Master's thesis

Motion and uncertainties management in intensity-modulated proton therapy for cervical cancer

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PREFACE AND ACKNOWLEDGMENTS

With this Master's thesis, my eight years journey at the Technical University of Delft comes to an end. After studying Life, Science and Technology for one year, I was happy to switch to the Bachelor Technical Medicine, because the clinical relevance of this multidisciplinary program and the link with the clinical practice excited me. However, I also realized that I had no idea what this bachelor's program would bring me as I was in the second cohort. It has been an amazing journey and I gained a lot of knowledge in the field that I love.

During the Radiation Therapy courses, given by my supervisor Jérémy, I was triggered by the fact that external-beam radiotherapy was able to treat cancer from the outside. During my internship at the Radiotherapy Department, I met the great multidisciplinary team and was fascinated by all the advanced modalities.

Therefore, I became interested in the present thesis project. This past year, I had the opportunity to work with the medical aspects in HollandPTC as well as technical aspects. I have enjoyed working on the project and I am glad that I could contribute to the improvements in the treatment of cervical cancer. I am really excited to work in a multidisciplinary environment as a Technical Physician and bring the technical and medical aspects together.

I would like to thank my supervisors Jérémy, Remi, Sander, and Rutger for providing me an opportunity to do my Master's Thesis at the Radiotherapy Department of the Erasmus MC and HollandPTC. I also would like to thank them for their guidance during my thesis, all the enthusiasm during the meetings, and their belief in me. Special thanks to Sander for the daily meetings, the great collaboration, and for working together on this amazing project!

Last but not least, I would also thank all my family and friends for always supporting me and making my time as a student unforgettable.

Eva Negenman
Rotterdam, September 2022

ABSTRACT

Purpose: Proton therapy has been proposed as an alternative to conventional photon therapy for the treatment of locally advanced cervical cancer (LACC) since these patients experience toxicities. Proton therapy may allow for significant sparing of the organs at risk, reducing the incidence of treatment-related morbidities. The aim of this study is to develop a treatment strategy that is robust to motion and uncertainties in intensity-modulated proton therapy (IMPT) for the treatment of LACC.
Materials and methods: Data from 14 LACC patients was included in this study. For each patient, a full and empty bladder planning CT (pCT) scans before treatment and four weekly repeat CT (reCT) scans after daily fraction were available. The full and empty pCT scans were used to create the patient-specific motion model of the cervix-uterus. An anisotropic CTV-to-ITV margin to expand this motion model was explored to account for uterine interfraction target motion. Subsequently, the motion model was divided into subranges to create a library of 1 to 4 plans, depending on the uterine motion due to bladder filling. Range and geometric uncertainties in the treatment of LACC are accounted for by robust optimization and evaluation. For each plan in the plan library, a treatment plan is created using the Erasmus-iCycle treatment planning system, taking into account EMBRACE-II constraints. To investigate whether the combination of margins, plan library, and robustness recipe is safe considering geometric and range uncertainties, ten treatments for each of the fourteen patients were simulated. These simulations were performed by recalculating the optimized treatment plans on the reCT scans with added uncertainties. We assumed that the target coverage was sufficient if the D95 of the target volumes was greater than or equal to 95% in at least 90% of the patients.
Results: Of the 3430 margin recipes that were tested, the margin recipe with >95% cervix-uterus overlap and the smallest target volume was 1, 5, 7, 3, and 3 mm in the left/right, posterior, anterior, cranial, and caudal directions, respectively. The subranges of the motion model were expanded with the anisotropic margin recipe, after which robust optimization (setup robustness 5 mm, range robustness 3%) and evaluation (32 scenarios) of the treatment plans were performed. The treatment simulations showed that the D95 was greater than 42.75 for 99% and 92% of the patients for the cervix-uterus target volume and nodal target volume, respectively.
Conclusion: The anisotropic margin and robustness recipe was robust to motion, geometric uncertainties, and range uncertainties when treating LACC patients with IMPT. Both values comfortably met the delivered dose criterion, indicating the strategy can be further improved.

