delineated the target volume as well as the bladder and rectum on the planning CT scan and on all 5 Conebeam CT scans. Systematic and random errors were calculated for the total patient group for the target volume. We established that the deformation of the target volume was very heterogeneous. To calculate the margin necessary we used the van Herk margin recipe, i.e. 2.5 Σ + 0.7 σ. The largest uncertainty found at the ventral

part of the upper mesorectum (female patients, supine position) with a systematic error of 7.5 mm and a random error of 4.8 mm, required a margin of up to 24 mm. We also established that the deformation of the target volume was pre-dominantly influenced by changes in rectum filling, not by changes in bladder filling.

In ***chapter 4*** we explored a different concept to the single fixed treatment plan. Since the largest margin was required at the ventral part of the upper mesorectum which is adjacent to small bowel and bladder we aimed to develop a concept that is able to locally reduce that margin. Our starting point was a strategy of a-priori plans already clinically used for bladder and cervix treatments. In that concept a-priori plans were created based on target volume changes as captured on a full and empty bladder planning CT scan. However, because bladder filling was not the dominant contributor of changes of the target volume for rectal cancer, as we established in chapter 3, we designed a plan selection strategy based on a single CT scan. In our concept we created three plans, each with different margins to the ventral part of the upper mesorectum. Remaining PTV margins to the target volume were fixed and based on population statistics from chapter 2 and 3, complemented with data from the literature for long course radiotherapy (LCRT) (25 x 2Gy) treatments. We described and analyzed the possible benefit of our concept by retrospectively simulating this plan selection strategy for 10 SCRT patients. Based on daily Conebeam CT scans used at the treatment machine to position the patient we retrospectively selected the plan with the smallest PTV margin that covered the target volume completely. We calculated the dose to the bladder and small bowel and compared this to the clinically used single fixed treatment plan. We found that with our concept of plan selection the benefit in term of dose to bladder and small bowel was limited for the total patient group but that it could be beneficial for individual patients. The largest difference we found was a 13% reduction in bladder V95%-fx. The largest reduction for small bowel we found was a reduction of 59 cm^3 for V15Gy-fx.

Our plan selection strategy enables selecting a plan based on daily Conebeam CT scans. Conebeam CT scans have limited soft tissue contrast as they result from kV images and motion artefacts can degrade the image quality. The success of plan selection starts with the ability to use the Conebeam CT scans to select the appropriate plan. In ***chapter 5*** we described the

implementation procedure that we used for (RTT-led) plan selection strategy and we analyzed the inter observer variation of selecting a plan based on Conebeam CT scans. We achieved a 75% consistency in selecting the smallest PTV encompassing the entire target volume, a percentage that gave us confidence to implement plan selection for both SCRT and LCRT to benefit the individual patient.

In ***chapter 6*** we retrospectively analyzed the actual benefit we achieved for the first 20 rectal cancer patients (10 SCRT and 10 LCRT) that we treated with plan selection. We compared the possible dosimetric benefit of plan selection compared the single fixed treatment plan we previously used clinically with respect to dose to the bladder and the small bowel for a range of dose parameters. We confirmed our results of chapter 5 that there was only a limited advantage of plan selection over single fixed treatment plan for the patient population but that plan selection could be beneficial for individual patients due to variations in patients anatomy.

Plan selection had a limited benefit because the variable margin was only applied locally to the ventral part of the upper mesorectum and sometimes still generously encompassed the target volume. Ideally a treatment plan should be adapted daily to the shape of the target volume using small PTV margins to only compensate for motion that occurs during treatment delivery. Software for automatic contouring of structures on medical images and automatic generation of treatment plans have become available, making this a clinical reality today. Therefore, in ***chapter 7*** we analyzed the possible benefit of an online re-planning strategy compared to plan selection, again in terms of dose to the bladder, small bowel and healthy tissue (volume receiving 95% of the prescribed dose or more minus CTV). We found substantial benefit for all dose parameters we analyzed for bladder, small bowel and healthy tissue. This encouraged us to develop and use this strategy when we installed a newly designed ring-based linear accelerator that operates an integrated platform for both treatment planning and delivery.

