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Effect of bladder volume changes and verification of CTV on CBCT for rectal cancer patients

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Supervision

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Popular scientific summary in Swedish

Ändtarmscancer är en av de vanligast förekommande cancersjukdomarna. Tillsammans med tjocktarmscancer är det den tredje vanligaste cancersjukdomen i världen. Den behandlas vanligen med kirurgi, under vilken en stor del av ändtarmen och dess omgivande fettvävnad tas bort. För att minska risken för återfall kan operationen kompletteras med strålbehandling, där patienterna oftast strålbehandlas innan de opereras. Under strålbehandlingen riktas då till området kring tumören, d.v.s. till ändtarmen och omkringliggande mjukvävnad. Den totala mängden strålning delas upp i flera fraktioner, så att patienten får strålbehandling dagligen 5 dagar i veckan i 1 eller 5 veckor.

Utöver att minska risken för återfall, medför den kompletterande strålbehandlingen en rad biverkningar till följd av att strålkänsliga, friska organ exponeras för strålning. Tunntarmen är ett av dessa organ. Då tunntarmen ligger nära ändtarmen är tunntarmen nästintill oundviklig att inte bestråla. För att minska biverkningarna används olika metoder som minskar den bestrålade tunntarmsvolymen, varav en är att låta patienten ha en full urinblåsa. Av naturliga skäl kommer urinblåsans volym dock att variera under behandlingens förlopp, vilket innebär att den bestrålade tunntarmsvolymen även kommer att variera. I detta arbete undersöktes huruvida det går att på ett enkelt och snabbt sätt översätta en förändrad urinblåsvolym till förändrad tunntarmsstråldos. Det undersöktes även om det finns det ett mönster i ändringen av urinblåsans volym, d.v.s. om den ökar eller minskar under strålbehandlingen gång.

Resultaten visade att urinblåsans volym vanligtvis är större i början av strålbehandlingsprocessen än under efterföljande strålbehandlingsfraktioner. Minskningen i urinblåsvolym resulterade dock inte i att tunntarmen utsattes för mer strålning än vad som rekommenderas, för någon av patienterna i studien. Ytterligare visade resultaten en klar koppling mellan urinblåsans volym och tunntarmsdos. Däremot finns det inte en generell formel för att översätta en minskning i blåsvolym till en ökning i tunntarmsdos då översättning är högst individuell för varje patient.

För att strålningen ska nå dit man vill, d.v.s. till ändtarmen och omkringliggande mjukvävnad, kontrolleras patientens position genom att ta röntgenbilder innan strålbehandlingen. På strålbehandlingsavdelningen i Herlev (Danmark) tas tvådimensionella röntgenbilden innan varje strålbehandlingsfraktion och patientens position kontrolleras genom att kolla på benstrukturerna i bilderna. Om det är möjligt vill man i framtiden byta ut de tvådimensionella röntgenbilderna mot tredimensionella bilder och verifiera patientens position genom att, utöver benstrukturer, även kolla på ändtarmen och annan mjukvävnad i bilderna. I detta arbete undersöktes om bildkvaliteten på de tredimensionella röntgenbilderna är tillräckligt bra för att man ska kunna urskilja ändtarmen och annan mjukvävnad. Ytterligare undersöktes hur mycket ändtarmen och omkringliggande mjukvävnad rör sig mellan strålbehandlingsfraktionerna.

Resultaten visade att bildkvaliteten var tillräckligt bra för att urskilja ändtarmen på 94 av 95 bilder. Något som försvårar möjligheten att urskilja mjukvävnaden är när patienten hade mycket luft i ändtarmen, då luften skapar mörka stråk i bilderna. Ändtarmen rör sig vanligtvis inom 5 mm från positionen den har när strålbehandlingen planläggs.

Abstract

Background and purpose: During radiotherapy, rectal cancer patients show inter-fractional internal motion that effects the delivered dose distribution. The purpose of this work is to study I) the inter-fractional bladder volume change, II) the effect of bladder volume change on bowel dose distribution, III) the effect of bladder optimization on the relationship between bladder volume and bowel dose and IV) the possibilities and difficulties of validating the clinical target volume (CTV) using a surrogate on cone-beam computed tomography (CBCT) scans. An additional purpose is to find the most appropriate surrogate of the CTV to use in the validation.

Material and methods: Twenty-eight rectal cancer patients treated with preoperative radiotherapy in the period February 2015 to January 2016 were included in the study. All treatments were delivered with RapidArc, using two arcs. Each patient had a planning CT scan and weekly CBCT were acquired the first three, four, five and six weeks for 23, 1, 1 and 3 patients, respectively. The bladder and the bowel was delineated on the CBCT scans and transferred to the CT scan Treatment plans not including a bladder optimization were re-optimized, to investigate possibilities with lowering the bowel dose. In accordance with the latest local guidelines, the re-optimized treatment plans included a bladder optimization and delivered the dose with three arcs instead of two.

A surrogate of the CTV was delineated on the CT and compared with corresponding structure on the CBCT. The surrogate was defined as the rectum where rectum and mesorectum could be distinguished and as the mesorectum elsewhere. Caudally from the rectum, the surrogate was defined by the circumference of the levator ani. No surrogate was delineated cranial from the rectum. The surrogate was divided into an upper, mid and lower section during the validation.

Results: The median bladder size was significantly smaller on the CBCT than on the CT. Out of the 28 patients, 13 patients had bladders consistently smaller and larger on the CBCTs. Six patients had consistently larger bladder volumes on the CBCTs than on the CT. For 9 patients, the relationship between the bladder volume on the CT and CBCTs varied. The bladder volumes on the CBCTs ranged from 0.1 to 3.5 times the bladder volume on the corresponding CT, with the majority (81/96) in the range between 0.3 and 2.0. The change in bladder filling did not result in a violation of the bowel constraint V_{45Gy}<195 cm^3 for any patient. The re-optimized treatment plans resulted in lower bowel doses, without compromising PTV coverage. The bladder optimization was not proven (p=0.46) having an effect the relationship between V_{45Gy} and bladder volume change.

The image quality was sufficient for a validation of the surrogate on 94/95 CBCT scans. The CBCT scan where the surrogate could not be validated suffered from major artifacts due to internal gas. The delineated surrogate did not extend as far cranially as the gross tumor volume (GTV) or the primary CTV for 12/28 and 19/26 patients, respectively. The variation of surrogate was within 5 mm in the mid and upper section on 40/70 and 56/90 CBCTs, respectively. Cranial-caudal shifts in the position of the sigmoideum and internal gas challenged the validation of the surrogate.

Conclusion: There is a correlation between bladder volume and bowel radiation dose. However, the dose constraint for the small bowel was not violated for any of the patients in this study. The relation between bowel dose and bladder volume is highly individual and not proven being effected by bladder optimization. The bowel dose can be reduced by optimizing the plans according to the latest local guidelines. The CTV can be validated on CBCT using a surrogate. The surrogate can be defined somewhat general caudal from the cranial border of rectum but not cranially from rectum. The variation of the surrogate is usually within 5 mm.

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Abbreviations and acronyms

IMRT	Intensity Modulated Radiation Therapy
IMAT	Intensity Modulated Arc Therapy
LCRT	Long-course chemo-Radiation Therapy
SCRT	Short Course Radiation Therapy
TME	Total Mesorectal Excision
CTV	Clinical Target Volume
PTV	Planning Target Volume
OAR	Organ At Risk
CT	Computed Tomography
CBCT	Cone-beam Computed Tomography
IGRT	Image Guided Radiation Therapy
MRI	Magnetic Resonance Imaging
HU	Hounsfield Units
RTT	Radiotherapy Technician

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1. Introduction

Rectal cancer is one of the most common cancer diseases [1–3]. Approximately 6 100 and 17 000 patients are diagnosed with anorectal cancer and colorectal cancer, respectively, every year in the Nordic countries [2,3]. Colorectal cancer is the third most common cancer in men and the second in women, worldwide [1]. Rectum is the 15 cm long, final part of the large intestine. It extends from the sigmoideum, which is the end of the sigmoid colon, and is followed by the anal canal [4].

In the therapy of rectal cancer, surgery remains the mainstay of curative treatment [4]. Introducing total mesorectal excision (TME), during which a major part of rectum and its surrounding lymphatic, adipose tissue (mesorectum) are removed, as the standard surgical treatment has significantly reduced the risk for recurrence [5]. Adding radiotherapy pre- or postoperatively has shown to improve the local control even further [6–11]. As preoperative radiotherapy is superior to postoperative, it is the standard in many countries [12]. The preoperative radiotherapy can be given either as long-course chemo-radiotherapy (LCRT) or short-course radiotherapy (SCRT). In SCRT, 25 Gy is delivered in 5 fractions and no chemotherapy is given concurrently. As the name intends, LCRT runs over a longer period of time and the radiotherapy is combined with chemotherapy. Moreover, it involves a higher prescribed dose (48.6-60 Gy) over more fractions. At Herlev Hospital in Denmark, LCRT with a total dose of 50.4 Gy over 28 fractions is the standard treatment for resectable rectal cancer. They recently went to the total dose of 50.4 Gy over 28 fractions from 54 Gy over 27 fractions to be in consistency with the other radiotherapy centers in Denmark.

