SAHLGRENSKA ACADEMY

STANDARDIZED ORGAN AT RISK VOLUME FOR EXTERNAL BEAM RADIATION THERAPY IN PROSTATE CANCER AND ITS RELATIONSHIP TO VOLUMES DEFINED BY CLINICAL PRACTICE

M.Sc. Thesis

Thao Dang

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Supervisor:	Caroline Olsson, Niclas Pettersson and Alexander Valdman
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Abstract

Background/ Purpose: In radiation therapy (RT), the radiation dose calculated in tumours and normal tissue depends on how the volumes are defined. It is difficult to standardize how tumour volumes should be defined because their anatomical extension can differ greatly between individuals. Organs at risk (OARs) are more uniform, but opinions about how to define and delineate them diverge in the radiation oncology community. When OAR volumes are defined according to different guidelines, it is difficult to compare dose and volume measures between patients as well as between clinics and the understanding of the relationship between dose and side effects is also limited. The anatomical location of the prostate gland makes rectum one OAR in the treatment of prostate cancer. The purpose of this study was to investigate how rectal volumes defined according to upcoming Swedish national guidelines (STRÅNG) differ from rectal volumes defined in clinical practice for patients treated with external beam RT for prostate cancer. Other objectives were to determine potential dose differences between the two strategies to define rectal volumes and implications for treatment decisions based on associated rectal dose tolerance doses.

Method: 121 patients with prostate cancer treated to 50 Gy (n=19), 66 Gy (n=71) or 70 Gy (n=31) in 2018 at the Sahlgrenska University Hospital in Göteborg, Sweden were studied with respect to planned rectum volumes and doses as calculated on pre-treatment CT images in the Eclipse treatment planning system. For these patients, the rectum was defined previously both according to local clinical practice and according to STRÅNG. Volume and dose differences between the two rectal definitions were investigated for each patient and volume overlap was quantified using the Dice similarity coefficient. Comparisons were also made with respect to treatment planning criteria at the Sahlgrenska University Hospital (version 2013-2019 and from 2019) and tolerance thresholds by QUANTEC from 2010.

Result: The clinical rectal volumes were on average larger than the volumes defined by STRÅNG ($p<0.01$). More patients had volume differences in caudal direction than in cranial direction, but the cranial volume differences were on average larger than the caudal volume differences ($p<0.01$). Dice ranged between 0.72 to 1.00 with no statistically significant average difference between the investigated treatment groups. There were small average differences in mean doses between clinically-defined rectum volumes and volumes according to STRÅNG (<1 Gy). Both rectal volumes generally satisfied the investigated criteria. However, there were 8 patients where the STRÅNG volume did not satisfy the Sahlgrenska University Hospital criteria used for the original treatment decisions although the clinical volume did. The result was similar for the QUANTEC criteria from 2010 that the clinically-defined rectum volumes satisfy the criteria better than volumes according to STRÅNG.

Conclusion: This was a first comparison of how rectal volumes defined according to upcoming Swedish national guidelines differ from real-life rectal volumes in prostate cancer RT. The clinical rectal volumes were generally larger than the guideline volumes but overall the dose differences between them were small and resulted in a limited impact on clinical decision making except for individual cases. The presented results can guide future studies on what to expect when comparing different ways to define OAR volumes. Evaluation of compliance to guideline-directed OAR definitions could represent other future directions of this research.

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1. Introduction

1.1 Prostate cancer

Prostate cancer is one of the most common forms of cancer in Sweden. The disease mainly affects older men and is unusual before the age of 50 (1). There are several treatment methods for prostate cancer. Which treatment is most appropriate depends on several factors, including how the physician judges to what extent the cancer has developed, what the cancer cells look like in a microscope, if the patients has additional diseases, his age and the patient's preferences.

In prostate cancer, radiation therapy (RT) is an alternative to surgery with similar possibilities of cure and similar risks of treatment-related side effects when the tumour grows within the prostate gland capsule (2). RT is often combined with hormonal therapy to suppress the male hormone testosterone that almost all prostate tumours need to grow. This is to shrink the tumour volume and slow down tumour growth so that the patient's chances of cure increases (3).

1.2 Radiation therapy

RT is usually given as external beam radiation therapy (EBRT), brachytherapy (BT) or a combination of EBRT and BT (4). Patients may receive curative treatment with the intent to cure the cancer disease or palliative treatment to alleviate symptoms when chances of cure are small. For EBRT, the treatment is typically given every weekday during four to eight weeks, the treatment is fractionated. For prostate cancer, treatment doses in the range 25-70 Gy delivered in 2- 6 Gy-fractions are common in Sweden, either as primary treatment or after the prostate gland has been surgically removed (postoperatively). The prostate gland or its resection area is located immediately anterior of the rectum and inferior of the bladder and is difficult to treat without irradiating surrounding tissue. Thus, in prostate cancer RT there is a risk that the patient will get side effects that originate from either rectum or bladder, which are also called organs at risk (OARs) (5).

In RT, the goal is to achieve cell death of all tumour cells while sparing healthy tissue as much as possible. The treatment is either given as a single fraction (fx) or divided into many fractions. By dividing the treatment into many fractions, the cells are allowed to repair radiation-induced damage before the next fraction of radiation is delivered. There is a difference in sensitivity to radiation between tumour and healthy tissues, which can be summarized in the four “R:s” of RT. This also explains why the treatment effect can be improved by fractionation (6). The four “R:s” are reparation, repopulation, redistribution and reoxygenation, together, they describe how healthy tissue can recover between fractions without affecting tumour cells to the same extent. Tumour cells do not have the same ability to repair damage as normal cells and therefore time between fractions work favourably for the repair of healthy tissue but does not impact the tumour effect notably. There is regrowth of cells between fractions but the speed may differ between tumours and healthy tissue. So called early responding tissue, which include most tumours, repopulate fast (hours-days) while repopulation of late responding tissue take longer (weeks-months-years). The repopulation rate can, therefore, work to the benefit of both tumour and normal cell growth and must be handled accordingly. The radiation sensitivity of a cell also depends on its place in the cell cycle with larger radiobiological effects in the more sensitive phases (e.g. M-phase). With their faster cell circle time, tumours are typically more affected by

this phenomenon than healthy tissue. This can especially work to the benefit to make the cells to be killed more easily or slowing cycling healthy cells. The dose is also fractionated to give hypoxic tumour cells time to increase their oxygen content, so-called reoxygenation. Normal tissues are well oxygenated, but tumours typically have a large number of hypoxic cells which are resistant to radiation. After the cell-killing effects of treatment, the tumour cells become better oxygenated and then also more radiation sensitive.

The dose per fraction is also of great importance for the risk of radiation-induced damage. For the same total dose, small doses per fraction can reduce the risk of late damage. Large doses per fraction lead to fewer number of fractions and shorter total treatment time, but will result in more radiation-induced damage if the total dose is not lowered and/or treatment time is prolonged. In RT, normal tissues are also schematically divided into serially constructed organs and parallel organs (7). The various parts of a parallel-built organ are independent of each other, meaning that one part of the organ can receive a large dose but the whole organ still can maintain its function up to a certain critical volume if the rest is irradiated to a low dose. In contrast, the various parts of a serially-built organ are dependent of each other, the whole organ will therefore loose its function if a small part of the organ is damaged. In this context, rectum is considered to be a serial organ. Keeping the radiation dose to OARs below dose tolerance levels are likely to reduce the risk off radiation-induced side effects.

1.3 Preparing for radiation therapy

In the beginning of the primary EBRT process, for patients with an intact prostate gland, gold markers are inserted into the prostate gland with a needle. This is done to help locate the treatment area both for the treatment planning and to increase the accuracy of the treatment delivery (8). Subsequently, the patient undergoes computerized tomography (CT) to obtain a 3D image of his anatomy but examinations with magnetic resonance imaging (MRI) or positron emission tomography (PET) cameras may also occur. MRI-based images provide better discrimination between different soft tissue compared to CT-based images and PET-based images are better in detecting the lymph nodes metastasis of prostate cancers (9). T2-weighted MRI is currently suggested as the best modality for imaging the anatomy of the prostate (10).

CT imaging maps transverse sections of the patient's body. The transverse sections show the variation in CT numbers in the body and are used to visualize patient anatomy. CT numbers are given using the Hounsfield unit (HU). The CT numbers are directly related to the relative electron density which provides the physical basis for dose calculation (7). If the CT numbers differ substantially, around 100 HU, structures can easily be visually identified, but smaller CT number differences are difficult to distinguish from one another. The CT number for air is by definition -1000 HU and 0 HU for liquid water. Least dense tissue is defined as -1000 HU (air) and most dense tissue, typically high-density bone, is around 3000 HU.