Finally, we reached our goal of daily online adaptation: we successfully treated the first 12 patients with online adaptive radiotherapy. The workflow was supported with artificial intelligence and structure guided deformation implying that the system automatically adapted the target volumes to match the anatomy on the Conebeam CT. If the system generated structures were

Summary

not acceptable the user was able to adjust them and after approval the system automatically generated a new treatment plan. In ***chapter 8*** we described the procedure and the feasibility of this workflow. Defined as the time from the pretreatment Conebeam CT scan to the post treatment Conebeam CT scan we were able to treat patients in 26 minutes (AVG, range 16-46) with PTV margins of 5 mm (LR and AP direction) and 8 mm (CC direction).

Further research should investigate if we have reached the optimal margins, or if there is still room for improvement. Online adaptive radiotherapy took more time at the treatment machine compared to plan selection impacting on departmental resources. Therefore, future research should involve the quantification of the benefit of the decreased dose to bladder and small bowel in terms of a reduction of side effects and improved quality of life for rectal cancer patients.

Samenvatting

Patiënt specifieke radiotherapie behandeling bij endeldarmkanker: Van concept tot klinische implementatie

Introductie

Voor de behandeling van gevorderde endeldarmkanker (rectum carcinoom) wordt radiotherapie voorafgaand aan een operatie gegeven, vaak gecombineerd met chemotherapie. Radiotherapie in deze setting wordt toegediend om te voorkomen dat de ziekte later op dezelfde locatie terugkeert dan wel om de tumor te verkleinen om zo de kans op een succesvolle operatie te vergroten.

Behandeling van gevorderde endeldarmkanker met radiotherapie bestaat niet alleen uit het bestralen van de tumor. Ook het direct omliggende vetweefsel (het mesorectale vet) dat tijdens de operatie verwijderd zal worden, moet dezelfde stralingsdosis krijgen. Behandeling met radiotherapie kan bijwerkingen opleveren, omdat ook aangrenzend gezond weefsel een (beperkte) hoeveelheid straling zal ontvangen.

Om er zeker van te zijn dat alle dagen de juiste hoeveelheid straling op de juiste plek terechtkomt wordt het te bestralen gebied voor de behandeling in beeld gebracht met een CT scan. De radiotherapeut definieert daarop het te bestralen gebied en vervolgens wordt er een bestralingsplan voor gemaakt. Dit proces kost normaal gesproken tussen de 3 en 5 werkdagen. Het afgeven van de dosis wordt over meerdere dagen verdeeld (5 of 25 dagen) om eventuele bijwerkingen te beperken. Bij het maken van dit bestralingsplan moet rekening gehouden worden met het feit dat de interne anatomie van de patient op de behandeldagen elke dag anders kan zijn als gevolg van verschillende blaas- en darmvulling. Een eet- en drinkinstructie om deze anatomische veranderingen te voorkomen is helaas niet effectief. Het te bestralen gebied wordt daarom vergroot met een marge die deze verschillen zal opvangen.

De afgelopen jaren hebben wij uitgerekend hoe groot deze anatomische veranderingen zijn en welke marge daarbij hoort. De anatomische veranderingen blijken zeer groot te zijn, vooral aan de voorzijde van het te bestralen gebied dat tegen de blaas en de darmen aan ligt. Lokaal zou de marge daar 25 mm moeten zijn. Blaas en darmen zijn gevoelig voor straling en dosis op deze organen kan zowel tijdens de behandeling als op de lange termijn bijwerkingen opleveren. Het doel van ons onderzoek was om de marge rondom het te bestralen gebied te beperken en daarmee zoveel mogelijk de bijwerkingen te verminderen.

Hieronder volgt een overzicht van de inhoud van dit proefschrift.

In ***hoofdstuk 1*** volgt een korte introductie, waarin het vóórkomen en de behandeling van endeldarmkanker wordt beschreven. In dit hoofdstuk wordt ook radiotherapie uitgelegd, alsmede de ontwikkelingen van de afgelopen jaren. Ook komen de algemeen gangbare technieken om bijwerkingen van radiotherapie te beperken aan bod.