Apart from reducing local recurrences, adjuvant radiotherapy comes with a number of side effects as a result of the exposure of normal tissues, such as the small bowel. By being in the close proximity of rectum, it is almost impossible to avoid irradiating the small bowel. Different methods are used to minimize the exposed volume, since the occurrence of small bowel toxicity depends on the volume of small bowel exposed to irradiation [13]. One of those methods is a full bladder protocol; when the patient have a full bladder, the small bowel can be pushed away from the high dose region [14]. However, as the bladder volume naturally varies during the course of treatment, the irradiated volume of small bowel will vary. A purpose of this study is to investigate if there is any trend in the bladder volume variation during the course of treatment, despite having formal bladder filing instructions. Furthermore, it is to study the effect of bladder volume change on bowel dose distribution. It will be investigated whether there is an easy way to translate bladder volume decrease into bowel dose increase.

In late 2015, the local guidelines for treatment planning of rectal cancer patients at Herlev Hospital were modified. In contrast to the former guidelines, the new included constraints on the bladder in the optimization of the treatment plan. An additional purpose of this study is to study the effect of including the bladder in the optimization, on the relationship between bladder volume and bowel dose.

Recent decades of technical and computational evolution has resulted in a more conformal radiotherapy. Nowadays, an intensity modulated beam is standard in rectal cancer treatments [15]. Intensity modulated radiotherapy (IMRT) and intensity modulated arc therapy (IMAT) significantly reduce the risk for bowel toxicity by minimizing the irradiated bowel volume while escalating the dose to the target [16,17]. However, some benefits of these techniques might be reduced due to anatomical changes occurring during the course of treatment. Both the target and organs at risk (OARs) are mobile structures with volumes varying on a daily basis. Therefore, rectal cancer patients will show inter-fractional anatomical differences that result in a blurred dose distribution. [18–20]. To avoid anatomical differences having adverse effect on the outcome of the treatment, the high dose gradients require a careful delineation of the targets and a sufficient consideration of geometrical uncertainties. With frequent imaging, image-guided radiotherapy (IGRT)

techniques aim to reduce the geometrical uncertainty. At the moment, the IGRT protocol for rectal cancer patients at Herlev Hospital consists of acquiring orthogonal, planar X-ray scans on a daily basis and cone-beam computed tomography (CBCT) scans during fraction 1, 6 and 11. When verifying the treatment position, bony structures are considered exclusively. If applicable, it is wishful to introduce a new IGRT protocol where the daily planar X-ray scans are replaced by CBCT scans. After performing a match on bony structures, the radiotherapy technicians (RTTs) would validate a surrogate for the clinical target volume (CTV). Since the CTV is not necessarily defined by an anatomical structure, a surrogate for the CTV is more applicable to validate, instead of the actual CTV. A purpose of this study is to investigate appropriate surrogates and to evaluate benefits and limitations of such an IGRT-protocol.

1.1 Aim and hypothesis

This project is divided into two studies, a bladder/bowel study and an IGRT study. Both studies concern rectum cancer patients exclusively. Questions to be answered in the bladder/bowel study are:

> *Is there any trend in bladder volume change during the course of treatment? Hypothesis: the bladder volume decreases over time, such that the bladder volume is larger on the planning CT image than on the CBCT scans acquired during the course of treatment.*
>
> *What is the effect of bladder volume on bowel dose distribution? Is there a simple relationship between a decrease in bladder volume and an increase in bowel dose?*
>
> *Does the inclusion of the bladder in the optimization routine of the treatment plan have an impact on the relationship between bladder volume and bowel dose? Hypothesis: the inclusion of the bladder in the optimization routine reduces the effect of bladder volume change on bowel dose.*

The following questions are to be answered in the IGRT study:

> *Is the image quality of the CBCT good enough to validate a surrogate of the CTV? What are the challenges?*
>
> *What is an appropriate surrogate for the CTV?*
>
> *How large are the variations of the surrogate of the CTV during the course of treatment?*

2. Theory

2.1 Treatment planning of rectal cancer patients

2.1.1 Target volume definition

As defined in the ICRU report 83, the GTV is the gross palpable or demonstrable extent of malignant growth and the CTV is the volume containing GTV and/or sub-clinical malignant disease [21]. For rectal carcinomas, the CTV can be divided into two groups, primary CTV (CTV-T) and elective CTV (CTV-E). The CTV-T is associated to the GTV-T and the CTV-E is an area adjacent to the CTV-T that is prophylactic irradiated. In some treatments, CTV-T and CTV-E are prescribed similar doses and in other treatments, a higher dose is given to CTV-T. At Herlev Hospital, CTV-T is defined as the rectum circumference plus the tumor and a margin (see Figure 1). The margin added to the rectum plus tumor is 10 mm in the cranial-caudal direction and 5 mm in all other directions. To ensure that the prescribed dose is delivered to all parts of the CTV-T, a margin of 12 mm cranial-caudally and laterally, 9 mm posteriorly and 15 mm anteriorly is added to CTV-T to generate PTV-T. The margin is such that PTV-T always includes mesorectum in the extent of CTV-T.

The CTV-E always comprises the entire mesorectum, the presacral space (CTV-E1) and a lateral region including lymph node regions along the internal iliac arteries (CTV-E2), see Figure 1. If the cancer has spread to gynecological or genitourinary structures, such as the uterus or the prostate, CTV-E can considered being expanded. At Herlev Hospital, a margin of 10 mm in the lateral direction and 5 mm elsewhere is added to the CTV-E to generate the PTV-E.

As magnetic resonance (MR) scans provide good soft tissue contrast, the patient usually undergoes a MR scan in addition to the planning CT scan, prior the start of the radiotherapy. The MR and CT scans are co-registered and the MR scans are used for optimal delineation, while the CT data is used for dose calculations.

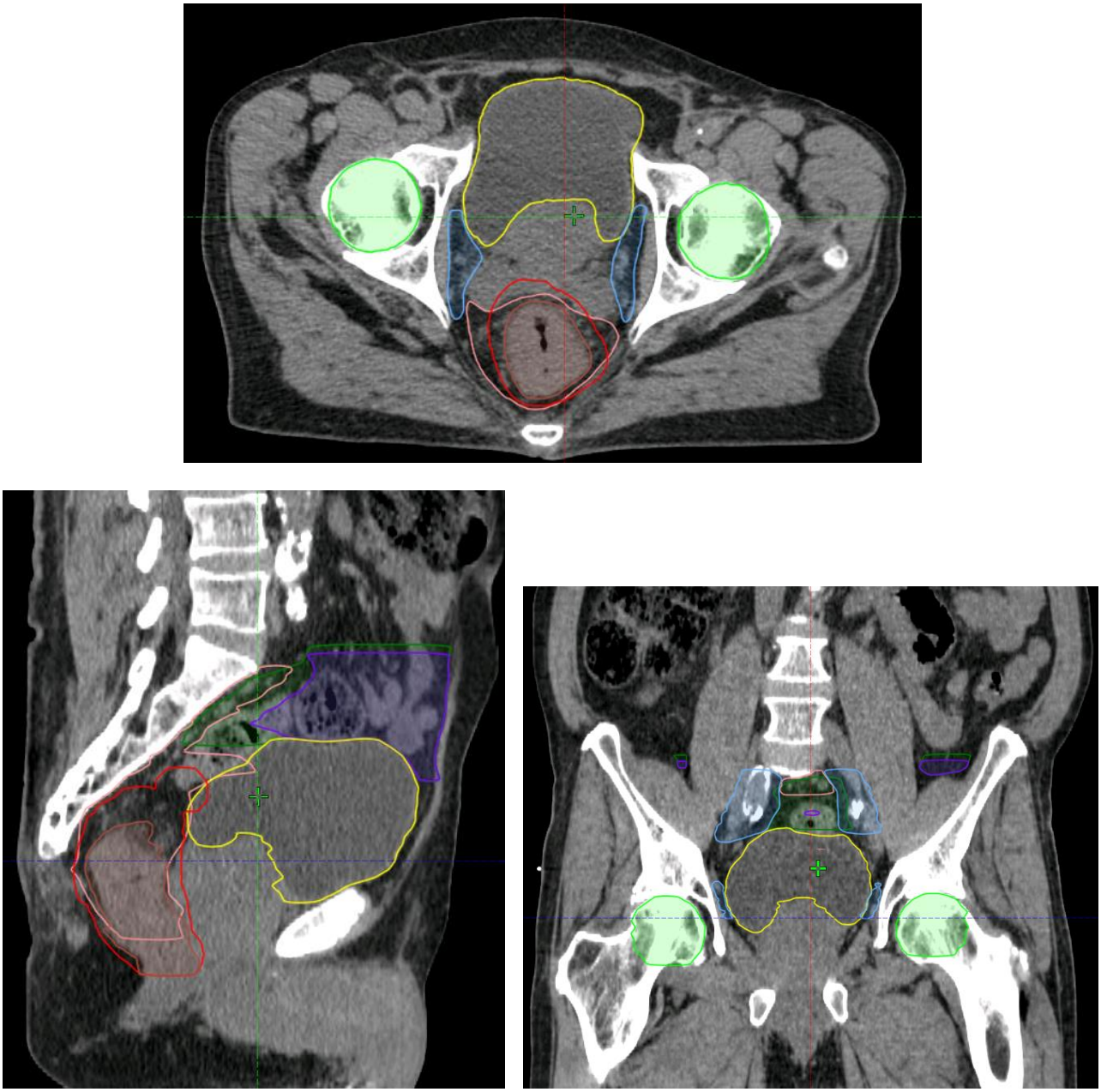

Figure 1. CT scans showing pelvic anatomy and target definition. Brown = surrogate, pink = CTV-E1, dark blue = CTV-E2, yellow = bladder, dark green = Bowel, purple = oBowel, light green = femoral heads.