The CT images are used in a treatment planning system (TPS) to identify the area to be irradiated as well as OARs that need to be avoided or given a limited radiation dose (7). Treatment planning personnel then optimize how the treatment should be practically carried out in so-called treatment plans, which show how the radiation dose is distributed in the patient. The treatment plans are assessed and approved by physicians and medical physicists, and are passed on as instructions to the equipment to deliver the treatment, e.g. the linear accelerator when it comes to EBRT. It is important that the prescribed dose and the dose distribution fulfil the treatment goals, i.e. that a sufficient treatment dose is delivered to the tumour and that the

dose thresholds for normal tissue are not exceeded. Once the dose distribution of treatment plan is calculated, it must be evaluated before being applied to the patient. The dose distribution of the tumour and other structures defined in the TPS can be visualized by using a dose volume histogram (DVH) which provides guidance on whether to accept or redo a treatment plan (7). An example dose distribution for a patient with prostate cancer is shown in Figure 1.

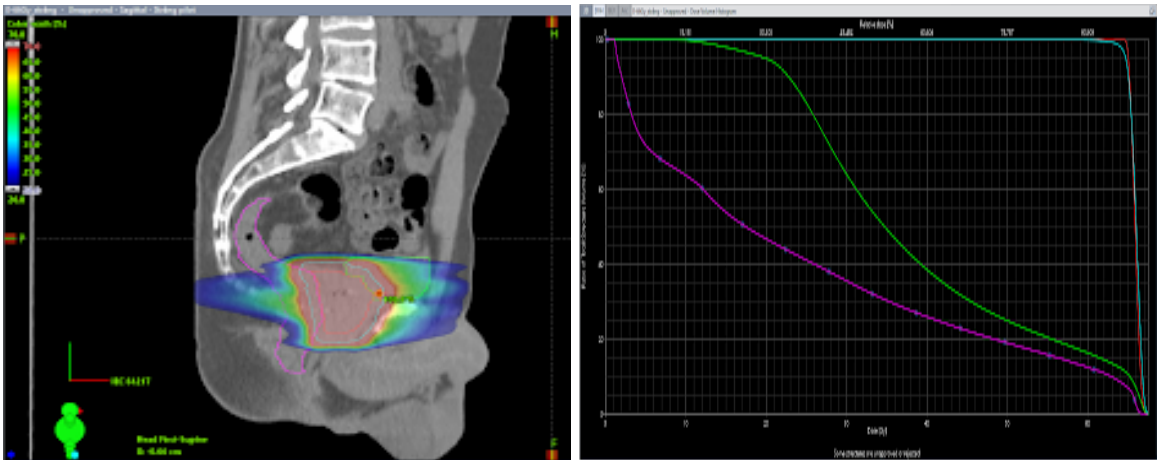

Figure 1: Dose distribution of a prostate cancer patient viewed in sagittal plane (left) and the associated DVHs for the tumour and OARs (right). The color wash in red corresponds to the prescribed dose and yellow-green-blue indicate increasingly lower dose levels (right). The DVHs to the right show the PTV (turquoise), the CTV (red), the rectum (pink) and the bladder (green). The y-axis shows percentages of the total structure volume and the x-axis shows the dose in Gy. The relative dose in percent is also plotted along the dose at the top.

1.4 Treatment volumes and organs at risk

Using the imaging data in the TPS, the tumour volume to be irradiated and the OARs that need to be avoided or limit the dose to are identified by physicians responsible for each patient's treatment. They also specify the dose levels that are expected to eradicate the tumour and which are likely to be acceptable for the OARs. There are international recommendations on how to define different structures and which doses to use, but in practice, the opinions often differ on which guideline to use, in particular for OARs.

The tumour volume is defined by different subvolumes according to international recommendations by the ICRU (12, 13). The gross tumour volume (GTV) comprises known tumour tissue, which can be identified by different imaging modalities. Clinical target volume (CTV) includes regions with suspected tumour cells and is an extension of the GTV. In the extended volume between the GTV and CTV, tumour cells cannot be demonstrated diagnostically, but the volume is likely to include them such as for regional lymph nodes to which the cancer often spreads. The target volume planning (PTV) is an extension of the CTV which includes margins for movement, during and between treatments and also machine uncertainties. The treated volume is defined as the volume which receives a radiation dose important for local cure or palliation. Irradiated volume is the volume that receives radiation dose that is considered important for normal tissue tolerance. An example of irradiated volume in prostate cancer is shown in Figure 1.

OARs are located in the vicinity of the tumour and are normal tissue with a dose tolerance which can significantly affect how the treatment is planned and delivered. The ICRU report 62 suggests the term Planning Organs At Risk Volume (PRV) as a safety margin for normal tissue, similarly as the PTV for the tumour (13). Example OAR volumes in prostate cancer RT is shown in Figure 2.

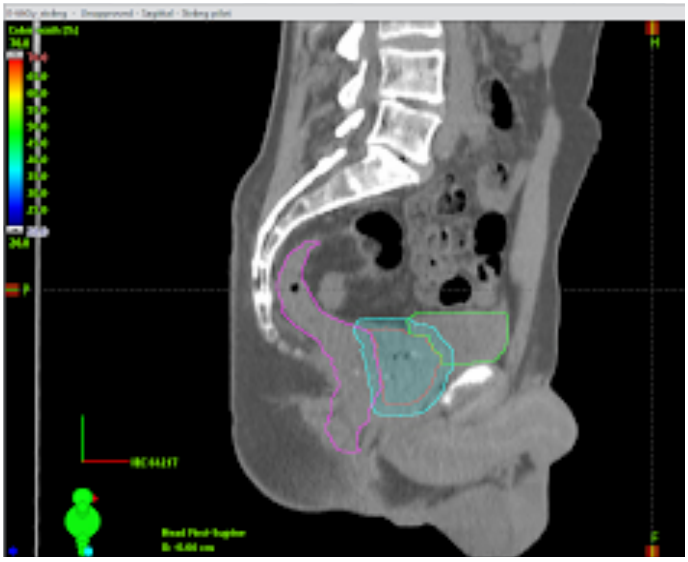

Figure 2: A CT of a prostate cancer patient viewed in sagittal plane with PTV, CTV and OARS. The area marked in turquoise is PTV, red is CTV, green is bladder and pink is rectum.

1.5 Side effects and toxicity criteria

In RT, side effects are separated into acute and late effects and depend to some extent on the type of cells the organs are made up of and how they are organized (7). Tumour cells typically considered to be early responding tissue while normal cells can be both early and late responding tissue. The damage also depends on how much of the organ is irradiated and other coexisting factors such as presence of chemotherapy or other dose-modifying factors (14). Acute effects occur already during treatment or immediately after it. The acute effects manifest themselves in tissues that divide quickly, for example in the skin, mucous membranes and bone marrow. The acute effects can be monitored during the period of treatment and the treatment can in critical cases be paused or interrupted if the situation becomes untenable and the effects become too severe. Late effects occur after treatment and primarily in the organs where the tissue renews slowly. In the clinic, the effects are quantified by different toxicity scales or grading systems such as the RTOG Acute Radiation Morbidity Scoring Criteria and the RTOG/EORTC Late Radiation Morbidity Scoring Scheme (15). Both of them have grades from 0 (no reaction) to 5 (reaction leading to death) with increasing severity of reaction. After radiotherapy for prostate cancer, gastrointestinal and genitourinary side effects as well as sexual dysfunction are common late effects. Late effects from the rectum can surface as rectal bleeding, cramping, bowel movement, pain or diarrhea. Late effects from the bladder can appear as frequent urination, blood in the urine, difficult or painful urination and cystitis (15).