In ***hoofdstuk 2 en 3*** worden de anatomische veranderingen gekwantificeerd en de bijbehorende marge uitgerekend. Om de grootste variatie aan de voorzijde van het te bestralen gebied op te kunnen vangen, een gebied dat direct grenst aan de blaas en de darmen, blijkt er lokaal een marge van 25 mm nodig te zijn.

In ***hoofdstuk 4*** onderzoeken we de eerste alternatieve strategie om de marges te verkleinen. Met deze strategie wordt niet 1 bestralingsplan gemaakt, maar een set van meerdere bestralingsplannen. Uit praktische overwegingen kunnen we maar een beperkt aantal plannen voorbereiden. Daarom is gekozen om in de basis 1 plan te hebben met vaste marges zoals uitgerekend in hoofdstuk 2 en 3. Dit bestralingsplan wordt vervolgens gekopieerd en aangepast met variabele marges voor de voorzijde van het te bestralen gebied tot een totaal van 3 verschillende bestralingsplannen.

We maken gebruik van de mogelijkheid om met een röntgenbuis, die geïntegreerd is in het bestralingstoestel, net voor de bestraling een 3D scan van de patient te maken, een zogenaamde Conebeam CT scan. Deze Conebeam CT scan laat de interne anatomie van de patiënt op dat moment zien. Wanneer op deze Conebeam CT scan blijkt dat de anatomische veranderingen beperkt zijn kan dan het plan met kleinere marge gekozen worden. Deze vorm van radiotherapie wordt ook wel plan selectie of adaptieve radiotherapie genoemd.

In dit hoofdstuk hebben we retrospectief uitgerekend of deze aanpak zou kunnen leiden tot verminderde dosis op de blaas en de darmen. We simuleerden daarvoor deze strategie op 20 patiënten, die we eerder conventioneel met 1 bestralingsplan hadden behandeld. De uitkomst van dit onderzoek liet zien dat er gemiddeld genomen niet veel verschil in dosis op de blaas en darmen was. Wel sprongen er enkele patiënten uit, waarbij de dosis op de blaas en/of darmen aanmerkelijk minder was.

De Conebeam CT scans, die dagelijks op het toestel nodig zijn voor het in beeld brengen van het te bestralen gebied, worden niet met dezelfde techniek gemaakt als CT scans en zijn in vergelijking met CT scans soms van mindere kwaliteit. Het was daarom van belang om te onderzoeken of deze Conebeam CT scans van voldoende kwaliteit waren om een bestralingsplan te kunnen kiezen. In ***hoofdstuk 5*** beschrijven we de klinisch gevolgde procedure voor de training van de radiotherapeutische laboranten en onderzochten we of zij eenduidig waren in het kiezen van een bestralingsplan. Uit dit onderzoek bleek dat in 75% van alle Conebeam CT scans eenduidig voor hetzelfde bestralingsplan was gekozen. Dit percentage bevestigde voor ons dat de Conebeam CT scans van voldoende kwaliteit waren voor het uitvoeren van plan selectie in de klinische praktijk.

Nadat de eerste 20 patiënten daadwerkelijk met deze plan selectie strategie waren bestraald, hebben we het onderzoek van hoofdstuk 4 nogmaals uitgevoerd voor 10 patiënten die in 5 dagen zijn bestraald en 10 patiënten die in 25 dagen zijn bestraald. In ***hoofdstuk 6*** beschrijven we dat we in dit onderzoek konden we bevestigen dat plan selectie voor de gemiddelde populatie niet direct tot een vermindering van dosis op de blaas en darmen leidde. Ook nu bleek er wel een duidelijke meerwaarde voor enkele individuele patiënten.

Zoals gezegd, de meerwaarde van de plan selectie strategie bleek beperkt tot individuele patiënten. De reden daarvoor was dat de variabele marge alleen werd toegepast op de voorzijde van het te bestralen gebied en het gekozen plan vaak nog erg ruim was. Er kon immers ‘maar’ gekozen worden uit 3 plannen waren de verschillen tussen de marges vrij groot waren (10 en 15 mm verschillen tussen de plannen).