2.1.2 Organs at risk

Avoidance organs to consider during treatment planning of rectal cancer is the femoral heads, the small bowel and the bladder [16–18,22] (see Figure 1). The small bowel is represented by two delineated structures, *Bowel* and *oBowel*. *Bowel* is the peritoneal volume in which the small bowel can move and often includes other bowel tissue in addition to the small bowel. It is delineated up to approximately 1 cm cranial from the PTV, to avoid unnecessary contouring effort. *oBowel* is defined as the part of *Bowel* outside the PTV and is used in the optimization of the treatment plan. It is important to recognize that all of rectum and most of the sigmoideum will be a part of the CTV and should therefore not be treated as avoidance structures in the treatment planning [23].

Side effects and dose limits
The Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, grade several types of gastrointestinal disorders. Different grades refer to different severity of the adverse effect. Grade 1 toxicities are of mild severity and negligible clinical consequences; grade 2 to 4 toxicities are of moderate, severe and life-threatening severity, respectively, and are usually scored in reports of radiotherapy-induced toxicity.

By being in the close proximity and sometimes a part of the PTV, the small bowel can be exposed to relatively high radiation doses. As an acute effect, cramping and diarrhea can occur 1 to 2 weeks after the start of the radiotherapy. Late obstruction, ulceration and bleeding can occur weeks or months after the radiotherapy [13]. After having reviewed several studies, Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) defines a dose limit of V_{45Gy}<195 cm^3 for a volume of peritoneal space in which the small bowel can move. The dose limit is set to minimize acute toxicity of Grade 3 or higher and to reduce late toxicity risk. If the volume receiving 45 Gy or higher is exceeded, the risk of acute toxicity escalates. Concurrent chemotherapy is associated with a higher risk of acute toxicity, since it has shown to add to radiotherapy induced acute small bowel toxicity [13].

Unlike the recommendations from QUANTEC, the constraint V_{45Gy}<195 cm^3 is set for the *oBowel* instead of the *Bowel*, at Herlev Hospital. Instead, the constraints V_{30Gy}<450 cm^3 and V_{45Gy}<300 cm^3 are set for the *Bowel*.

2.1.3 Recurrence
As mentioned in section 1, the addition of preoperative radiotherapy reduces the risk for recurrence, compared to surgery alone [8,10,11,24]. Kapitejn *et al.* [11] report a local recurrence rate at 2 years of 2.4 % in the radiotherapy-plus-surgery group and 8.2 % in the surgery-alone group. The Dutch TME group [24] reports an overall 5-year recurrence rate of 4.6 % and 11.0 % for patients receiving radiotherapy plus surgery and surgery alone, respectively. Additionally, they report the presacral space as the area where local recurrence is mostly occurring for both patients receiving and not receiving radiotherapy before TME.

3. Material and methods

3.1 Patient material and patient selection

A list of 100 patients with locally advanced rectal cancer treated with radiotherapy at Herlev Hospital was available as patient material for this work. The patients were treated during the period March 2014 to January 2016. Out of the 100 patients, 67 were men and 33 were women. Ninety-five patients were treated preoperatively, 3 were treated postoperatively and 2 were treated for recurrence. As the majority of the patients were treated preoperatively, the others were excluded from the study. Among the preoperatively treated patients, 13 received SCRT and 82 received LCRT. The 13 patients receiving SCRT were excluded because no CBCT scans were acquired during the course of treatment. Out of the 82 remaining patients, the 28 treated most recently were selected to be part of the study. These patients were treated during the period February 2015 to January 2016, with one of the following treatments schedules:

A: 48.6 Gy in fractions of 1.8 Gy to primary and elective PTV.

B: 50.4 Gy in fractions of 1.8 Gy to primary and elective PTV.

C: 48.6 Gy in fractions of 1.8 Gy to elective PTV, with a sequential boost up to 54 Gy in fractions of 2 Gy to primary PTV.

D: 50 Gy in fractions of 1.67 Gy to elective PTV, with a sequential boost up to 60 Gy in fractions of 2 Gy to primary PTV.

Out of the 28 patients, 2, 9, 14 and 3 patients had treatment code A, B, C and D, respectively. Information about each patient is presented in Appendix I. All patients were treated in supine position with a knee cushion. The treatments were delivered as RapidArc, Varian Medical Systems' version of IMAT, using either Varian Clinac iX 2300 or Varian TrueBeam linear accelerators (Varian Medical Systems, Palo Alto, CA). All linear accelerators were equipped with On-Board Imagers (OBI).

3.2 Image material

Each patient underwent a planning CT scan prior the treatment. During the image acquisition, they were instructed to have an empty bowel (including rectum) and a moderately filled bladder. A moderately filled bladder is achieved by emptying the bladder and drinking two glasses of water 30 minutes prior the scan. To increase the reproducibility during subsequent treatments, a new planning CT is acquired if the diameter of the rectum exceeds 5 cm due to air or defecation. The scans were acquired with 2 mm thick slices and an in-plane resolution of 0.8 to 1.2 mm (730 to 512 pixels).

Each patient had weekly low-dose CBCT scans acquired during the course of treatment. Out of the 28 patients, weekly CBCT scans were acquired the first three, four, five and six weeks for 23, 1, 1 and 3 patients, respectively. This resulted in a total of 95 CBCT scans. If a patient had CBCT scans acquired more often than once a week, only one CBCT scan per week was included in this study. The scans were acquired with 2 mm thick slices and an in-plane resolution of 1.2 mm (384 pixels). As for the acquisition of the planning CT, the patients were instructed to have an empty bowel and a moderately filled bladder during each fraction.

4. Bladder/bowel study

4.1 Material and methods

4.1.1 Organ delineation

Target and OAR structures had been delineated according to section 2.1 on all CT scans. The CTV-T and the CTV-E was separated on all scans except two. In addition to the predefined bowel structures, *Bowel* and *oBowel*, a bowel structure named *rBowel*, where the letter r stands for reference, was defined during this project. *rBowel* was generated by subtracting tissues such as mesorectum, bladder and uterus from *Bowel* for the patients whose delineated *Bowel* included those tissues. It was generated to be used when comparing the bowel dose between patients, since it comprised all potential small bowel tissue and was delineated similarly for all patients.

The comparisons of bladder volume and bowel dose between the CT and CBCT scan were based on the online match, corresponding to the position where the patients were treated. The online match consisted of an automatic, bony match in three degrees of freedom (excluding rotations), with the HU-interval set to [100, 3000]. The bladder was delineated on the weekly CBCT scans and transferred to the CT image for each patient. The bowels corresponding to CBCT bladder volumes were generated on the CT image using Boolean operators in the Contouring module of Eclipse™ (Version 13.6, Varian Medical Systems, Palo Alto, CA). It was assumed that a change in the bladder volume only affected the small bowel, such that the volume left behind by a reduced bladder volume was filled up by the small bowel and vice versa. The *Bowel* of the CBCT was generated using the following equation:

$$\mathrm{Bowel}_{\mathrm{CBCT}} = (\mathrm{Bowel}_{\mathrm{CT}} \cup \mathrm{Bladder}_{\mathrm{CT}}) \setminus \mathrm{Bladder}_{\mathrm{CBCT}} \qquad \textit{Equation 1}$$

where $\mathrm{Bowel}_{\mathrm{CT}}$ is the delineated *Bowel* of the CT image and $\mathrm{Bladder}_{\mathrm{CT}}$ and $\mathrm{Bladder}_{\mathrm{CBCT}}$ is the delineated bladder of the CT and CBCT image, respectively. Similar equation was used to generate the *rBowel*. $\mathrm{oBowel}_{\mathrm{CBCT}}$ was generated by subtracting PTV-T and PTV-E from $\mathrm{Bowel}_{\mathrm{CBCT}}$. All bowel structures generated from the bladder volumes of the CBCTs were post processed such that no bowel extended caudally from the bottom of the CT bladder or in other places where no bowel is naturally found. This was done to avoid incorrect generated bowel substantially affecting the dose-volume data. Examples of parts of the *rBowel* that were cleared during post processing are presented in pink color in Figure 5 (page 18).

4.1.2 Data analysis

Dose-volume data were exported from Eclipse™ (Varian Medical Systems, Palo Alto, CA) to Matlab R2015b. A Wilcoxon sign rank test was performed on the CBCT bladder volume data, in values relative to the CT bladder, to investigate if there was a significant difference in bladder volumes between the CT and the CBCT scans. The test assumed the null hypothesis "the group of relative CBCT bladder volumes comes from a distribution with median 1" and was performed at the 0.05 significance level. A non-parametric test was used because it was unknown what distribution the data belonged to.

The effect of bladder volume on bowel dose distribution was studied using V_{45Gy} and V_{30Gy} as measures of bowel dose. A first grade polynomial was fitted to the data when plotting V_{45Gy} against bladder volume in absolute values. To investigate if the correlation between V_{45Gy} and bladder volume were significant, a Wilcoxon sign rank test was performed on the slopes. Again, a non-parametric test was used because it was

unknown what distribution the data belonged to. The test assumed the null hypothesis "the slopes come from a distribution whose median is zero" and was performed at the 0.05 significance level.

The effect of bladder optimization on the relationship between bladder volume and bowel dose was investigated by comparing the slopes of the patients having and not having the bladder included in the optimization. To investigate if there was a significant difference between the slopes of the two groups, a Wilcoxon rank sum test with the null hypothesis "the slopes of the two groups are samples from distributions with equal medians" at a 5 % significance level was performed.