To avoid side effects, different dose tolerance thresholds are suggested which are based on scientifically identified relationships between dose and risk. These are given as points on a DVH and referred to as dose-volume criteria, either as $V_{d\ (\%)}$ or $D_{v\ (\%)}$. $V_{d\ (\%)}$ describes the percent volume of organ receiving a dose of d (%) of the prescribed dose which should be kept

lower than a certain volume (%). $D_{v\ (\%)}$ describes the dose to the percent volume of the organ which should be kept lower than a certain dose (%). In this thesis, the dose-volume evaluation criteria for rectum used in the treatment of prostate cancer at Sahlgrenska University Hospital between 2013-2019 as well as the QUANTEC-criteria are investigated (16-18) (Table 1.1)

Table 1.1: Dos-volume criteria at the Sahlgrenska University Hospital and the QUANTEC-criteria

Sahlgrenska 2013-2019	Sahlgrenska 2019	QUANTEC
$V_{50\%} < 50\%$ $V_{80\%} < 35\%$ $V_{90\%} < 15\%$	$V_{50\%} < 40\%$ (postoperative) $V_{77\%} < 30\%$ (primary) $V_{90\%} < 15\%$ (primary) $V_{90\%} < 20\%$ (postoperative) $D_{2\%} < 100\%$ (both)	$V_{50Gy} < 50\%$ $V_{60Gy} < 35\%$ $V_{65Gy} < 25\%$ $V_{70Gy} < 20\%$ $V_{75Gy} < 15\%$

1.6 Effects of different guidelines for organs at risk

For tumours, it is difficult to standardize the treatment volumes because they can differ greatly between individuals. OARs are more uniform and standardization less controversial. Although there are guidelines (RTOG, ASTRO and ESTRO ACROP) (10, 19), some OARs can be defined both according to anatomical extensions or with respect to certain distances from the tumour. The radiation dose calculated in these volumes may therefore vary depending on how the volumes were anatomically defined. This makes it difficult to compare dose and volume measures between patients as well as between clinics and also limits the understanding of the relationship between dose and side effects. For prostate cancer the rectum volume can for instance be defined from above the anal canal to the turn into the sigmoid colon, with or without the rectal contents (20). To compare two different volumes according to different guidelines and evaluate the volume of overlap the Dice coefficient is often used, as defined in Figure 3 (21). The index equals twice the volume overlap of two sets or volumes divided by the sum of both and ranges from zero to one. If the two volumes are identical, the coefficient is equal to 1.0, while if they are completely separated, it is equal to 0. Otherwise it is somewhere in between.

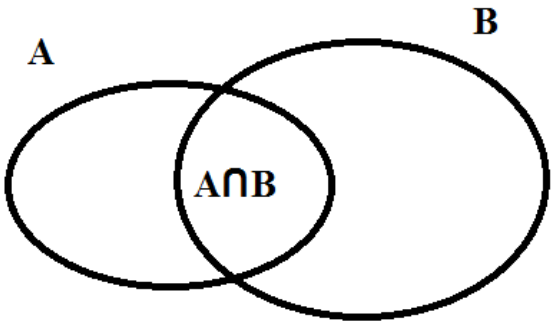

Figure 3: Intersection of two sets A and B. Dice coefficient = $\frac{2|A \cap B|}{|A| + |B|}$

In Sweden, an ongoing national project STRÅNG (Strålbehandling NormalvävnadsGruppen-Strong in English) aims to standardize OAR volumes in RT (19). The project builds on previous standardization initiatives in radiotherapy such as the Swedish naming convention for tumour

volumes and normal tissues (17, 22). A first STRÅNG sub-project to determine guidelines for the rectum has recently been successfully completed and these are in the process of being evaluated. One specific issue is to determine how much a specific OAR volume differs in terms of dose and volume dimensions for a given treatment when it is defined according to this proposed guideline compared to when it is defined in clinical routine.

1.7 Aim

To investigate how rectal volumes defined according to upcoming Swedish national guidelines differ from rectal volumes defined in clinical practice for patients treated with radiation therapy for prostate cancer. Other objectives were to determine potential dose differences between the two strategies to define rectal volumes and implications for treatment decisions based on associated rectal dose tolerance doses.

2. Material and methods

2.1 Study population

Patients with prostate cancer treated in 2018 at the Sahlgrenska University Hospital in Göteborg, Sweden were studied with respect to planned rectum volumes and doses as calculated on pre-treatment CT images in the Eclipse treatment planning system (Version 15.6; Varian Medical System, Palo Alto, CA, USA). Patients had been treated with EBRT with possible addition of BT, some had also undergone surgery pre-RT. All the patients were identified via a dedicated data base query from the Eclipse TPS during the time period 1 Januari-30 September, 2018, based on the ICD-code for prostate cancer (C61) and with different planned total doses (50Gy-primary/66Gy-primary/70Gy-postoperative). Exclusion criteria for patients were to have been planned for treatment in another treatment planning system, having non-restorable treatment plans, not having a clinical rectum volume defined, or having been treated to non-standard total doses.

Ethical approval for the study was granted by the Regional Ethical Review board in Göteborg (Dnr: 641-17 and T1115-18).

2.2 Data management and data processing

2.2.1 Data import and export

Pseudonymized information was imported from the clinical version of the Eclipse TPS into its research version for studying. Treatment characteristics were described by prescribed dose (50/66/70 Gy), dose/fx (2 or 3 Gy), and total number of fx (22/25/35). For rectal structures, information about volumes (cm^3) and absorbed doses (Gy) were summarized in cumulative DVHs (0.1Gy-bins). The DVH information in Eclipse was then transferred to Microsoft Excel and MATLAB (Version R2018b, Update 2, 9.5.0.1033004, The MathWorks Inc., Natick, MA, USA) for further processing.

2.2.2 Rectal volumes

Rectum was described by the clinical volume as delineated in clinical routine (*Rectum*), the standardized volume as suggested by STRÅNG (*Rectum Strång*), the differences between the clinical and the standardized volumes in cranial direction (*Rectum Cranial*) and in caudal direction (*Rectum Caudal*) as well as the intersection between the clinical and the standardized volume (*Rectum*∩*Rectum Strång*). The *Rectum Strång* volumes were defined based on the *Rectum* volumes with adjustments in the cranial or caudal direction only. All remaining volumes had been delineated by a same person or created using the Boolean operators in the TPS.

The clinically-defined rectum volumes were defined if applicable, 5 cm in the cranial direction from the centre of the prostate and in the caudal direction down to and including the anus (23). The STRÅNG-volumes were defined until the rectum loses its round shape in the axial plane and connects anteriorly with the sigmoid in cranial direction and from the lowest level of the ischial tuberosities in caudal direction (10, 24).

Rectum's and *Rectum Strång*'s respective positions to each other were used to find the most cranial point and the most caudal point of both structures (positive upward and negative downward), see Figure 4.

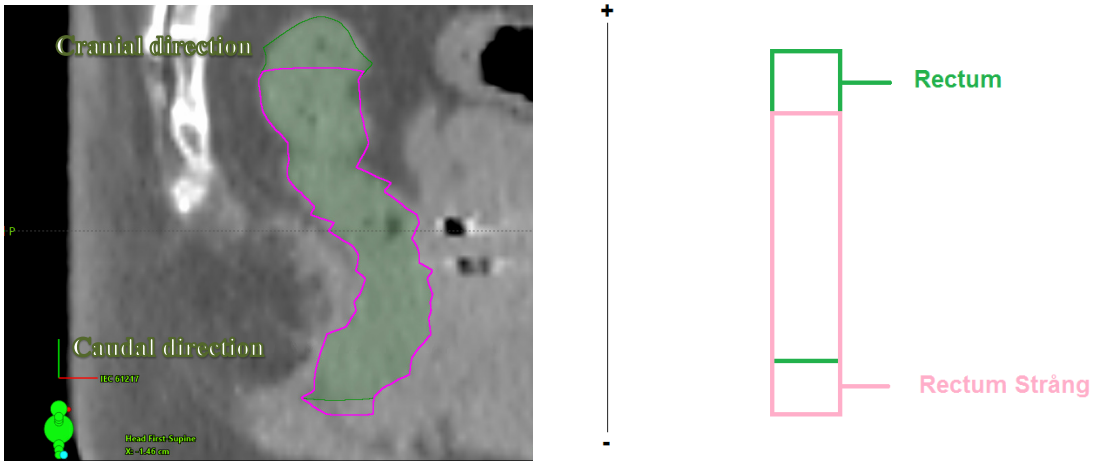

Figure 4: A sagittal view of the pelvic region of a prostate cancer patient with the clinically-defined (green) and STRÅNG-defined (pink) rectum volumes where *Rectum* is more cranially defined than *Rectum Strång* (left). A schematic image of the rectum volumes (right).

The most cranial coordinate of *Rectum* was subtracted form the most cranial point of *Rectum Strång* leading to a positive difference at the cranial border indicating that the clinically-defined volume was more cranially delineated than *Rectum Strång*. A positive difference at the caudal border indicated instead that the clinically-defined volume was less caudally delineated than *Rectum Strång*.

2.3 DVH tolerance thresholds

Three recommendations on DVH tolerance thresholds to keep risks of rectal toxicity low were investigated. These were (1) the clinically used DVH planning criteria at Sahlgrenska University Hospital between 2013-2019, (2) new DVH planning criteria at Sahgrenska University Hospital from 2019 and (3) DVH tolerance thresholds by QUANTEC from 2010 (17). The QUANTEC thresholds were defined for conventionally-fractionated prostate cancer treatment up to 78 Gy to limit the risk of late Grade 2 rectal toxicity to <15% and the risk of Grade 3 late rectal toxicity to 10%. The tolerance doses according to (1)-(3) are presented in Table 2.1, Table 2.2 and Table 2.3, respectively.

Table 2.1: Dose-volume criteria for various prostate cancer RT prescribed doses at the Sahlgrenska University Hospital between 2013-2019.