Idealiter zou er op basis van de Conebeam CT scan elke dag een nieuw te bestralen gebied gedefinieerd moeten worden met een bijbehorend plan zodat alle dagelijkse anatomische vormveranderingen opgevangen kunnen worden. Deze vorm van bestraling wordt dagelijkse adaptieve radiotherapie genoemd. Ontwikkelingen op het gebied van techniek en software gingen razendsnel vooruit, waarbij dit al snel tot onze klinische mogelijkheden zou gaan behoren. Om die reden onderzochten we in ***hoofdstuk 7*** wat de meerwaarde van online adaptieve radiotherapie zou kunnen zijn in vergelijking met de inmiddels klinisch geïmplementeerde plan selectie strategie. Uit de resultaten van dit onderzoek bleek dat de meerwaarde zeer groot was, en niet alleen voor enkele patiënten maar voor de hele groep.

Samenvatting

Inmiddels zijn er 6 bestralingstoestellen op onze afdeling geïnstalleerd die over de techniek beschikken voor het uitvoeren van dagelijkse adaptieve radiotherapie op basis van Conebeam CT scans. Omdat vorig onderzoek uitwees dat de dosis op de blaas en darmen duidelijk verminderde werd deze strategie als eerste ontwikkeld en geïmplementeerd voor de behandeling van de gevorderde endeldarmkanker.

In ***hoofdstuk 8*** beschrijven we de procedure van dagelijkse adaptieve radiotherapie en onze eerste ervaringen en bevindingen voor de patiënten groep die in 5 dagen bestraald werd. De procedure kost op dit moment nog meer tijd op het bestralingstoestel (30 versus 15 minuten) en elke dag is een voltallig team nodig bestaande uit 2 radiotherapeutisch laboranten, 1 radiotherapeut en 1 fysicus.

Aanvullend onderzoek moet evalueren wat de optimale resterende marges zouden moeten zijn en of de verminderde dosis op blaas en darmen ook daadwerkelijk betekent dat patiënten minder last van bijwerkingen ervaren.

Dankwoord

Dankwoord

In 2005 zette ik mijn eerste voorzichtige stappen in de onderzoekswereld toen in het Antoni van Leeuwenhoek ziekenhuis de werkgroep IGRT werd opgericht. Geometrische onzekerheden bij het rectum carcinoom stonden al snel op de agenda in de zoektocht naar de juiste marges voor IMRT bestralingen. Ik had daarin vooral een assisterende rol en Jasper Nijkamp promoveerde op '(Un-)Certainties in radiotherapy of rectal cancer', zie hoofdstuk 2 en 3.
In 2012 verhuisde ik naar het Amsterdam UMC, locatie AMC waar ik verder met het onderwerp aan de slag kon gaan. We ontwikkelden én implementeerden zowel plan selectie als later online adaptieve radiotherapie voor rectum kanker in de kliniek. En ik mocht daarbij een grotere rol pakken. Dat resulteerde in het boekje dat nu voor jullie ligt. Ik ben trots op het eindproduct, maar bovenal heb ik genoten van het proces!
Daarvoor wil ik een aantal van jullie danken:

Allereerst mijn promotoren omdat ik zonder hun steun nooit zover zou zijn gekomen.
Beste Coen, in 2005 bood jij mij de kans om me te ontwikkelen binnen de werkgroep IGRT en sindsdien heb je mijn comfortzone beetje bij beetje opgerekt, totdat ik open stond voor een promotietraject. Jouw vertrouwen in mij in dit proces is onontbeerlijk geweest. Al die jaren met jou mogen werken heeft mij enorm geïnspireerd. Ik kan je daarvoor niet genoeg bedanken.
Beste Arjan, toen ik in 2012 in het AMC begon was ik zoekende naar mijn rol op deze afdeling en jij nam met plezier de rol van mentor op je. Jij had altijd het volste vertrouwen in mij en gaf me 3 jaar geleden dat extra zetje (lees: flinke duw), dat ik nodig had om dit avontuur aan te gaan. Je gaf me alle ruimte om de dingen op mijn manier en op mijn tempo te doen, maar tegelijkertijd kon ik altijd op je rekenen voor aanmoediging, kritische feedback en vele, vele spiegelmomenten. Het is een eer dat jij nu mijn promotor bent.
Binnen deze kaders was het een voorrecht om me kunnen ontwikkelen en mogen leren.