To investigate the possibility of lowering the bowel dose, the treatment plans for patients not having the bladder included in the original optimization was re-optimized. In accordance with the latest local guidelines, the re-optimized treatment plan included a bladder optimization and delivered the dose with tree arcs instead of two. Both the original and the re-optimized treatment plan fulfilled the requirements $V_{95\%}$>99 % for the PTV-T and $V_{95\%}$>98 % for the PTV-E. A first grade polynomial was again fitted to the data when plotting V_{45Gy} against bladder volume. The slopes of the original and re-optimized plan were compared by performing a paired Wilcoxon rank sum test. The test assumed the null hypothesis "(x-y) comes from a distribution with zero median", where x and y are the slopes of the original and re-optimized treatment plan, respectively, and was performed at a 5 % significance level.

4.2 Result

4.2.1 Bladder volume over time

All of the CBCT scans had sufficient quality to delineate of the bladder. The volume of the bladder on the CT and CBCT scans of every patient is presented in Figure 2; the bladder volumes on the CBCTs ranged from 0.1 to 3.5 times the bladder volume on the corresponding CT, with the majority (81/96) in the range between 0.3 and 2.0. Out of the 28 patients included in this study, 6 patients had bladders volumes consistently larger on all CBCTs than on the CT and 13 patients had bladder volumes consistently a smaller. For 9 patients, the relationship between the bladder volume on the CT and CBCT scans varied. This corresponds to the CBCT bladder volume being smaller than the CT bladder volume on 64/95 CBCTs. Furthermore, performing a statistical analysis showed ($p=0.011$) that the median bladder volume is significantly smaller on the CBCTs than the CT scans. During the first fraction, 15/28 patients had a bladder volume larger than during the planning CT acquisition.

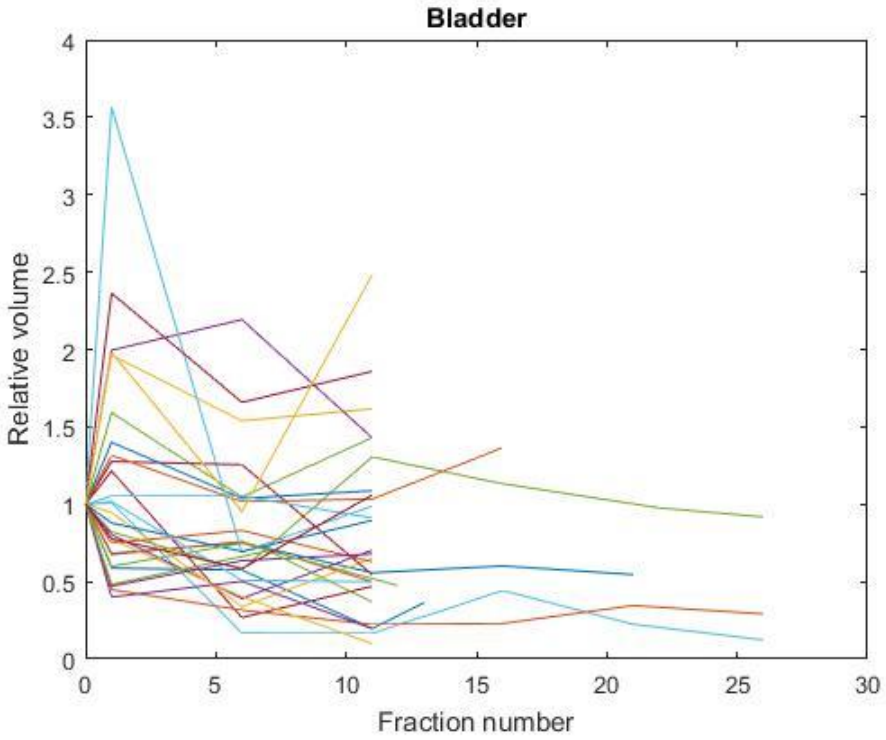

Figure 2. Relative bladder volume versus fraction number, where fraction number 0 represents the planning CT. A line is drawn between the values for each patient and each line represents a patient

4.2.2 Bowel dose versus bladder volume

Studying the effect of bladder filling on the bowel dose distribution, the change in bladder filling did not result in a violation of the clinical constraint V_{45Gy}<195 cm^3 for *oBowel* for any patient, see Figure 3. Regarding the constraints V_{30Gy}<450 cm^3 and V_{45Gy}<300 cm^3 for *Bowel*, a majority of the patients (24/28 and 17/28, respectively) did not fulfill the constraints at any fraction, including the planning CT. A reduced bladder volume resulted in a violation for 4 and 1 patient, respectively. Since a change in bladder volume had similar effect on V_{30Gy} and V_{45Gy} for all patients, V_{45Gy} was exclusively used as a measure of the bowel dose in the further analysis of data.

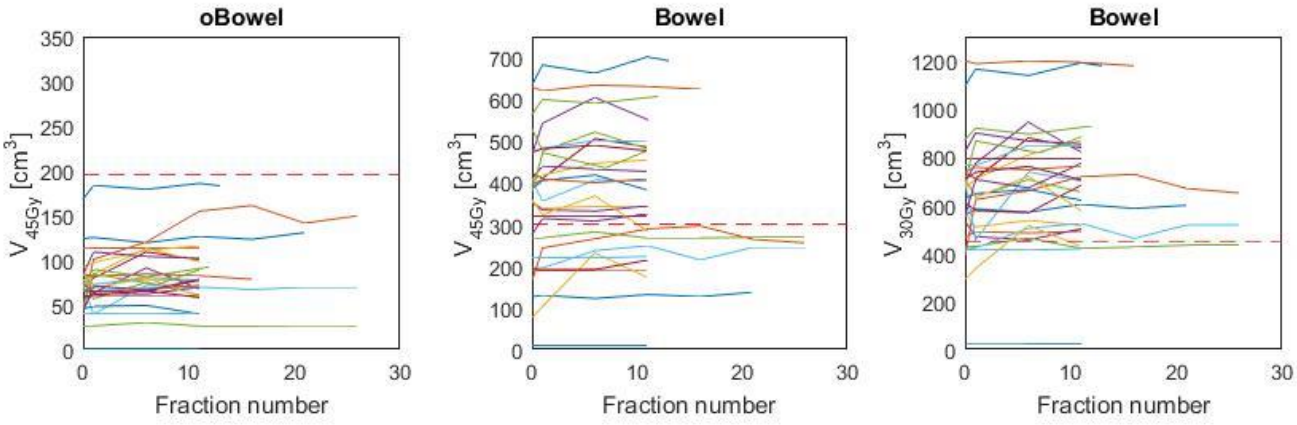

Figure 3. Bowel dose against fraction number for the delineated Bowel and oBowel. Fraction number 0 represents the planning CT and each line represents a patient. The constraints V_{45Gy}<195 cm^3, V_{30Gy}<450 cm^3 and V_{45Gy}<300 cm^3 are demonstrated by a dashed red line in each plot.

Bowel dose against bladder volume, including data from both CT and CBCT scans, is presented in Figure 4. Since the relationship between the two variables tends to be linear, a first grade polynomial was fitted to the data for each patient. The slope of the polynomial for each patient is presented in Appendix I. Performing a Wilcoxon sign rank test on the group of slopes resulted in $p<0.01$, thus, verifying the correlation between bowel dose and bladder volume. However, the largest relative change in bladder volume did not result in the largest relative change in V_{45Gy} of the *rBowel* or *oBowel*.

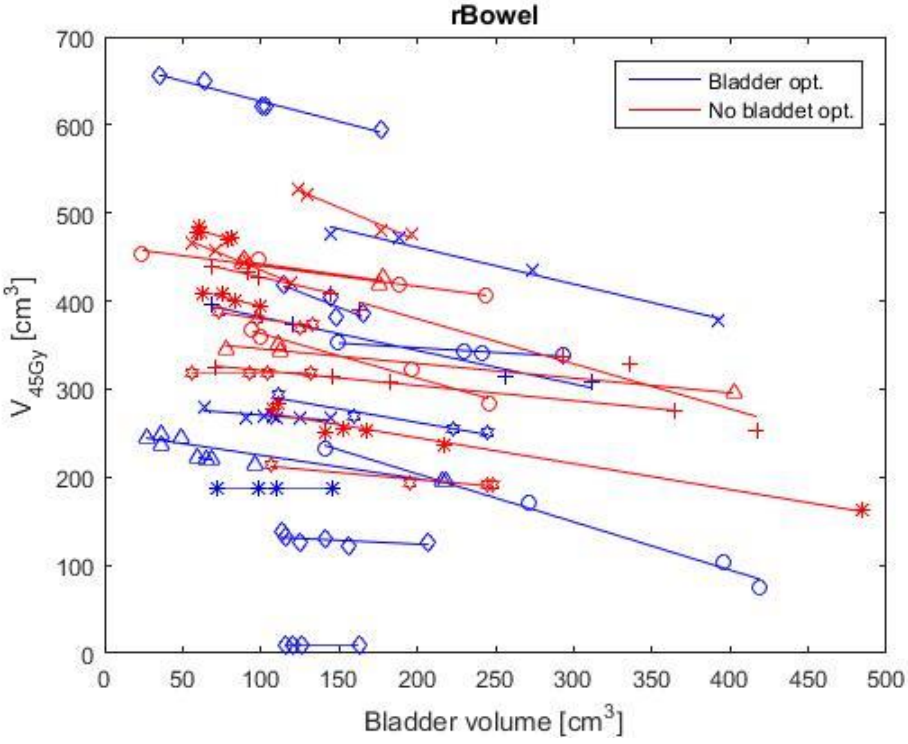

Figure 4. Absolute V_{45Gy} of rBowel versus absolute bladder volume, in which a first grade polynomial is fitted to the data of each patient. Blue = patients with bladder optimization, red = patients with no bladder optimization.