Dose (Gy)/ Criteria	50 Gy	66 Gy	70 Gy
$V_{50\%} < 50$ %	$V_{25\ Gy} < 50$ %	$V_{33\ Gy} < 50$ %	$V_{35\ Gy} < 50$ %
$V_{80\%} < 35$ %	$V_{40\ Gy} < 35$ %	$V_{52.8\ Gy} < 35$ %	$V_{56\ Gy} < 35$ %
$V_{90\%} < 15$ %	$V_{45\ Gy} < 15$ %	$V_{59.4\ Gy} < 15$ %	$V_{63\ Gy} < 15$ %

Table 2.2: Dose-volume criteria for various prostate cancer RT prescribed doses at the Sahlgrenska University Hospital from 2019.

Dose (Gy)/ Criteria	50 Gy	66 Gy	70 Gy
$V_{50\%} < 40$ % (postoperative)			$V_{35\ Gy} < 40$ %
$V_{77\%} < 30$ % (primary)	$V_{38.5\ Gy} < 30$ %	$V_{50.8\ Gy} < 30$ %	
$V_{90\%} < 15$ % (primary)	$V_{45\ Gy} < 15$ %	$V_{59.40\ Gy} < 15$ %	
$V_{90\%} < 20$ % (postoperative)			$V_{63\ Gy} < 20$ %
$D_{2\%} < 100$ % (both)	The dose to 2% of the volume should not be higher than the prescribed dose.		

Table 2.3: QUANTECs dose-volume criteria normalized to the prescribed doses in use for prostate cancer RT at the Sahlgrenska University Hospital.

Dos (Gy)/ Criteria*	50 Gy	66 Gy	70 Gy
$V_{64\%} < 50$ %	$V_{32\ Gy} < 50$ %	$V_{42.2\ Gy} < 50$ %	$V_{44.8\ Gy} < 50$ %
$V_{77\%} < 35$ %	$V_{38.5\ Gy} < 35$ %	$V_{50.8\ Gy} < 35$ %	$V_{53.9\ Gy} < 35$ %
$V_{83\%} < 25$ %	$V_{41.5\ Gy} < 25$ %	$V_{54.8\ Gy} < 25$ %	$V_{58.1\ Gy} < 25$ %
$V_{90\%} < 20$ %	$V_{45\ Gy} < 20$ %	$V_{59.4\ Gy} < 20$ %	$V_{63\ Gy} < 20$ %
$V_{96\%} < 15$ %	$V_{48\ Gy} < 15$ %	$V_{63.4\ Gy} < 15$ %	$V_{67.2\ Gy} < 15$ %

2.4 Statistics

2.4.1 Subgroups

Patients were analyzed by groups of treatment approach and by prescribed total EBRT dose, EBRT only (66 Gy), EBRT+BT (50 Gy) and surgery+EBRT (70 Gy).

2.4.2 Volume overlap

The volume overlaps between clinical and standardized rectal volumes were quantified by the Dice coefficient, which was calculated in Microsoft Excel by using Equation 1

$$Dice = \frac{2|Rectum \cap Rectum\ Strång|}{|Rectum| + |Rectum\ Strång|} \quad \text{(Equation 1)}$$

where *Rectum* and *Rectum Strång* are volumes in cm^3.

2.2.3 Calculating volume and dose differences

Descriptive statistics for volumes, doses and Dice were calculated with mean values and standard deviations (SD) or median values and range (minimum and maximum values). Differences between different rectal volumes were calculated with *Rectum Strång* as reference for the whole population and for each treatment group when applicable. DVH tolerance threshold were investigated both for absorbed dose (Gy) and percentage of dose (%) as

normalized to the different prescribed doses. The differences between treatment groups were investigated by paired hypothesis testing, parametric testing (Student's t-test) or non-parametric testing (Mann-Whitney test), depending on the underlying distribution of data. All tests were two-tailed and conducted at 0.05 significance level. The statistical analysis was performed in Microsoft Excel with T.TEST and RANG.

3. Results

3.1 Study population

There were 135 patients identified during the studied period, but only 121 patients fulfilled the inclusion criteria. All patients had their clinical rectum volume defined and all treatment plans could be reactivated. The excluded patients were treated to non-standard prescribed doses (30 Gy, 54 Gy, 58 Gy, 63 Gy and 68 Gy; n=5) or their treatment plan had not been planned in Eclipse (n=9). Among included patients, most were prescribed 66 Gy (n=71). The different prescribed doses, doses per fraction and total number of fractions for different treatment groups are shown in Table 3.1.

Table 3.1: Number and treatment characteristics of patients in the groups 50 Gy, 66 Gy and 70 Gy.

Prescribed dose (Gy)	50 Gy	66 Gy	70 Gy
Number of patients	19	71	31
Dose/fx (Gy)	2	3	2
fx (no.)	25	22	35

Abbbreviations: fx=fraction; Gy=Gray; no.=number.

3.2 Dose-volume characteristics

The DVH characteristics of the rectal structures for all patients are summarized in Figure 3.1. Using the volumes defined by STRÅNG resulted in a wider spread of DVHs in the study population.

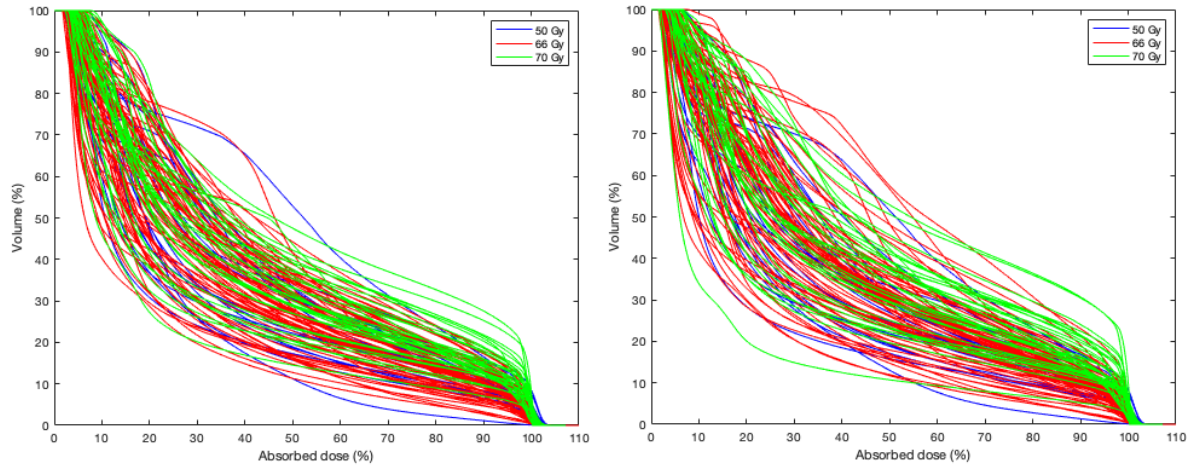

Figure 3.1: DVHs of clinically-defined rectum volumes (left) and volumes defined according to STRÅNG (right). Volumes and doses are given as percentages of total volume and prescribed dose, respectively.

The information about rectal volumes (cm^3) for all patients and different treatment groups are presented in Table 3.2. The clinical rectal volumes were around 4 cm^3 larger than the volumes defined according to STRÅNG (75.6 ± 34.0 cm^3 versus 71.9 ± 34.2 cm^3; $p<0.01$), with somewhat smaller volumes but larger standard deviation in the 66-Gy group compared with the other two groups. *Rectum Cranial* were on average larger than *Rectum Caudal* (8.6 ± 9.6 cm^3 versus 1.6 ± 1.8 cm^3; $p<0.01$). The higher numbers were found in the 66-Gy group (9.7 ± 10.2

cm^3 and 1.8 ± 2.0 cm^3) and the smaller numbers in the 50-Gy group (5.9 ± 7.0 cm^3 and 1.0 ± 1.0 cm^3).

Table 3.2: Descriptive volume statistics for the investigated rectal volumes per treatment group.