Contents

INTRODUCTION

Cervical cancer is the most common gynecological cancer diagnosed worldwide with 604,000 new patients detected in 2020.[1] In the Netherlands, 800 women were diagnosed in 2020.[2] About half of these women are younger than 60 years, with 25% even younger than 45 years.[2] About 30% of women with cervical cancer are diagnosed with locally advanced cervical cancer (LACC) meaning the tumor is more than 4 cm or has grown into the tissue around the cervix, but has not spread out to any other organs.[3]

The current treatment for LACC consists of external beam radiotherapy (EBRT) using photons, combined with concurrent chemotherapy followed by brachytherapy.[4]

The Erasmus Medical Centre (Erasmus MC), participates in the International Study "Image guided intensity modulated External beam radiochemotherapy and MRI based adaptive Brachytherapy in locally advanced cervical cancer" (EMBRACE), initiated by the gynecological working group of the association of the Groupe Européen de Curiethérapie and the European Society for Radiotherapy and Oncology (GEC-ESTRO).[5] The study protocol consists of daily EBRT in 25 fractions (5 fractions per week) combined with five courses of concurrent chemotherapy (usually cisplatin (40mg/m2)).[6] These fractions are followed by three to four fractions of magnetic resonance imaging (MRI)-guided brachytherapy. This treatment has proven to be very effective, however toxicities remain.[7] In order to reduce toxicities, proton therapy has been proposed. This study will allow the clinical introduction of proton therapy for the treatment of LACC.

Background: Radiation therapy in LACC

Two types of radiation therapy are applied in the treatment of LACC, namely EBRT and brachytherapy.[6] In photon EBRT, the dose is delivered from the outside of the body using high-energy photons while in brachytherapy the radioactive source is placed inside and around the cervix. Brachytherapy is performed to give a higher local dose to the high-risk area.

External beam radiotherapy

With EBRT, the target volume is irradiated with 45 Gy in 25 fractions, so 1.8 Gy per fraction. If lymph nodes are involved, a simultaneous integrated boost (SIB) of 55 or 57.5 Gy in 25 fractions is administered. The EBRT techniques that are currently used in photon therapy are intensity-modulated radiotherapy (IMRT) and volumetric arc therapy (VMAT).

A challenge for accurate dose delivery in irradiating LACC patients is the large daily anatomic variations mainly caused by bladder filling.[8,9] Variations in bladder filling have a major impact on the shape and position of the cervix and uterus, and thus on the target volume.[10–12] Filling the bladder can cause the uterus to shift up to 15 mm and the cervix to shift up to 6 mm.[12] Such shifts may result in underdosage of the target volume. One solution to prevent this underdosage is to increase the irradiated volume. However, this also increases the proportion of healthy tissue within the irradiated volume, which potentially leads to an increase in morbidity.

The strategy used in the Erasmus MC to predict this cervix-uterus motion is the use of a three-dimensional patient-specific motion model.[9] This model predicts the shape and position of the uterus based on a full and empty bladder computed tomography (CT) scan. To create this model, the target volume is delineated on both CT scans. These CTs are rigidly matched on the pelvic bones. After bone matching, the deformation of this target volume between the full and empty bladder is determined using a non-rigid registration algorithm. This deformation is used to create the patient-specific motion model that can predict the position and shape of the target volume based on the bladder volume.

This model can be used to create a plan-of-the-day (PotD) library consisting of treatment plans that belong to a bladder volume range. The full range target volume is called the internal target volume (ITV) and can be divided into ITV subranges (subITV) belonging to a bladder volume range. This is an online adaptive strategy where the treatment plan is selected from a library of plans before each treatment.

The workflow for EBRT for LACC is illustrated in Figure 1.

Contouring and creation of planning volumes

For treatment planning, a diagnostic MRI scan is used in addition to the full and empty bladder CT scans. This MRI scan is used to identify the cervix-uterus target volume and is matched to the full bladder CT scan so that the delineated structures on the MRI scan can be used on the full bladder CT scan. All organs at risk (OARs) and target volumes are delineated on this full bladder CT scan. The empty bladder CT scan is also matched with the full bladder CT to create the patient-specific motion model.

The diagnostic MRI is also used to identify the pathological lymph nodes if present. This clinical target volume of the pathological lymph nodes (CTV_N) is again matched on the full bladder pCT scan used for treatment planning.

This nodal pathology determines to what level the LACC patient will be irradiated.[6] The nodal region is combined with the CTV_N to create the elective clinical target volume (CTV_E). This CTV_E is included in the treatment planning as the second target volume which also has a prescribed dose of 45 Gy. The prescribed dose for the CTV_N is either 55 or 57.5Gy by using SIB.

Treatment planning
A treatment planning system (TPS) is used to create a deliverable radiation distribution. The input for this TPS are the delineated structures (target volumes and OARs) and the planning goals for the target volumes and OARs. Using this input, the TPS calculates the weight of each radiation beam, which corresponds to the delivered dose. This treatment plan is optimized to fulfill all goals. For all subITVs in the plan library, a treatment plan is created.