Effect of bladder optimization

The bladder was included in the optimization for 13/28 patients. Comparing the slopes of the blue and red lines in Figure 4, the bladder optimization does not seem to have an impact on relationship between bladder volume and bowel dose. Neither could a significant difference in slopes be proven by performing a statistical analysis on the data (p=0.46). Instead, the PTV-T and PTV-E was considered more crucial to the relationship between bladder volume and bowel dose. As an example, consider patient 7 and patient 11 in Figure 5, who both had the bladder included in the optimization. During fraction 11, both patients had a smaller bladder volume than on the CT. The effect of the bladder volume decrease on bowel dose distribution was, however, very dissimilar. Regarding patient 7, a bladder volume decrease of 78 % resulted in an V_{45Gy} increase of 126 % for the *rBowel*, while, for patient 11, a bladder volume decrease of 35% resulted in a V_{45Gy} increase of approximately 230 %.

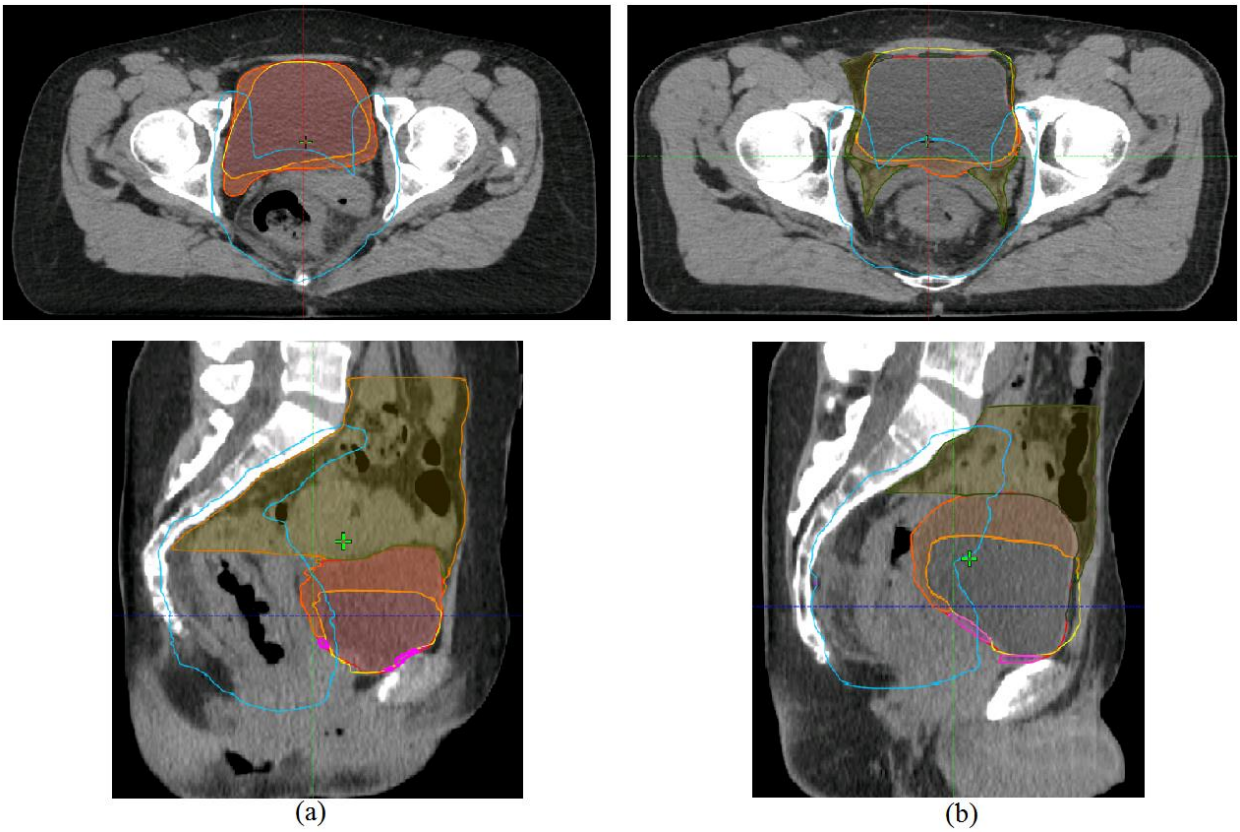

Figure 5. Axial and sagittal frames of the planning CT image of (a) patient 7 and (b) patient 11. Blue = PTV-T plus PTV-E., dark green = rBowel (CT), red = bladder (CT), orange = rBowel (CBCT fraction 11), yellow = bladder (CBCT fraction 11), pink = excluded part of rBowel (CBCT fraction 11) after post processing.

Effect of re-optimization

Figure 6 presents the relationship between bowel dose and bladder volume for the original and re-optimized treatment plan. Comparing the red and the green line of each patient, the green line is consistently below the red line, indicating a lower bowel dose for each bladder volume value in the re-optimized treatment plan. Moreover, the re-optimized treatment plan resulted in polynomials with significantly less steep slope ($p<0.01$) for all patients except one (see Appendix I).

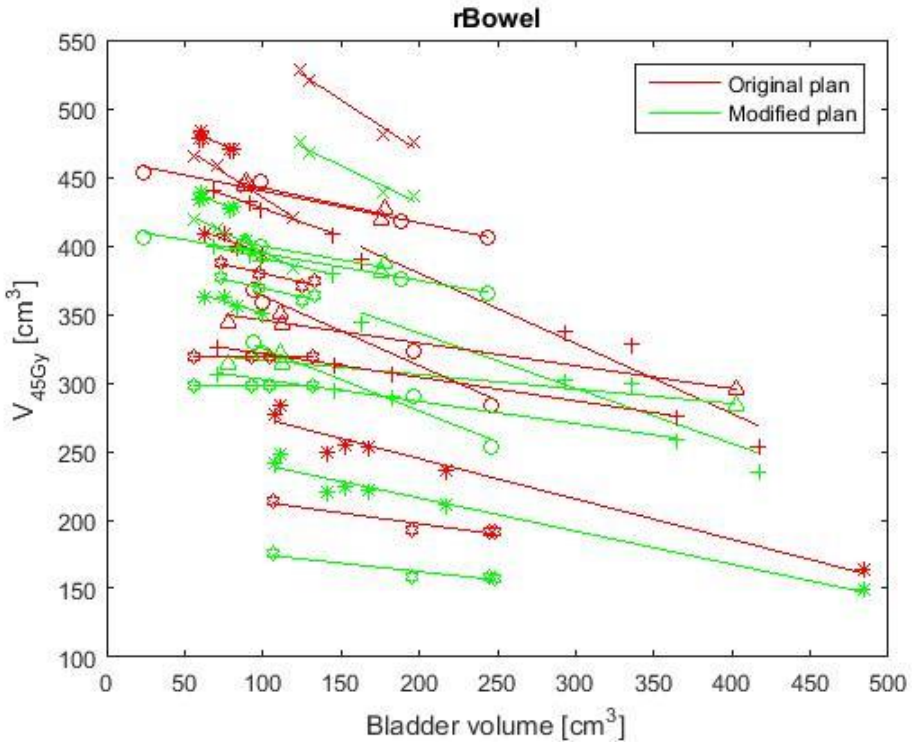

Figure 6. Absolute V_{45Gy} of rBowel versus absolute bladder volume of the original and re-optimized treatment plan, for the patients not having the bladder included in the original treatment plan. The data points are denoted by the same marker type for each patient, independent of the treatment plan. A first grade polynomial is fitted to the data of each patient. Red = original treatment plan (the same as the red markers and lines in Figure 4), green = re-optimized treatment plan.

4.3 Discussion

4.3.1 Bladder volume over time

The small bowel is an important dose-limiting organ during the radiotherapy of rectal cancer. Full bladder protocols, prone positioning and belly boards have been used to displace the small bowel from the target area and reduce the exposed volume of small bowel [14,19,25]. Kim *et al.* showed that the dose delivered to the bowel is highly correlated to the bladder volume and identified the full bladder protocol as the superior method to minimize the bowel dose [14]. A disadvantage of the full bladder protocol method is, however, the day-to-day variation of bladder volume. As in other studies [19,26], results in this study show large inter-fractional variation in bladder volume, even though the patients were given bladder instructions. In consistency with Chong *et al.* [19] and Nijkamp *et al.* [18], a majority of the patients had smaller bladder volumes on the CBCT scans than on the CT scans. This can be a result of a combination of several factors. Performing a statistical analysis verified ($p=0.011$) the hypothesis that the bladder volume is larger during the planning CT acquisition than during the following radiotherapy sessions. Nonetheless, this was not consistent for all patients or all examination point.

Due to scatter and beam hardening effects it is well known that the CBCT has poorer image quality than CT [27]. Even though it was possible to delineate the bladder on all CBCT scans, the inferiority in image contrast potentially causes larger inter-observer variations. However, these variations are considered negligible compared to the bladder volume changes.