Structures (cm^3) mean±SD median (range)	50 Gy (n=19)	66 Gy (n=71)	70 Gy (n=31)	All patients (n=121)
Rectum	76.6 ± 30.0 74.1 (33.2-164.8)	74.9 ± 38.3 64.5 (33.6-248.9)	76.4 ± 25.8 69.4 (31.7-166.5)	75.6 ± 34.0 67.0 (21.7-248.9)
Rectum Strång	75.7 ± 27.5 65.3 (29.4-138.4)	70.6 ± 39.1 56.4 (34.8-264.4)	72.6 ± 25.2 66.3 (31.7-144.1)	71.9 ± 34.2 63.6 (29.4-264.4)
Rectum - Rectum Strång	0.9 ± 9.0 -0.2 (-17.1-26.4)	4.3 ± 12.2 1.9 (-29.7-49.9)	3.8 ± 11.4 1.2 (-31.9-34.4)	3.6 ± 11.6 1.2 (-31.9-49.9)
Rectum Cranial	5.9 ± 7.0 3.4 (0.1-25.6)	9.7 ± 10.2 5.9 (0.6-45.8)	8.0 ± 9.6 4.5 (0.3-32.6)	8.6 ± 9.6 5.25 (0.1-45.8)
Rectum Caudal	1.0 ±1.0 0.6 (0.2-3.5)	1.8 ± 2.0 1.1 (0.1-11.9)	1.5 ± 1.6 1.1 (0.1-7.1)	1.6 ± 1.8 1.0 (0.1-11.9)
Rectum∩Rectum Strång	72.7 ± 26.3 64.6 (28.8-136.6)	67.6 ± 36.9 55.2 (31.1-248.9)	70.2 ± 23.8 63.2 (30.8-144.1)	69.1 ± 32.3 62.2 (28.8-248.9)

Abbreviation: SD=standard deviation.

Dose characteristics of different rectal structures and different treatment groups are shown in Table 3.3. On average, maximum dose were around 103 % of prescribed doses, minimum doses around 4 % of prescribed doses and mean doses around 38 % of prescribed doses. In general, differences in maximum, minimum and mean doses between clinically-defined rectum volumes and volumes according to STRÅNG were small. The largest differences were around 1 Gy for mean dose comparisons in the 66-Gy and the 70-Gy treatment groups. Averaged differences between cranial and caudal volumes in the different treatment groups ranged between 0.8-14.7 Gy (maximum dose), 0.2-0.5 Gy (minimum dose) and 0.5-2.0 Gy (mean dose). The smaller differences were generally in the 50 Gy group and the higher differences were generally in the 70 Gy group.

Table 3.3: Descriptive dose statistics for the investigated rectal volumes per treatment group.

Structures/ Characteristics	Max dose (Gy)			Min dose (Gy)			Mean dose (Gy)		
	50 Gy (n=19)	66 Gy (n=71)	70 Gy (n=31)	50 Gy (n=19)	66 Gy (n=71)	70 Gy (n=31)	50 Gy (n=19)	66 Gy (n=71)	70 Gy (n=31)
Rectum	51.7±0.6	68.1±0.6	72.2±1.5	1.6±0.6	2.2±0.7	2.9±1.0	17.7±3.7	23.4±4.5	27.3±5.0
Rectum Strång	51.6±0.6	68.1±0.6	72.2±0.5	1.6±0.5	2.3±0.8	3.0±0.9	17.7±3.6	24.6±5.2	28.6±6.3
Rectum Cranial	6.1±9.4	13.4±16.5	17.2±19.3	1.8±1.2	2.9±2.2	3.7±2.0	2.8±2.6	5.3±4.7	6.7±5.1
Rectum Caudal	6.9±11.4	5.6±8.4	2.5±12.0	2.1±0.6	2.4±0.7	3.9±4.8	3.3±2.5	3.3±1.7	5.1±6.9
Rectum ∩ Rectum Strång	51.7±0.6	68.0±0.6	72.2±0.5	1.7±0.6	2.6±1.1	3.2±1.0	18.3±3.7	25.4±5.2	29.2±6.0

The DVH characteristics of the rectal structures for different treatment group are summarized in Figure 3.2. In general, the shape of the averaged DVHs of the rectal structures were similar for all the treatment groups with the larger differences in the lower dose range (<20 Gy). The differences were larger in the 66-Gy and the 70-Gy groups than in the 50-Gy group (up to 4.5 cm^3 differences versus up to 1.5 cm^3 differences).

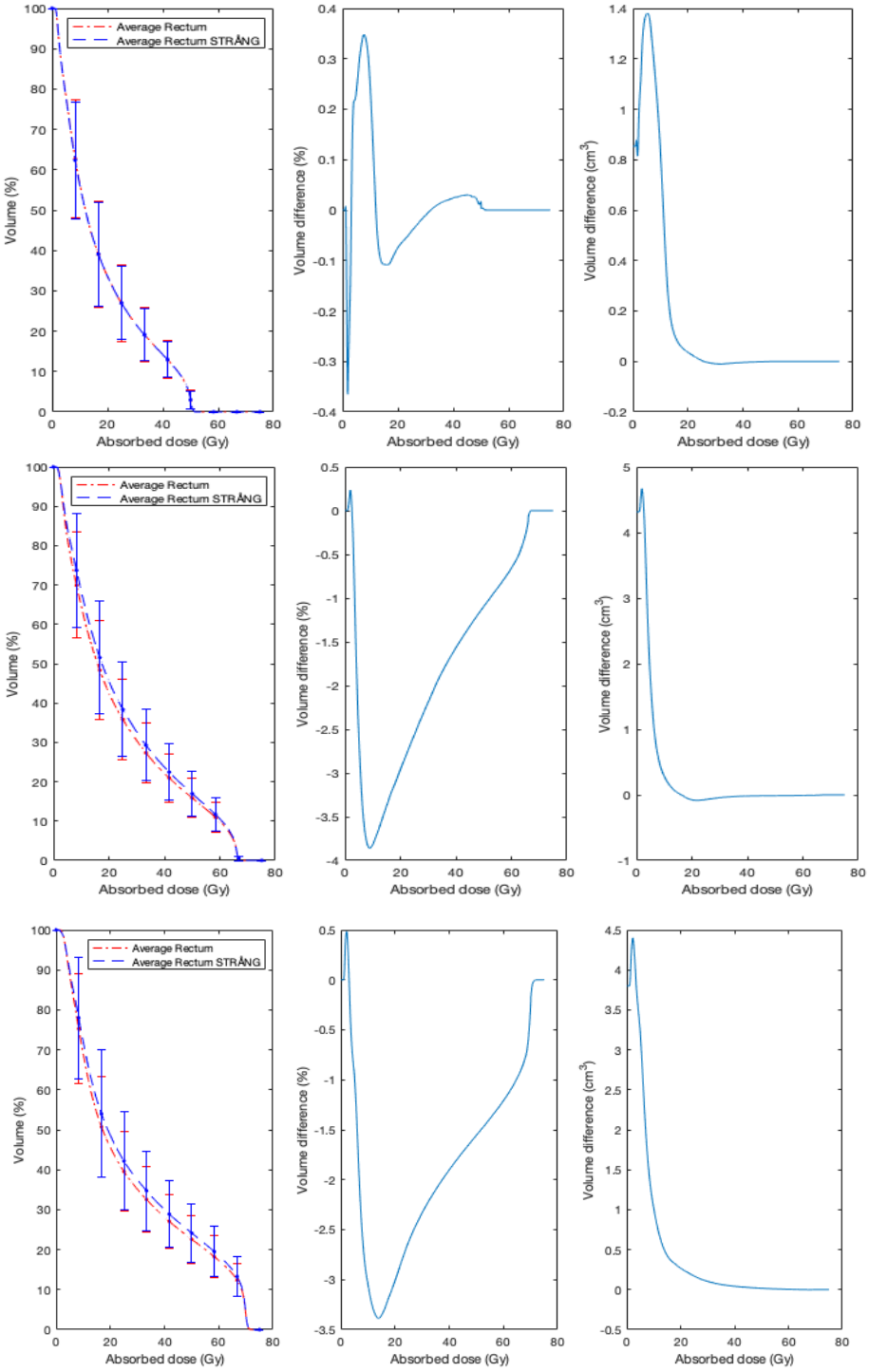

Figure 3.2: Averaged DVHs of clinically-defined rectum volumes and volumes defined according to STRÅNG (left) and volume differences in percent (middle) and in cm^3 (right) for the 50-Gy (top), 66-Gy (middle) and 70-Gy (bottom) treatment groups.

3.3 Rectal volumes

The differences between clinical rectal volumes and volumes defined according to STRÅNG in cranial direction and caudal direction are shown in Figure 3.3 and described in Table 3.4. There were 79 patients with differences both in cranial and caudal directions (65 %). Overall, there were more patients who had differences in caudal direction (87 %) than in cranial direction (78 %), but the mean differences were higher in cranial direction (4.9 ± 12.0 mm) than in caudal (0.9 ± 8.7 mm). The differences in cranial direction was largest for the 66-Gy group and smallest for the 50-Gy group (5.1 ± 12.5 mm versus 3.8 ± 11.5 mm) and the mean differences in caudal direction was largest for the 50-Gy group and smallest for the 66-Gy group (3.5±4.6 mm versus 0.3±9.1 mm). However, neither differences reached statistical significance, p=0.45 and p=0.14, respectively.