Treatment delivery
The treatment plan is delivered in 25 fractions. Before each fraction, the patient follows the drinking instruction to have a full bladder during the irradiation. This full bladder is preferable to an empty bladder because the full bladder pushes the bowel out of the treatment field.[13] The patient is positioned in the supine position, as in the CT scans. The patient position is optimized by reducing the setup error based on the alignment between the pretreatment cone-beam CT (CBCT) and the pCT. This is done by moving the table or repositioning the patient. Based on this CBCT, a treatment plan is selected from the plan library and the dose is delivered to the patient.

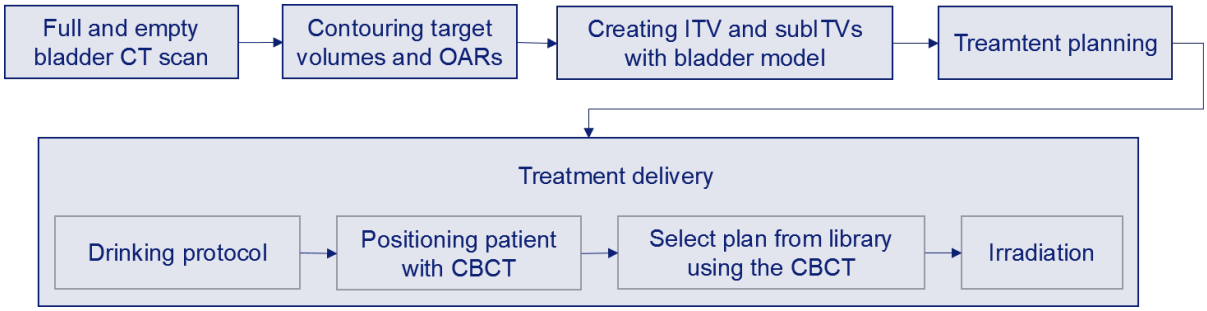

Figure 1: Workflow of external beam radiotherapy for locally advanced cervical cancer. CT = computed tomography, CBCT = cone-beam computed tomography, OARs = organs-at-risk, ITV = internal target volume, subITV = subrange ITV.

Brachytherapy

EBRT is followed by brachytherapy (BT) to deliver a higher local dose to the high-risk area (CTV_HR). The final dose of 21 Gy for CTV_HR is administered in three to four fractions.[6] A radioactive source is placed in or around the cervix using an inserted applicator and needles to deliver this high-dose-rate therapy. An MRI scan with the applicator in situ is used to create the daily treatment plan.

Toxicities in the treatment of LACC

This chemoradiation and brachytherapy have been shown to be effective with a good 5-year local control of 90.4% in LACC patients.[7] The 5-year pelvic control and cancer-specific survival are 85.3% and 70.2%, respectively.[7]

However, 70.3% of these patients suffer from some degree of toxicity, mainly involving the gastrointestinal and genitourinary tracts.[7] Because these patients are relatively young and have a high long-term survival rate after treatment, these toxicities have a serious impact on their quality of life.[14,15]

The combination of chemotherapy and radiotherapy also increases the risk of hematologic toxicity (HT).[16,17] Huang *et al.* observed HT grade 2 or higher in 69.5% of the cervical cancer patients undergoing chemoradiation.[18] Reduced overall survival and progression-free survival have also been associated with radiation-induced lymphopenia, which indicates a lower tumor control probability.[19–21] Besides a lower tumor control probability, a potential consequence of HT and lymphopenia is stopping or postponement of chemotherapy, as well as hospitalization or blood transfusion.[22,23]

To further spare OARs and reduce the risk and severity of toxicities, radiation techniques need to be improved. Proton therapy is a promising radiation modality that allows high localized dose deposition in the target volume while reducing the dose to the OARs.

Intensity-modulated proton therapy

Proton therapy allows for higher localized dose deposition in comparison with photon therapy. It takes advantage of the finite range of the protons and the sharp dose fall-off outside the target volume.[24] Several planning studies

have shown that proton therapy is able to cover the target while reducing the dose of the OARs in cervical cancer patients compared to IMRT and VMAT.[25,26]

Van de Sande *et al.* showed a 29% reduction in the Dmean (the mean dose in volume) of the pelvic bones and a 28% reduction in the V15 (volume receiving 15 Gy) of the bowel bag with intensity-modulated proton therapy (IMPT) compared with IMRT.[25] This reduction in dose in the OARs implies a decrease in radiation-related toxicity.