Beste Jorrit, voor jou de eerste keer de rol van copromotor. Jouw deur (of Teams-link/Whatsapp) stond altijd voor me open. Zoveel manuscripten gelezen en van constructieve feedback voorzien, zoveel discussies en zoveel geleerd. Dank ook voor je altijd nuchtere blik en relativeringsvermogen. Ik gun iedere PhD-student zo'n geweldige copromotor.

Ik wil de leden van de commissie hartelijk danken voor hun tijd en deelname. Ik ken de meesten van jullie al jaren en jullie horen voor mij bij de rock stars van de radiotherapie.

Uiteraard mijn paranimfen, dank dat jullie deze taak op je wilden nemen, vooral omdat ik er in de zomer twee maanden tussenuit trok om zorgeloos door de bergen te lopen. Aan jullie de taak om de voorbereidingen voor deze promotie door te laten gaan. ☺
Ik heb jullie al vroeg in het traject gevraagd want het stond voor mij als een paal boven water dat ik niemand liever aan mijn zijde had tijdens dit traject. Irma, je bent een groot voorbeeld voor mij en een hele fijne collega. Laila, ook jij bent een groot voorbeeld en vooral een geweldige vriendin door dik en dun. Dank voor alle aanmoediging en afleiding.

Ik ga even terug in tijd waar het allemaal begon en wil mijn oude IGRT-collega's uit het AvL bedanken: Jasper (natuurlijk!), Suzanne-Anja-Maddalena-Danny (CB-babes), Peter, Simon, Jan-Jakob, Lennart en Folkert.

Marcel, ik ontmoette je voor de eerste keer in 1994 voor mijn afstudeerproject van de MBRT 'implementatie van een EPID systeem'. Vanaf die eerste ontmoeting tot aan de dag van vandaag heb ik ontzettend veel van je geleerd over radiotherapie en genoten van je vriendschap.

Big thanks to all my ESTRO collegues and faculty members over the years. I have loved all our travels and professional encounters, always an inspiration to further develop radiotherapy clinical practice at home. I hope to see you all soon in person after these crazy times.

Mijn collega's van de werkgroep rectum: Niek, Jorrit, Debby, Koen en Jan. Al ons werk van de afgelopen jaren staat in dit boekje en mooi werk als dit is altijd een team effort. Karin en Nina, als rectum artsen overal nauw bij betrokken. Ik heb me altijd gerealiseerd wat een voorrecht het is om binnen zo'n groep aan onderzoek, ontwikkeling en implementatie te werken.

Mijn AMC IGRT collega's: Karin, Marije, Lianne, Richard, Martijn, Nicole, Emina en Arnout. Wat hebben we samen met veel plezier veel bereikt.

Karen en Sjaak, altijd de juiste woorden op het juiste moment. Namasté!

Ernst en Rob, en niet alleen voor de geweldige ICT-ondersteuning tijdens dit promotie werk, maar gewoon altijd.

Petra, mijn kamergenootje en Hans, mijn bonus-kamergenoot. Wat een geluk dat ik altijd kon rekenen op jullie luisterend oor, enorme ervaring en wijze raad.

Jeroen, jij wilde je grafische vaardigheden weer eens voor ten volle benutten en bood aan om mijn boekje te ontwerpen. Ik voel me vereerd dat je dat voor me hebt willen doen. Het ziet er prachtig uit!

Al mijn collega's van de afdeling Radiotherapie: Vanaf dag één heb ik me hier thuis en gewaardeerd gevoeld. We hebben 3 bijzonder turbulente jaren achter de rug met onder andere een fusie, personeelstekort en Covid-19. Toch, werken met jullie is voor mij elke dag een feestje geweest! Ik hoop dat er nog veel mooie jaren voor ons liggen.

Blond & Oud bruin: Tijd om één en ander in te halen!