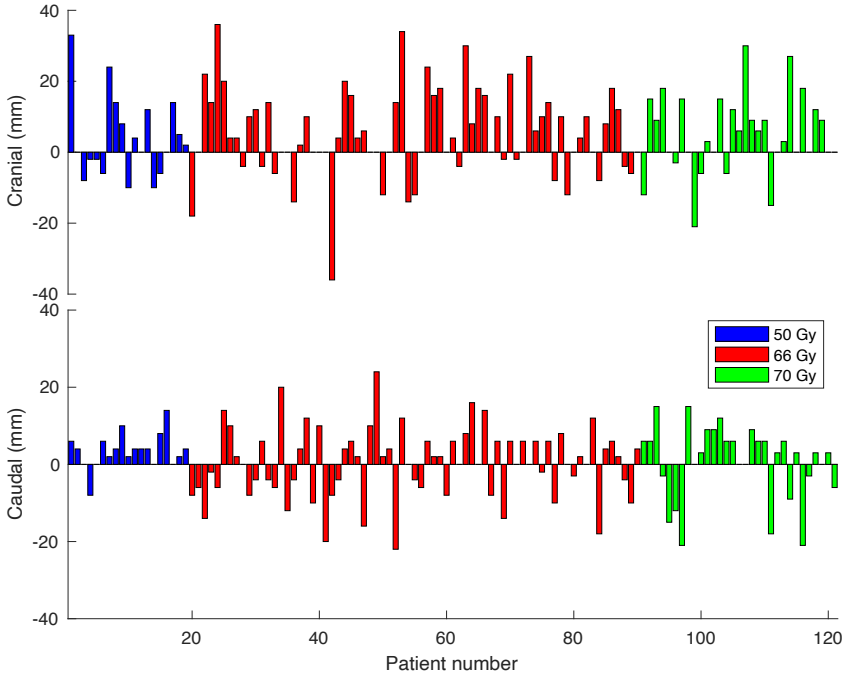

Figure 3.3: Differences between *Rectum* and *Rectum Strång* in cranial direction (top) and caudal direction (bottom). A positive difference cranially means that the clinically-defined volume is more cranially delineated than *Rectum Strång*. A positive difference caudally means that the clinically-defined volume is less caudally delineated than *Rectum Strång*.

Table 3.4: Number of patients (no.) with delineation differences in cranial and caudal directions.

	50 Gy (n=19)		66 Gy (n=71)		70 Gy (n=31)		All patients (n=121)	
	Cranial	Caudal	Cranial	Caudal	Cranial	Caudal	Cranial	Caudal
(No.) patients (%)	16 (84%)	15 (79%)	55 (77%)	63 (89%)	23 (74%)	27 (87%)	94 (78%)	105 (87%)
	Both: 12 (63%)		Both: 47 (66%)		Both: 19 (61%)		Both: 79 (65%)	

Abbreviations: no.=number; %=percent.

3.4 Volume overlap

The volume overlaps between *Rectum* and *Rectum Strång* quantified by the Dice coefficient for the different treatment groups are shown in Figure 3.4 and described in Table 3.5. The coefficient ranged between 0.72 to 1.00 with the lower values in the 66-Gy treatment group. There were no statistically significant differences when comparing Dice between the different treatment groups (50 Gy versus 66 Gy (p=0.06), 50 Gy versus 70 Gy (p=0.62) and 66 Gy versus 70 Gy (p=0.15)).

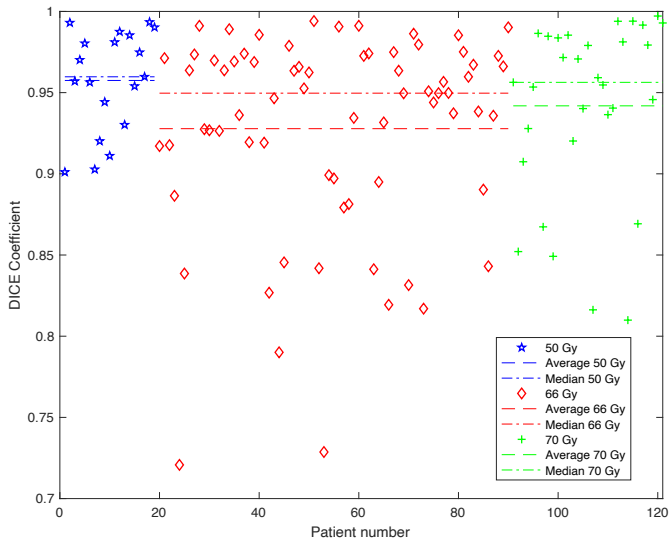

Figure 3.4: Dice coefficient for different treatment groups.

Table 3.5: Mean values with standard deviation (SD) and median value with range of Dice coefficient.

	50 Gy (n=19)	66 Gy (n=71)	70 Gy (n=31)	All patients (n=121)
Mean + SD	0.96 ± 0.03	0.93 ± 0.06	0.94 ± 0.05	0.94 ± 0.06
Median (Range)	0.96 (0.90-0.99)	0.95 (0.72-0.99)	0.96 (0.81-1.00)	0.95 (0.72-1.00)

3.5 DVH tolerance thresholds

The averaged DVHs of the rectal structures for different treatment group with dose-volume criteria used at Sahlgrenska University Hospital between 2013 and 2019 and dose-volume criteria used at Sahlgrenska University Hospital in 2019 are summarized in Figure 3.5. Generally, all points of the averaged DVHs were below the dose-volume criteria.

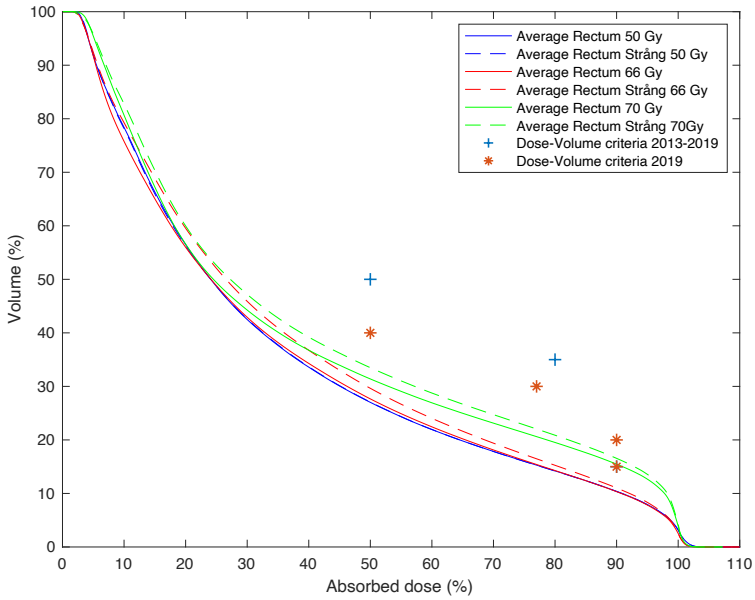

Figure 3.5: Averaged DVHs of *Rectum* and *Rectum Strång* for different treatment groups and the investigated three groups of dose-volume tolerance thresholds. Note that $V_{90\%} < 15\%$ and $V_{90\%} < 20\%$ relates to different treatment groups (primary and postoperatively, respectively).

Each patient's individual DVH values for *Rectum* and *Rectum Strång* and their relationships to the investigated dose-volume criteria are shown in Figure 3.6.1, Figure 3.6.2 and Figure 3.6.3. There were 22 patients where both *Rectum* and *Rectum Strång*, did not satisfy the dose-volume tolerance thresholds used at Sahlgrenska University Hospital between 2013 and 2019, which were used for the original clinical decision making. There were also 8 patients where the STRÅNG volumes did not satisfy these criteria although the clinical volume did. In general, the rectal volumes satisfied the dose-volume volume tolerance thresholds used at Sahlgrenska University Hospital between 2013 and 2019 as good as the dose-volume criteria used at Sahlgrenska University Hospital from 2019. There were few patients with rectal volumes which did not satisfy the dose-volume criteria for $V_{90\%} < 20$ % of the new Sahlgrenska University Hospital criteria from 2019 and the criteria of the adjusted QUANTEC tolerance thresholds from 2010.