4.3.2 Bladder volume versus bowel dose

Result show that the bowel dose is highly correlated with the bladder volume. With a p value of 0.46, any difference in slopes between patients with and without bladders optimization could not be proven from the data in Figure 4. Considering Figure 6, the re-optimization resulted in a nearly parallel shift of the line of each patient, thus, reducing the bowel dose without compromising PTV coverage. Although the re-optimization also resulted in significantly less slope, the change in the slope is barely visible and so small that it is not clinically relevant. Furthermore, the re-optimization not only included a bladder optimization, but also the addition of a third arc; is not possible to separate the contributions from them two. However, comparing the results from Figure 4 and Figure 6, the bladder optimizing seem to have very little (if even existent) influence on the effect of bladder volume changes on V_{45Gy} for the bowel.

The position and extent of the PTV is considered more crucial. If the PTV is close to or overlaps the bladder, a reduction in the bladder volume has a larger effect on the bowel dose distribution. Consequently, the relationship between V_{45Gy} for the bowel and bladder volume is not general, but highly individual. When suspecting that the bowel is receiving a noteworthy higher dose due to a bladder volume change, the procedure of delineating the "new" bladder, generating a corresponding "new" bowel and recalculating the treatment plan has to be done. Using the approximately linear relationship between V_{45Gy} and bladder volume (Figure 4), the bladder volume only has to be delineated a few times before a first grade polynomial can be estimated and used to predict the bowel dose. Using the polynomial to predict bowel dose, however, implies that the pattern of bladder deformation is strictly dependent on bladder volume.

4.4 Conclusions

The bladder volume is significantly smaller on the CBCT acquired during the course of treatment than on the planning CT. However, the reduction in bladder volume did not result in any violation of the constraint $V_{45Gy}<195$ cm^3 and many patients had larger bladder volumes on the CBCT scans as well.

There is a significant correlation between bladder volume and bowel dose. By adding a third arc in the optimization of the treatment plan, it is possible to decrease the bowel dose as a function of bladder volume. However, the bladder optimization does not have a clinically relevant effect on the relationship between V_{45Gy} for the bowel and bladder volume. There is no common translation between bladder volume and V_{45Gy} for the bowel since it is highly dependent on the PTV's position.

5. IGRT study

5.1 Materials and method

5.1.1 Delineation of the surrogate

The surrogate was defined as the rectum where rectum and mesorectum could be distinguished and as the mesorectum elsewhere (Figure 7b). Caudally from the rectum, the surrogate was defined by the circumference of the levator ani (Figure 7c). The surrogate was delineated in the extent of CTV-T and CTV-E1 (CTV-T/E1) up to the cranial border of rectum on the CT scans. No surrogate was delineated cranial from the rectum because the definition of the surrogate could not be done consistently; what to use as surrogate cranial from the rectum was highly individual. Glands, tumors or other tissues in close proximity of rectum, mesorectum and levator ani were included in the surrogate whenever appropriate. Figure 7a demonstrates an example of when a positive lymph node in the close proximity of rectum was included in the surrogate. The lymph node was appropriate to include because it was visible on the CBCT scan.

Since the elective dose is either equal or close to the primary dose, the surrogate was delineated in the extent of CTV-E as well as of the CTV-T. During the validation, the surrogate was divided into three sections, as different rectal movement changes has been observed in different parts of rectum [18,19]. In accordance with a study by Chong et al [19], the inferior border of L5 was used as a reference when defining the upper, mid and lower section. The three sections were defined as the caudal distance taken 0.0-5.0 cm, 5.1-10.1 cm and >10.1 cm from the inferior border of L5, respectively.

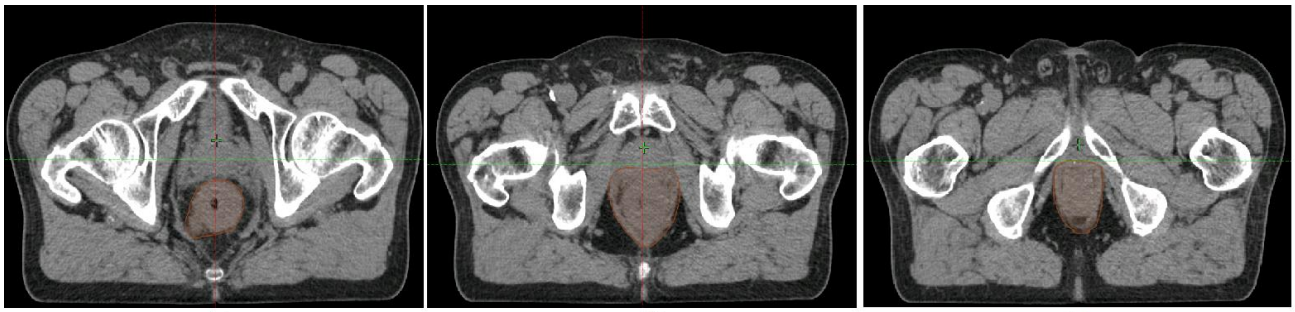

Figure 7. Surrogate of the CTV delineated as (a) rectum and positive lymph node in close proximity to rectum, (b) mesorectum and (c) levator ani muscle.

5.1.2 Validation of the surrogate

The surrogate delineated on the CT was compared with the corresponding structure on the CBCT scans using the online match between the CT and CBCT. The online match corresponds to the position that the patients were treated in. It consisted of an automatic, bony match in three degrees of freedom (excluding rotations), with the HU-interval set to [100, 3000]. Both CT and CBCT scans were studied using the "pelvis" window level. Minor modification of the window level was made whenever necessary, for example when the patient had much internal gas. Symmetrical, rolling ball margins were added to the surrogate on the CT scans to determine the deviation between the surrogate on the CT and the CBCT scans. The margins added were 1, 3, 5, 7, 10, 15 and 20 mm.

5.2 Result

5.2.1 Delineation of the surrogate

Finding an appropriate surrogate cranially from rectum was challenging. To use the sigmoideum and the colon as surrogates was usually inappropriate due to their mobility and the poor soft tissue contrast of the CBCT. As a consequence of not delineating the surrogate cranially from rectum, the surrogate did not extend as far cranially as the GTV or the CTV-T for 12/28 and 19/26 patients, respectively. It never extended as far as the CTV-E1. Furthermore, because the rectum did not extend to the upper section, only 2/28 patients had a surrogate delineated there. For one of the two patients, no surrogate was delineated in the lower section because the CTV-T/E1 did not extend that far caudally. For another patient, the CTV-T/E1 did not extend to the mid section and therefore, no surrogate was delineated there.

For only one patient did the surrogate not extend as far caudally as the CTV-T/E1. For that patient, the CTV-T/E1 extended to the anus and to sections where no surrogate delineation was considered appropriate.

For 7 patients, the CBCT scans did not cover the entire CTV-T/E1. The caudal border of the surrogate was therefore limited by the length of the CBCT scan.

5.2.2 Validation of the surrogate

Out of the 95 CBCT scans, only one was considered having too poor image quality for validation of the surrogate. An axial frame of that CBCT scan and the corresponding axial CT frame are presented in Figure 8. As can be seen in Figure 8b, the borders of the surrogate (rectum) were not distinguishable due to artefacts from air in rectum. It was concluded, however, that the surrogate definitely was outside the 15-mm-margin of the CT-surrogate and probably inside the 20-mm-margin.

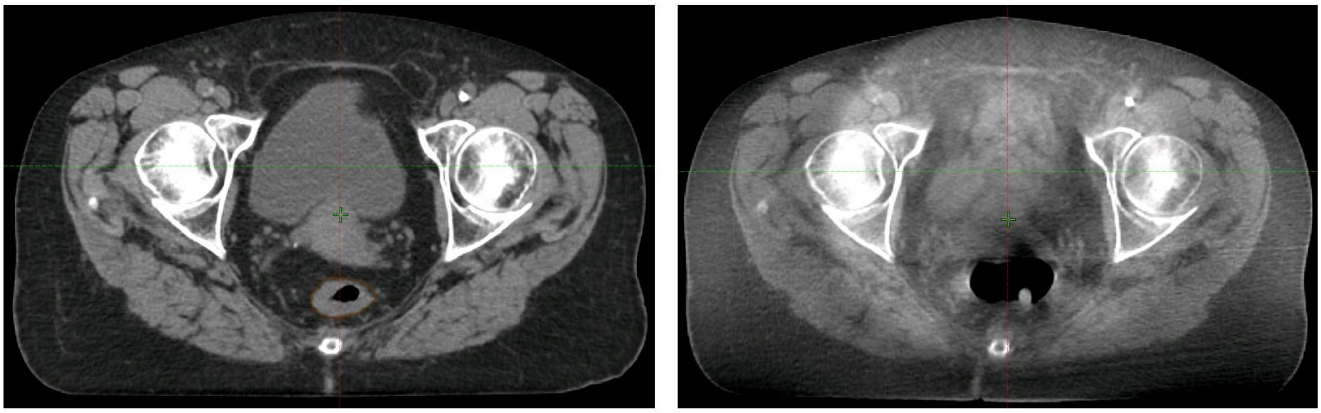

Figure 8. (b) An axial frame of the CBCT scan considered having too poor image quality for surrogate validation and (a) corresponding CT scan. The surrogate is delineated as the rectum on the CT scan and is indicated by a brown line.

Figure 9 presents the size of the variations in the upper, mid and lower surrogate. A majority of the CBCT scans had surrogates within the 5-mm-margin (40/70 and 56/90 in the mid and lower section, respectively). A few patients had CBCT-surrogates exceeding the 20-mm-margin and on 5 of the CBCTs, the rectum was outside the border of the total PTV (PTV-T plus PTV-E, see section 2.1.1). The larger deviations (≥10 mm) were often an effect of change in both rectum position and rectum volume.