Lieve Jelle en Tim. Lieve Anja en Femke. Mijn familie, het meest geweldige support systeem dat er is. (O-)pa en (o-)ma zouden trots op ons zijn.

Portfolio & CV

Portfolio & CV

Full name:

Maria Antonia Johanna de Jong (Rianne)

Date and place of birth:

27-11-1971 te Roosendaal en Nispen

Qualifications/Education

2011 - 2012	Research in Healthcare, InHolland Hogeschool, Haarlem
1990 - 1994	Medisch Beeldvormende en Radiotherapeutische Technieken (MBRT), Hogeschool, Eindhoven
1984 - 1990	Gymnasium Juvenaat H. Hart, Bergen op Zoom

Professional Experience/Appointments

2021 - current	Editorial board member Journal Technical Innovations and Patient Support in Radiation Oncology
2018 - current	PhD candidate, Amsterdam UMC, Location AMC, Department of Radiation Oncology, Amsterdam, The Netherlands
2012 - current	Radiotherapy Technician (RTT), Research and Development IGART & ART, Amsterdam Medical Centre, Department of Radiation Oncology, Amsterdam, The Netherlands
1995 - 2012	RTT, Antoni van Leeuwenhoek Ziekenhuis/Netherlands Cancer Institute, Department of Radiation Oncology, Amsterdam
2011 - 2012	Project group IGART
2005 - 2010	Project group IGRT
1994 - 1995	RTT, Mutterhaus der Borromaërinnen, Strahlentherapie, Trier, Germany

Teaching Appointments *(29 ECTS)*

European SocieTy for Radiation and Oncology (ESTRO) Teaching Course on "Image Guided Radiation Therapy in Clinical Practice". European Region, Faculty, 2007/2008/2009/2010/2011/2012/2013/2014/2015/2016/2017/2018/2019/2020/2021

ESTRO Teaching Course on "Advanced Skills for Modern Radiation Therapy". European Region, Course Director, 2014/2015/2016/2017/2018/2019

ESTRO Teaching Course on "Advanced Technologies", Asia-region, Faculty, 2010/2011/2012/2014/2015/2016/2018/2019

Multi-disciplinary internal education 2005 - current (RTTs, residents, radiation oncologists, medical physicists). Antoni van Leeuwenhoek ziekenhuis, Amsterdam UMC.

Peer reviewed publications

1. "Adaptive Radiotherapy for Prostate Cancer Using Kilovoltage Cone-Beam Computed Tomography: First Clinical Results." Jasper Nijkamp, Floris J. Pos, Tonnis T. Nuver, Rianne de Jong, Peter Remeijer, Jan-Jakob Sonke, Joos V. Lebesque. Int J Radiat Oncol Biol Phys, 70 (2008), pp. 75-82. doi.org/10.1016/j.ijrobp.2007.05.046

2. "Target volume shape variation during irradiation of rectal cancer patients in supine position: comparison with prone position." Nijkamp J, de Jong R, Sonke JJ, van Vliet C, Marijnen C. Radiother Oncol. 2009 Nov; 93(2):285-92. doi:10.1016/j.radonc.2009.08.007

3. "Target volume shape variation during hypo-fractionated preoperative irradiation of rectal cancer patients." Nijkamp J, de Jong R, Sonke JJ, Remeijer P, van Vliet C, Marijnen C. Radiother Oncol. 2009 Aug; 92(2):202-9. doi: 10.1016/j.radonc.2009.04.022. Epub 2009 May 18.

4. "Repeat CT assessed CTV variation and PTV margins for short- and long-course pre-operative RT of rectal cancer." Nijkamp J, Swellengrebel M, Hollmann B, de Jong R, Marijnen C, van Vliet-Vroegindeweij C, van Triest B, van Herk M, Sonke JJ. Radiother Oncol. 2012 Jan 10. doi: 10.1016/j.radonc.2011.11.011. Epub 2012 Jan 10.

5. "Interfractional position variation of pancreatic tumors quantified using intratumoral fiducial markers and daily cone beam computed tomography." van der Horst A, Wognum S, Dávila Fajardo R, de Jong R, van Hooft JE, Fockens P, van Tienhoven G, Bel A. Int J Radiat Oncol Biol Phys. 2013 Sep 1. doi: 10.1016/j.ijrobp.2013.05.001. Epub 2013 Jun 19.