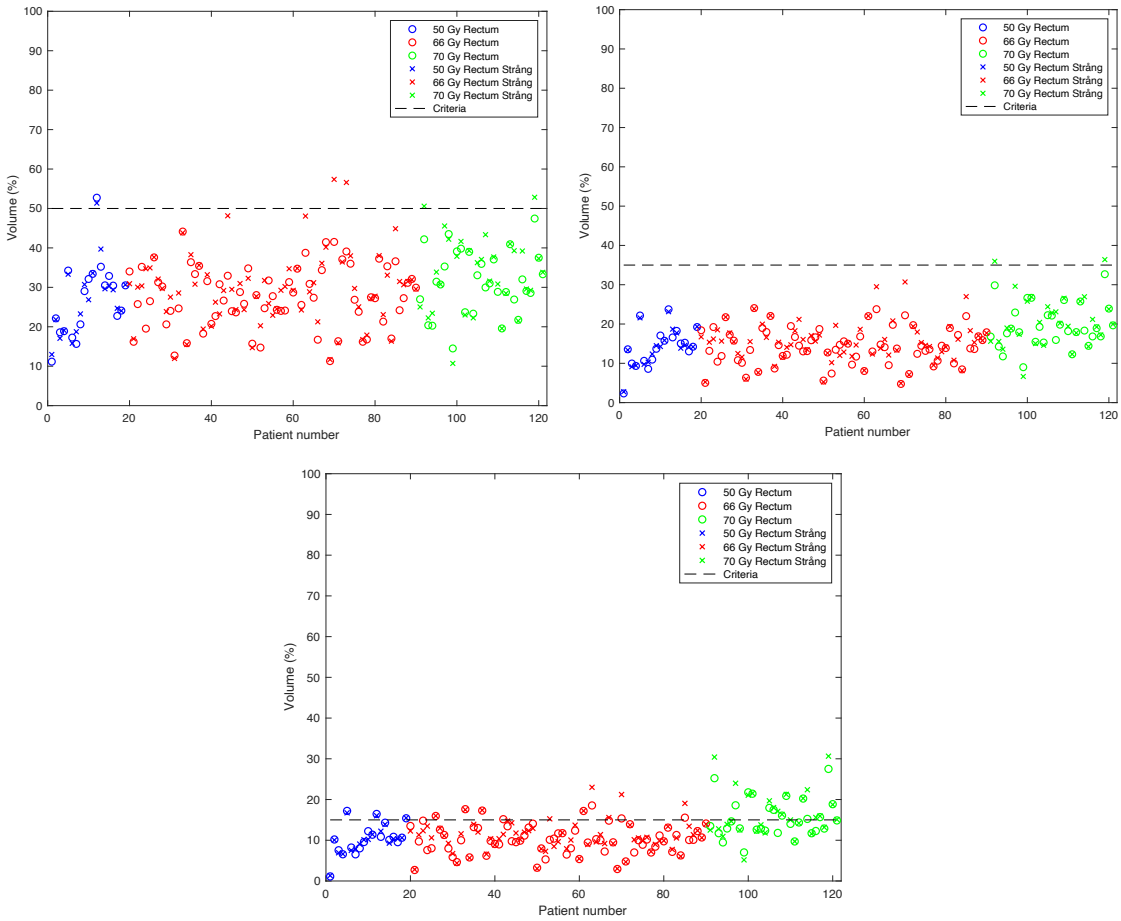

Figure 3.6.1: The investigated patients individual DVH values for *Rectum* and *Rectum Strång* and their relationships to the DVH criteria used for the planning of prostate cancer RT at Sahlgrenska University Hospital between 2013-2019: $V_{50\%} < 50\%$ (top left), $V_{80\%} < 35\%$ (top right) and $V_{90\%} < 15\%$ (bottom) .

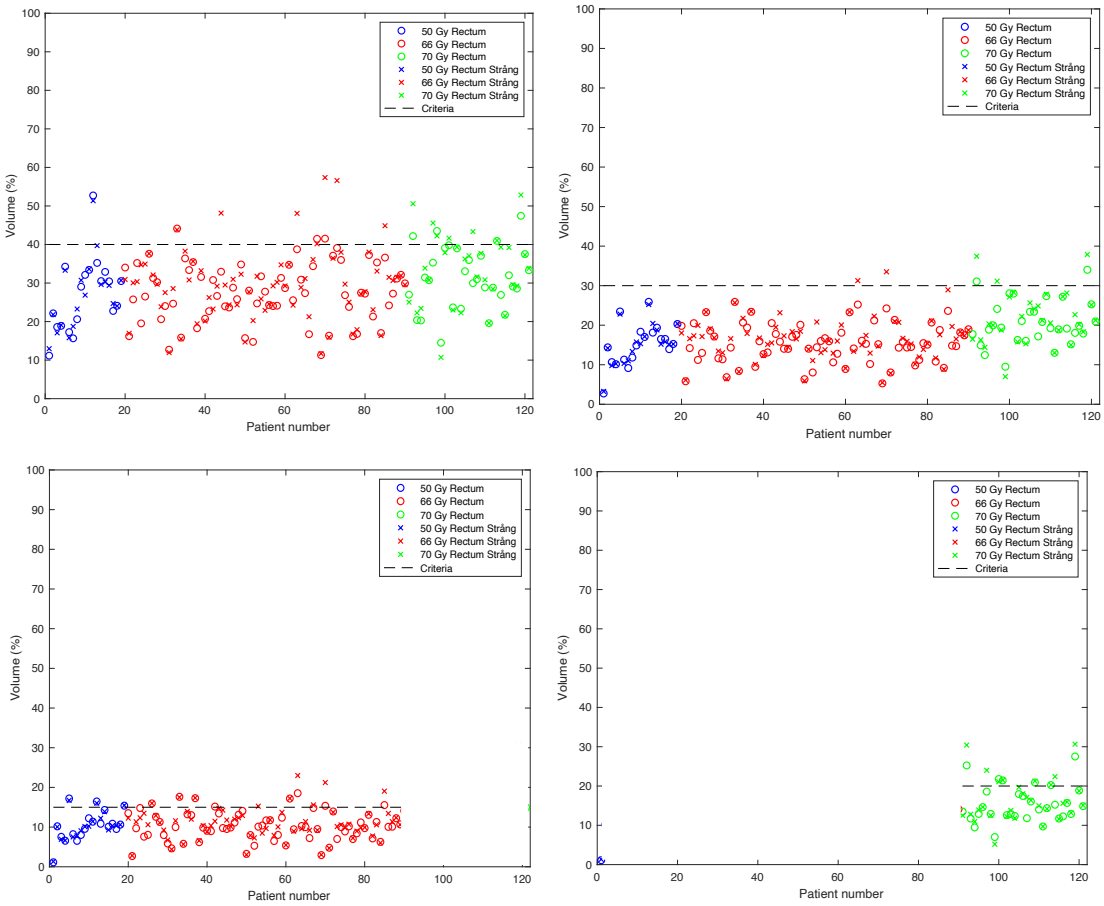

Figure 3.6.2: The investigated patients individual DVH values for *Rectum* and *Rectum Strång* and their relationships to the DVH criteria used for the planning of prostate cancer RT at Sahlgrenska University Hospital between from 2019: $V_{50\%} < 40\%$ (top left), $V_{77\%} < 30\%$ (top right), $V_{90\%} < 15\%$ (bottom left) and $V_{90\%} < 20\%$ (bottom right).