On 21 CBCT scans, anatomical changes resulted in a cranial-caudal shift in the position of the sigmoideum, so the transition between the rectum and sigmoideum was more cranial on the CT scan than the CBCT scan. The sections where this occurred were not included in Figure 9, since a validation of the surrogate would imply a comparison between two different organs (rectum versus sigmoideum). Hence, 3, 21 and 1 upper, mid and lower surrogates, respectively, were not included in Figure 9. The problem concerned many patients (11/32), as it occurred on many CBCT scans (22/95).

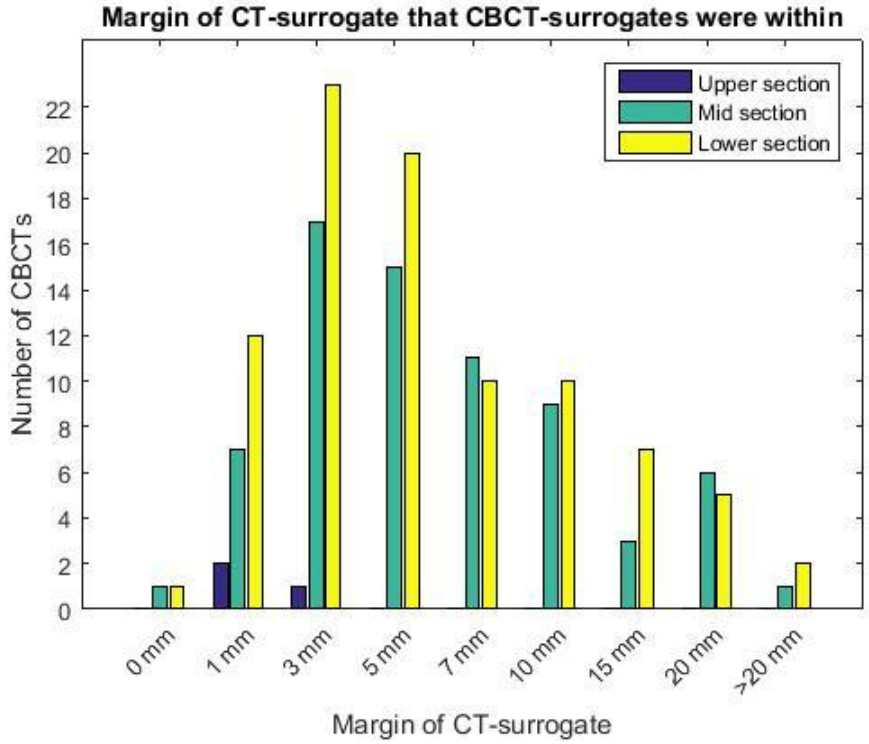

Figure 9. A bar plot showing how many upper, mid and lower CBCT-surrogates that were within which margin of the CT-surrogates.

5.3 Discussion

5.3.1 Delineation of the surrogate

In order to be consistent in the definition of the surrogate for all patients, no surrogate was delineated cranial from the rectum for any patient. Figure 10 demonstrates the complexity in defining a surrogate cranial from rectum. Looking at the lower axial frame in Figure 10a, where the rectum passes to the sigmoideum and no surrogate is delineated, a suggestion of a surrogate is delineated as a dashed yellow line. Looking at the corresponding CBCT frame in Figure 10b (the lower axial frame), the suggested surrogate is distinguishable from other bowel tissue and thus seem appropriate. However, scrolling to a more cranial slice (the upper axial frame in Figure 10a), the delineation of the surrogate drastically becomes more challenging. Even though it is hard to decide the anterior-posterior extension of the surrogate, a suggestion has again been delineated as a dashed yellow line. Looking at the corresponding CBCT slice in Figure 10b (the upper axial frame), the suggested surrogate can not be distinguished. The mobility of the bowel makes the suggested surrogate inappropriate.

Setting detailed guidelines for surrogate delineation without having CBCT scans for guidance is difficult. The CBCT scans facilitate the delineation as it reveals the answer to the mobility and visibility of the tissues. A way of working in a future IGRT protocol could be to re-delineate the surrogate after for example five fractions, with daily CBCT scans. The delineation can be modified to include some of the sigmoideum if considered appropriate. Otherwise, one might settle with a visual validation of the entire soft tissue area that the CTV comprises.

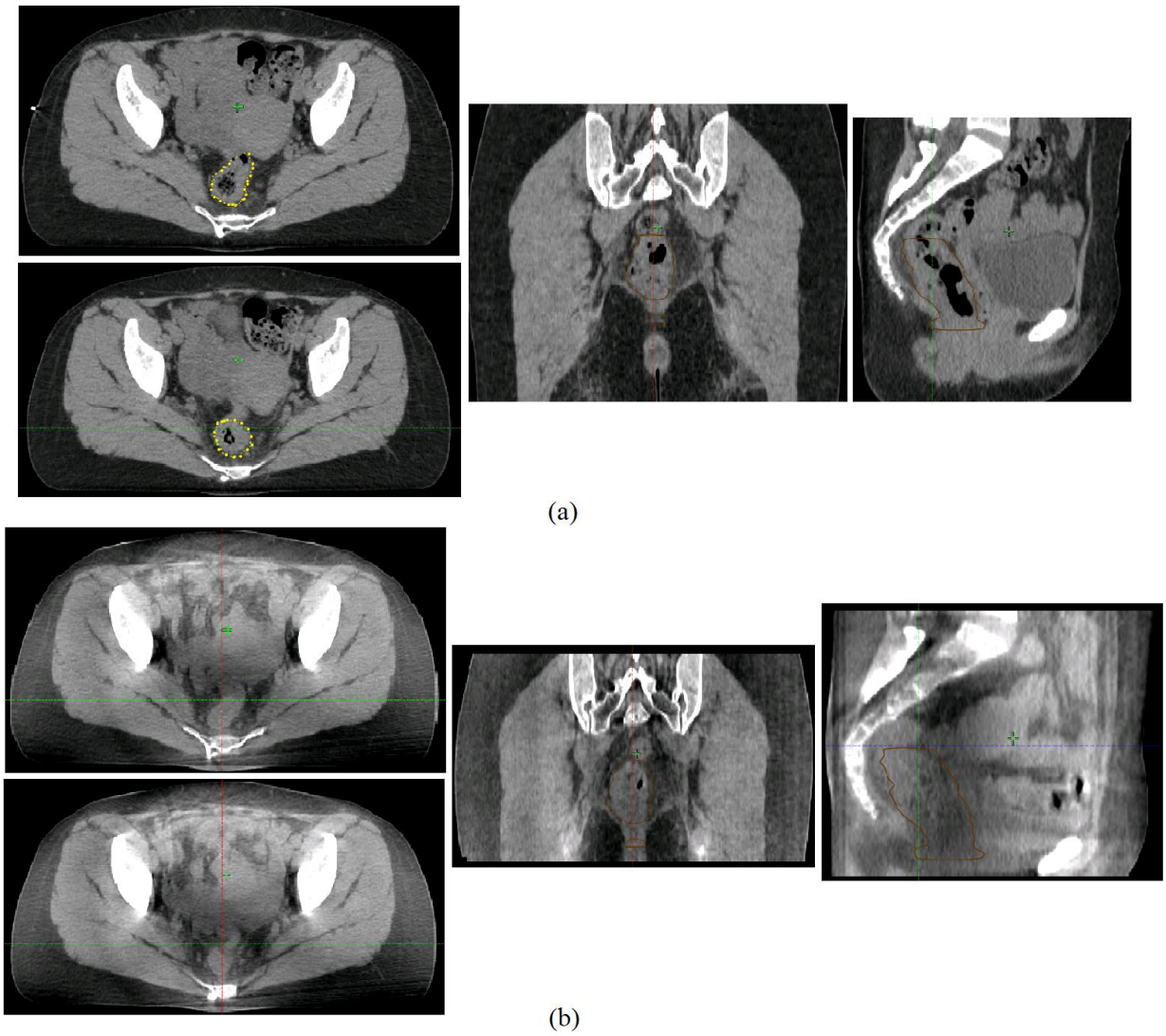

Figure 10. (a) CT scans and (b) corresponding CBCT scans demonstrating the difficulties occurring when delineating a surrogate cranial from the rectum. The upper and lower axial frames in (a) and (b) are separated by a distance of 2 mm. The surrogate is delineated by a brown line and is visible on the sagittal and the coronal frames. The dashed yellow lines in axial frames in (a) represents a suggestion of the surrogate.

Not validating the entire target area, including the area receiving elective radiation, is a problem indeed. According to the Dutch TME trial [24], presacral space is the most common area for recurrence for rectal cancer patients, both those receiving and not receiving radiotherapy preoperatively. To recall from Figure 1,

however, is that the presacral lymph nodes are located adjacent to the bony anatomy. Variation in their position is thus, to a large extent corrected by the online setup corrections. After changing the couch position according to the online bony match, the change in CTV position is probably smaller there than along the rectum [28]. The same yields for the iliac lymph vessels in CTV-E2 [29].

Since the rectum not always include the GTV-T and never include the whole CTV-T or CTV-E, its appropriateness as a surrogate is questionable. Confining most of the GTV and CTV and, therefore, incorporating most of their motion in its motion (Figure 1), mesorectum is a more appropriate choice. However, the mesorectum is more challenging to differentiate than the rectum on the CBCT [30]. In this study, the mesorectum could not be reliably contoured where the rectum and mesorectum were separated on due to unsatisfactory image quality of some of the CBCT scans. The motion of the rectum and mesorectum is, nevertheless, correlated. Studying the target volume shape variations in rectal cancer patients, Nijkamp *et al*. [28] showed that mesorectum deformation is primarily caused by rectum volume changes.