6. "Limited role for biliary stent as surrogate fiducial marker in pancreatic cancer: stent and intratumoral fiducials compared." van der Horst A, Lens E, Wognum S, de Jong R, van Hooft JE, van Tienhoven G, Bel A. Int J Radiat Oncol Biol Phys. 2014 Jul 1. doi: 10.1016/j.ijrobp.2014.03.029. Epub 2014 May 3.

7. "Marker-based quantification of interfractional tumor position variation and the use of markers for setup verification in radiation therapy for esophageal cancer. " Jin P, van der Horst A, de Jong R, van Hooft JE, Kamphuis M, van Wieringen N, Machiels M, Bel A, Hulshof MC, Alderliesten T. Radiother Oncol. 2015 Dec. doi: 10.1016/j.radonc.2015.10.005. Epub 2015 Oct 20.

8. "Quantification of renal and diaphragmatic interfractional motion in pediatric image-guided radiation therapy: A multicenter study." Huijskens SC, van Dijk IW, de Jong R, Visser J, Fajardo RD, Ronckers CM, Janssens GO, Maduro JH, Rasch CR, Alderliesten T, Bel A. Radiother Oncol. 2015 Dec. doi: 10.1016/j.radonc.2015.09.020. Epub 2015 Sep 30.

9. "Evaluation of delivered dose for a clinical daily adaptive plan selection strategy for bladder cancer radiotherapy." Lutkenhaus LJ, Visser J, de Jong R, Hulshof MC, Bel A. Radiother Oncol. 2015 Jul. doi: 10.1016/j.radonc.2015.06.003. Epub 2015 Jun 18.

10. "Potential dosimetric benefit of an adaptive plan selection strategy for short course radiotherapy in rectal cancer patients". Lutkenhaus LJ, de Jong R, Geijsen ED, Visser J, van Wieringen N, Bel A. Radiother Oncol. 2016 Jun;119(3):525-30. doi: 10.1016/j.radonc.2016.04.018. Epub 2016 Apr 26.PMID: 27130729

11. “Quantification of respiration-induced esophageal tumor motion using fiducial markers and four-dimensional computed tomography.” Jin P, Hulshof MC, de Jong R, van Hooft JE, Bel A, Alderliesten T. Radiother Oncol. 2016 Mar;118(3):492-7. doi: 10.1016/j.radonc.2016.01.005. Epub 2016 Jan 28. PMID: 26830696

12. “Plan selection strategy for rectum cancer patients: An interobserver study to assess clinical feasibility”. de Jong R, Lutkenhaus L, van Wieringen N, Visser J, Wiersma J, Crama K, Geijsen D, Bel A. Radiother Oncol. 2016 Aug;120(2):207-11. doi: 10.1016/j.radonc.2016.07.027. Epub 2016 Aug 16. PMID: 27543254

13. “Interfractional renal and diaphragmatic position variation during radiotherapy in children and adults: is there a difference?” van Dijk IWEM, Huijskens SC, de Jong R, Visser J, Fajardo RD, Rasch CRN, Alderliesten T, Bel A. Acta Oncol. 2017 Aug;56(8):1065-1071. doi: 10.1080/0284186X.2017.1299936. Epub 2017 Mar 10. PMID: 28281356

14. “Dosimetric benefit of an adaptive treatment by means of plan selection for rectal cancer patients in both short and long course radiation therapy.” R. de Jong, J. Visser, K. F. Crama, N. van Wieringen, J. Wiersma, E. D. Geijsen & A. Bel. Radiat Oncol. 2020 Jan 13;15(1):13. doi: 10.1186/s13014-020-1461-3

15. “Online adaptive radiotherapy compared to plan selection for rectal cancer: quantifying the benefit” R. de Jong, K. F. Crama, J. Visser, N. van Wieringen, J. Wiersma, E. D. Geijsen, A. Bel, Radiat Oncol. 2020 Jul 8;15(1):162. doi: 10.1186/s13014-020-01597-1.