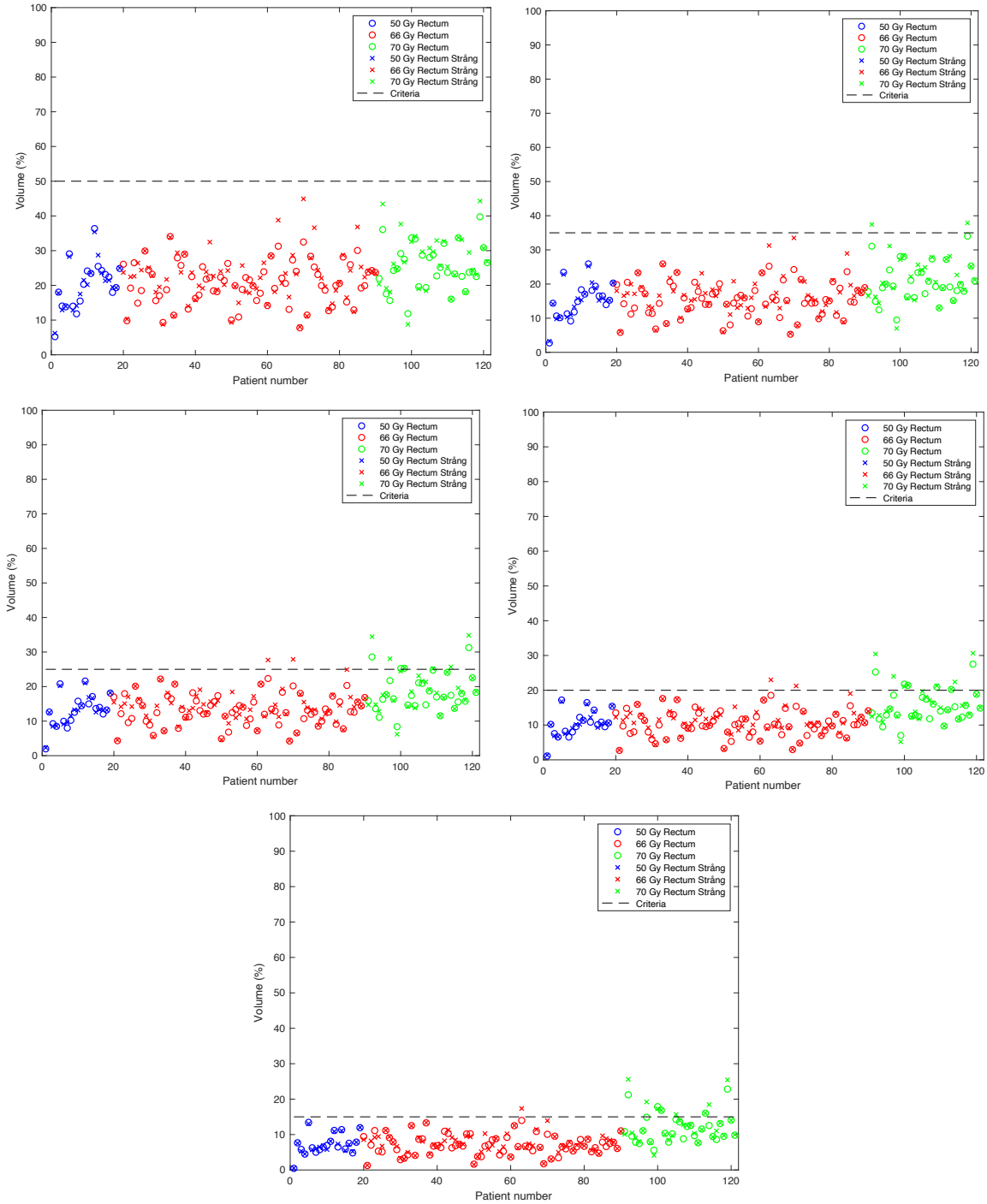

Figure 3.6.3: The investigated patients individual DVH values for *Rectum* and *Rectum Strång* and their relationships to the DVH tolerance thresholds suggested by QUANTEC in 2010: $V_{64\%} < 50\%$ (top left), $V_{77\%} < 35\%$ (top right), $V_{83\%} < 25\%$ (middle left), $V_{90\%} < 20\%$ (middle right) and), $V_{96\%} < 15\%$ (bottom).

4. Discussion

The purpose of this study was to investigate how rectal volumes defined according to upcoming national guidelines (*Rectum Strång*) differed from rectal volumes defined in clinical practice (*Rectum*) for patients treated with external beam radiation therapy to 50 Gy, 66 Gy, or 70 Gy for prostate cancer. The main finding was that the clinical rectal volumes were on average larger than the volumes defined according to STRÅNG. There were more patients who had volume differences in caudal direction than in cranial direction but the mean volume differences were larger in cranial direction than in caudal. The volume overlaps between *Rectum* and *Rectum Strång* quantified by the Dice coefficient ranged between 0.72 to 1.00. A second purpose was to determine potential dose differences between the two strategies to define rectal volumes and implications for treatment decisions based on associated rectal dose tolerance doses. In general, dose differences between *Rectum* and *Rectum Strång* were small (mean dose differences ≤ 1 Gy). Approximately 7% of patients would have needed a revised treatment plan to fulfil the planning criteria according to the dose-volume tolerance thresholds used at Sahlgrenska University Hospital between 2013-2019 if using *Rectum Strång* instead of *Rectum*. In general, the rectal volumes satisfied the dose-volume tolerance thresholds used at Sahlgrenska University Hospital between 2013-2019 as good as the new dose-volume criteria proposed in 2019.

The results of this study showed that the clinical rectal volumes on average were about 4 cm^3 larger than the volumes defined according to STRÅNG. The smallest and the largest volume differences were found in the 50-Gy and the 66-Gy groups, respectively. The volumes defined by STRÅNG resulted in a wider spread of values for the overall study population. This was demonstrated by *Rectum Strång* having a somewhat larger range between maximum and minimum rectal volumes than *Rectum* (235 cm^3 versus 227 cm^3, respectively). This indicates that STRÅNG volumes may better reflect anatomical differences between individuals. There were more patients who had volume differences in caudal direction (87%) than in cranial direction (78%) which can be explained by *Rectum* being more consistently delineated caudally (down to and including anus) than cranially (5 cm above the center of PTV, if applicable). However, the cranial volumes were on average larger than the caudal volumes (9 cm^3 versus 2 cm^3) with the larger values in both directions typically found in the 66-Gy group. The clinically-defined volumes were also more cranially defined and less caudally defined than *Rectum Strång*, but the average Dice coefficient was close to 1 meaning that the two volumes overall were similar. With respect to a previous Swedish study by Nyholm et al. where they studied contour overlap of rectal volumes in prostate cancer RT between different users given the same guidelines, the Dice coefficient was around 0.8 (20). These differences were larger than the variation between the two strategies to delineate rectum as investigated in this project (20).

There were only small dose differences between clinically-defined rectum volumes and volumes according to STRÅNG. The largest difference was for mean dose in the 70-Gy group (1 Gy), with the somewhat higher dose values found for *Rectum Strång*. The cranial volumes always had higher dose than the caudal volumes, but typically differences were in the lower dose range (<10 Gy). This was confirmed in more detail by the averaged DVHs of the two strategies to define rectal volumes with the shapes of the DVHs not differing notably. Since the clinical rectum volumes in general were larger and the contouring differences occurred in regions with low dose, the average relative volume DVHs were placed below the average STRÅNG DVHs (Figure 3.2, leftmost plots). On the other hand, the absolute volumes receiving

intermediate to high doses differed on average very little (Figure 3.2, rightmost plots) since the central parts of the two rectum volumes were identical.

During the studied period of time, acceptable rectal dose distributions for prostate cancer patients were decided based on the Sahlgrenska University Hospital criteria 2013-2019. When changing the clinically-defined rectal volumes into *Rectum Strång*, there were eight patients where the dose-volume tolerance thresholds were violated. The majority of them were found in the 66-Gy and 70-Gy treatment groups. It is unknown if this difference would have led to a different clinical treatment plan in practice, but even a small difference in volume can make a difference in the treatment decision. When the mean DVHs of the studied structures are below the dose-volume criteria, this means that the risk of rectal side effects is likely to be clinically acceptable for a majority of the patients of that treatment group. For the studied dose distributions, the mean DVH of the 70-Gy treatment group were placed above the dose-volume criteria for $V_{90\%} < 15\%$ of the Sahlgrenska University Hospital criteria between 2013-2019 for both *Rectum* and *Rectum Strång* indicating that they did not satisfy the criteria for some patients. In the more recent criteria from 2019, $V_{90\%}$ is less strict for this treatment group (changed to $V_{90\%} < 20\%$) leading to the corresponding mean DVH now being placed below this dose-volume criteria.

The pseudonymized data for 121 patients were successfully extracted and studied to answer the research questions in this M.Sc. project. The fact that we only studied the patients who had their treatment planned in the same treatment planning system (Eclipse) and who had been treated to standard total doses facilitated the study. Different treatment planning system have different programs and treatment options which can produce different dose distributions. The study population was large enough to produce meaningful results, but stronger statistics would have been achieved from a larger population and a similar number of patients for each treatment group. The other limitations of this study relate to the volumes and the doses of the rectal structures which were also studied by mean values with standard deviation and median with range. Mean values and range are usually used in research to present results but these can be affected by population size. A large population may produce more reliable average values and larger range values. With respect to the delineations of different rectal structures, there may have been small undetected overlaps which were missed since the accuracy of the delineations were limited by the resolution of the CT-images.

Finally, investigations of how rectal volumes defined according to various guidelines differ to each other will makes it easier to compare and relate dose to treatment outcomes. But there are many other factors which can also affect the treatment decisions, such as patient's eating habits, smoking habits and comorbidities. Including both relevant clinical factors and knowledge about how much a specific OAR volume differs in terms of dose and volume when it is defined according to various guidelines will improve the treatment decisions. Although the results presented here hopefully can be used as a reference for similar studies in the future, it is important to keep in mind that they were based on patients treated for a specific cancer during a certain period of time at a single hospital in Sweden, which may not be applicable for treatments delivered under other circumstances.

5. Conclusions

We investigated how rectal volumes defined according to upcoming national guidelines differed from rectal volumes defined in clinical practice for patients treated with external beam radiation therapy for prostate cancer. On a group level, the clinical rectal volumes were larger than the volumes defined according to STRÅNG but the dose differences between them were small. This resulted in a limited impact on clinical decision making for the three investigated recommendations on DVH tolerance thresholds to keep risks of rectal toxicity low. For individual cases, however, the differences can be large enough to impact treatment planning and potentially treatment outcomes. The presented results can guide future studies regarding how to define organs at risk volumes for external beam radiation therapy and their relationships to the dose calculated in these volumes. Evaluation of compliance to guideline-directed OAR definitions could represent other future directions of this research.

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