It was challenging to delineate the surrogate when the rectum was surrounded by tissue with similar HU-values, such as glands and tumors. Tissues that were distinguishable from the rectum on the CT scan were not always distinguishable on the CBCT scans, due to the inferiority in image contrast of the CBCT. Since this study was performed retrospectively and the CBCT scans were already acquired, the answer on what was visible and separable on the CBCT was known. The answer (the CBCT scan) is, however, normally not known when the surrogate is delineated. Again, a way of working in a future IGRT protocol could be to modify the delineated surrogate after for example five fractions with daily CBCTs.

5.3.2 Validation of the surrogate

In contrast to a study by Chong *et al.* [19], the result in Figure 9 present a similar distributions in the mid and lower surrogate. Studying the rectal motion during preoperative radiotherapy of rectal cancer, Chong *et al.* found that the rectal diameter varied most in the upper rectum, followed by the mid rectum, with the smallest changes seen in the lower rectum [19]. This is consistent with result from a Dutch study [29] that found larger rectal wall movements in the mid and upper rectum compared with the lower rectum. The Dutch study, however, only included patients receiving radiotherapy postoperatively, which could affect the rectal movement.

Even though the image contrast was sufficient for the validation of the surrogate on 94/95 CBCT scans, the relatively poor image quality of the CBCT scan came with some difficulties during the validation. Moreover, the degraded image contrast of the CBCT resulted in blurry borders of the surrogate, leading to an increased risk for misjudgment of the deviation between the surrogate on the CT and CBCT. The misjudgment is, however, usually only in the size of 1 mm. Furthermore, it was challenging to differentiate the rectum and the bowel from each other on the CBCT scan, but not on the CT scan.

Scans with internal gas present were generally more challenging to validate since the quality of the CBCT was affected by internal gas. On one of the CBCT scans, the internal gas even prevented a validation to be conducted. As a contrast to the challenging CBCT slice in Figure 8, suffering from major artefacts, a CBCT slice relatively easy to validate is presented in Figure 11. The image quality of Figure 11 is not only enough for the rectum to the distinguished, even the mesorectum is distinguishable.

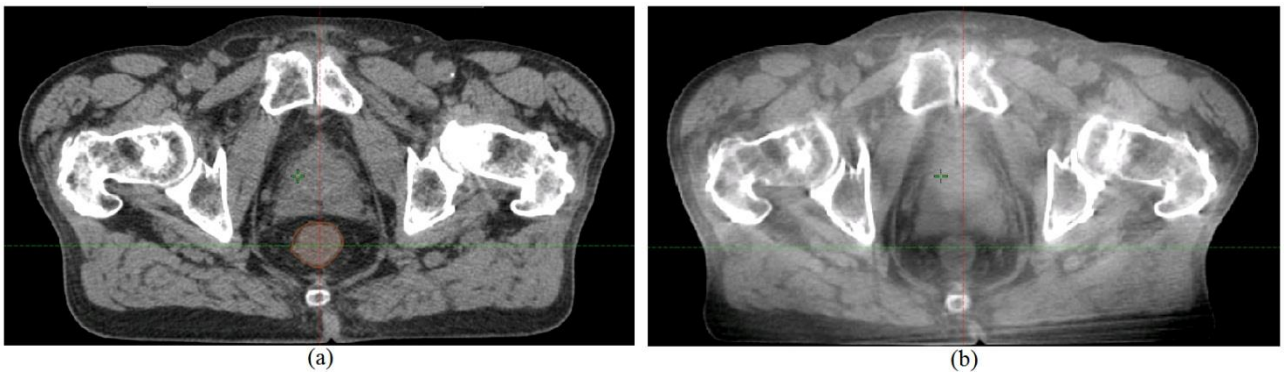

Figure 11. (a) CT and (b) CBCT scan relatively easy to validate.

Another problem arising during the validation was when the position of the sigmoideum was shifted in the cranial-caudal direction. As a consequence, the sigmoideum of the CBCT was to be compared with the rectum of the CT. Implementing a new IGRT protocol, it has to be decided if one should consider the change in cranial-caudal position of sigmoideum. Instead of delineating a surrogate close to the transition between rectum and sigmoideum, one might settle with a visual validation, if possible.

5.4 Conclusions

The image quality of the CBCT is sufficient to validate the CTV using the rectum as surrogate. A drawback of using the rectum as surrogate is, however, that it does not always include the GTV-T and never include the whole CTV-T or CTV-E. Due to inter-fractional organ motion it is challenging to define a surrogate close to the transition between the rectum and sigmoideum and cranial from rectum. The answer to what an appropriate surrogate caudal from rectum is, is very individual. Moreover, the validation of the surrogate becomes more challenging when internal gas is present.

The variation was similar throughout the delineated surrogate. On a majority of the CBCT scans, the variation of the surrogate was within 5 mm.

6. Future perspective

The next step of this project will be to start up daily CBCT acquisition with verification of the CTV. The idea is that the RTT's performs an online bony match between CT and CBCT and also validate the surrogate. To make it possible, guidelines with clear action levels must be set. My suggestion is the following. If the variation of the surrogate is within a value corresponding to the CTV to PTV margin, the treatment will proceed without any further actions. Variations outside this value will trigger different actions to be made depending on e.g. the size of the variation, the frequency and whether the variation is random or systematic. The data of the surrogate variations from the daily CBCTs can be used as material in a more extensive, prospective study, in which the influence of tumor position and tumor size can be studied as well.

The next step in the IGRT protocol would be to introduce a redefinition of the surrogate after e.g. five fractions, when knowledge about the visibility on the CBCT is known. Furthermore, the data of the surrogate variations obtained could be used as input to a more adaptive strategy e.g. adapt the CTV to PTV margin or generate more than one treatment plan to cover different deviations.

Today, the image quality of the CBCT makes it difficult to use the mesorectum as surrogate. Hopefully, new reconstruction methods that increase the image quality can make this possible in the future. Ideally would be to have an MR linear accelerator, since it can provide scans with high soft tissue contrast.

A long term goal is to automatically receive dose-volume data for both the target and the OAR after acquisition of the CBCT (or MR) scans by using deform image registration. However, a reliable deform registration algorithm require good soft tissue contrast, which is not often provided with today's CBCT. A short time goal would be to start using deform registration to delineate the bladder on the CBCT. At the moment, Herlev Hospital and Varian (Varian Medical Systems, Palo Alto, CA) collaborates in a project concerning deform registration for bladder cancer patients. The idea is to develop an algorithm that automatically delineates the bladder on the CBCT using the delineated bladder on the CT. Knowing daily bladder volume, the linear relationship between the bladder volume and bowel dose (Figure 4 and Figure 6) can be used to provide a quick estimate of the bowel dose. However, the next step is of course to incorporate Equation 1 in the software and also automatically generate a new bowel volume. Ultimately, high quality scans together with a reliable deform registration would generate an even more true representation of the bowel.

In this study, $V_{45Gy}<195\ cm^3$ was exclusively considered as a measure of bowel dose. It would be interesting (and clinically valuable) to relate the dose-volume data to biological complications. Even though the bladder volume change did not result in a violation of the clinical constraint $V_{45Gy}<195\ cm^3$ for the *oBowel* for any patient, the change in radiation dose of the entire bowel might have relevant effect on biological complications.

It would also be interesting to further investigate why the bladder volume usually is larger on the CT than on the CBCT and also investigate actions to reduce the bladder volume variations. Starting with daily CBCTs makes it possible for the RTTs to give the patient feedback on the day's bladder volume. Gaining information on when the bladder volume is adequate, too small or too large, the patient can easier understand how to obtain an adequate bladder volume.

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Appendix I – Patient information

Information about each patient included in the study is presented in the table below.

Patient nr.	**Sex**	**Treatment schedule**	**Number of weekly CBCTs**	**Bladder optimization**	**Slope of line in Figure** 4 **[ ]**	**Slope of line in Figure** 6 **[ ]**
1	Female	D	4	Yes	-0.09	--
2	Male	B	3	Yes	0.00	--
3	Male	D	3	Yes	-0.11	--
4	Male	D	3	Yes	-0.31	--
5	Female	B	6	Yes	-0.14	--
6	Male	B	6	Yes	-0.27	--
7	Female	B	3	Yes	-0.38	--
8	Female	B	3	Yes	-0.46	--
9	Male	B	6	No	-0.29	-0.24
10	Male	B	3	Yes	-0.55	--
11	Male	B	3	No	-0.51	-0.40
12	Male	B	3	No	-0.75	-0.55
13	Male	C	3	No	-0.17	-0.11
14	Female	C	3	No	-0.16	-0.12
15	Male	C	3	Yes	-0.70	--
16	Male	C	3	No	-0.44	-0.35
17	Female	C	3	No	-0.23	-0.20
18	Female	C	3	No	-0.40	-0.26
19	Male	C	3	No	-0.73	-0.57
20	Male	C	3	No	-0.25	-0.20
21	Female	C	3	No	0.00	0.00
22	Male	A	3	Yes	0.00	--
23	Male	C	4	No	-0.49	-0.40
24	Male	C	3	No	-0.51	-0.45
25	Male	A	3	No	-0.17	-0.16
26	Male	C	3	Yes	-0.42	--
27	Male	C	3	Yes	-0.31	--
28	Male	C	3	No	-0.26	-0.26