16. “Evaluation of Ultra-low-dose Paediatric Cone-beam Computed Tomography for Image-guided Radiotherapy.” A. Bryce-Atkinson, R. de Jong, A. Bel, M. C. Aznar, G. Whitfield, M. van Herk, Clin Oncol (R Coll Radiol) 2020 Oct 13;S0936-6555(20)30381-2. doi: 10.1016/j.clon.2020.09.011.

17. “Feasibility of Conebeam CT-based online adaptive radiotherapy for neoadjuvant treatment of rectal cancer.” R. de Jong, J. Visser, N. van Wieringen, J. Wiersma, E. D. Geijsen, A. Bel. Radiat Oncol. 2021 Jul 23; 16(1): 136. doi: 10.1186/s13014-021-01866-7

Conference presentations *(8 ECTS)*

2021 “Feasibility CBCT-based online adaptive 5x5Gy radiotherapy for neoadjuvant rectal cancer treatment.” – proffered paper, European Society for Radiotherapy and Oncology, ESTRO

2020 “Quantifying the benefit of online adaptive radiotherapy for rectal cancer compared to plan selection”- proffered paper/Highlight proffered paper, ESTRO

2019 “Dosimetric benefit of a clinically applied adaptive strategy for rectal cancer – plan selection” – proffered paper, ESTRO

2019 “Image guided and Adaptive Radiotherapy in rectal cancer” – pre meeting invited lecture, ESTRO

2018 “Challenges and opportunities using plan selection in daily clinical practice” – invited lecture, ESTRO

2017 “Adaptive strategy for rectal cancer: Evaluation of plan selection of the first 20 clinical patients” – proffered paper, ESTRO

2016 “Implementation of daily plan selection for rectal cancer patients” – invited lecture, ESTRO

2014 “Development and Implementation of IGRT protocols” – invited lecture, ESTRO

2014 “Optimizing cone-beam CT presets for children to reduce imaging dose” – proffered paper, ESTRO

2013 “Plan selection for cervix patients inter-observer study: Is CBCT image quality good enough to make a decision?” – proffered paper, ESTRO

2011 “First results of a worldwide survey on responsibilities and recourses in modern radiation therapy”- proffered paper, ESTRO

2010 “Geometrical uncertainties in radiation therapy of rectal cancer patients” – invited lecture, ESTRO

2009 “Image Guidance in Radiation Therapy” – invited lecture, ESTRO

2008 “Geometrical uncertainties in radiotherapy for rectal cancer” – invited lecture, EMCCC

2006 “Intra fraction motion of rectal patients in prone position compared to supine position” – proffered paper, ESTRO

2002 “Late ischaemic disease after left breast irradiation: possible improvements – proffered paper, ESTRO

Posters European Society for Radiotherapy and Oncology (ESTRO) *(4 ECTS)*

2012 “Feasibility of generation a library of plans for cervical cancer based on a pre-treatment full and empty bladder CT scan”

2008 “Interfraction CTV shape variability of rectum cancer patients

2007 “Inter- and intrafraction set up variability of rectum cancer patient in prone position with and without bellyboard”

2004 “A Quality assurance protocol for Cone-Beam CT for the radiation therapy technologist

Societal Impact

“Image Guided Radiation Therapy”, NVMBR, 2010, jaargang 60, nummer 2.

Faculty Elekta courses at Antoni van Leeuwenhoek Ziekenhuis on the clinical use of Conebeam CT, 2009-2012

Supervising *(1.5 ECTS)*

Bachelor students of Medische Beeldvormende en Radiotherapeutische Technieken (MBRT) from Hogeschool InHolland, Haarlem, The Netherlands

2018 “Een comfortabele volle blaas: De invloed van het tijdstip op de dag” – Jikke Wams

2017 “Evaluatie darmbelasting bij adaptieve vs. non-adaptieve radiotherapie van het cervix carcinoom” – Patricia van der Groen, Rebecca Reuser

2015 “Geometrische variatie van de okselklieren bij de mamma bestraling” – Simone Looijen, Iris Roozema


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