However, the actual reduction in toxicity by this sparing of OARs should be investigated in patients with LACC. The PROTECT study was designed to investigate the potential of IMPT to reduce the dose to the OAR and to determine the difference in treatment-related morbidity between IMPT and IMRT/VMAT in clinical practice in LACC patients undergoing chemoradiation.[27]

Uncertainties in proton therapy

The main challenge in proton therapy is the robust delivery of the dose to the target.

Proton therapy suffers from the same sources of uncertainties as conventional photon therapy, e.g., variations in delineation, patient movement, setup uncertainties, and imaging uncertainties.[28] However, dose delivery in proton therapy can be more concerning due to the additional range uncertainty since protons have a finite range and a sharp distal dose fall-off.[28] This range is highly dependent on the material the protons transverse. The position of the dose gradient is very important to achieve adequate target coverage. As a result of this sharp dose fall-off, even a motion a few millimeters can lead to underdosage in the target volume or overdosage in the OARs.[28]

There are several factors that lead to this range uncertainty. Some of these factors cause uncertainties in the range calculation in the TPS, such as inaccuracies in the conversion from the pCT Hounsfield units (HU) to proton stopping power, inaccuracies in the HU values, beam hardening, or noise.[28,29] Another factor leading to uncertainties in the calculation of this range is the inaccuracies resulting from the dose algorithm.

In addition, range uncertainties result from discrepancies between planned and delivered doses. Because the finite range of protons is highly dependent on the material they traverse, geometric changes can result in large dose discrepancies in the target volumes and surrounding OARs. Geometric changes such as the density heterogeneity relative to the proton beam and patient movement can cause these discrepancies.

In addition, the relative biological effectiveness (RBE) can cause differences between the planned and delivered doses.[30] The RBE value defines the ratio between the photon dose and the proton dose to achieve the same level of biological effect.[31] In current clinical practice, an RBE value of 1.1 is used for proton beams. However, since the properties of protons vary along the beam path, the RBE should also vary along this beam path.[31,32]

Because all of these factors affect the position of the sharp dose fall-off at the distal end of the Bragg peak, it is important to know precisely the sources and magnitudes of the uncertainties affecting the proton range in order to make plans that are robust to these uncertainties.

Strategies to address uncertainties

Strategies such as margins and robust optimization can provide practical solutions to these uncertainties.

The planned target volume (PTV) concept is used in conventional radiotherapy to account for motion and uncertainties. However, this PTV concept is not suitable for IMPT since the concept assumes invariance in the dose distribution under small shifts.[33–36]

Instead of the PTV concept, robust planning, consisting of robust optimization and evaluation, is now used in IMPT to ensure target coverage. In robust optimization, error scenarios are included in the optimization. These scenarios have setup robustness (SR) and relative range robustness (RR). The SR is simulated by shifting the isocenter of the beam and the RR is simulated by scaling the mass density of the patient.[37] The SR shift and RR scaling are often combined to create scenarios that have both setup and range errors.

Subsequently, these optimized plans are evaluated by recalculating the dose distribution in different scenarios.[37] In general, the same SR and RR are used in the evaluation as used for optimization, but more scenarios, i.e., shifts in more directions, are used.

A literature review conducted in December 2021 showed that there is limited research on the robustness settings and margins that should be used in clinical practice for IMPT to account for the motion and uncertainties in cervical cancer. This literature review can be found in Appendix A.

Goals and Objectives

The PROTECT trial aims to reduce the risk and severity of toxicities by using IMPT in the treatment of LACC. As IMPT for LACC needs to be implemented in clinical practice, treatment planning, optimization, and evaluation need to be investigated.

The goal of this study is to develop a treatment strategy is robust to motion and uncertainties in IMPT for the treatment of LACC. This is done by investigating what margins and robustness settings are required to account for these uncertainties.

IMPT for LACC involves irradiation of two target volumes, namely the cervix-uterus and the nodal region. The cervix-uterus is subject to more interfraction motion than the nodal region. However, the robustness settings cannot be different for each target volume due to the optimization function in the TPS. Using robustness alone requires consideration of the structure with the greatest motion and will be too conservative for the other target and therefore increases the dose to OARs. Therefore, we used the patient-specific motion model to predict the uterus shape and position.[9] A CTV-to-ITV margin for the motion model is explored to guarantee good target coverage.

Consequently, the study is divided into two successive parts. The first part focuses on finding an anisotropic margin recipe to account for the interfraction target motion of the cervix-uterus using the patient-specific motion model.

In the second part of this study, range and geometric uncertainties (including the interfraction motion of the nodal region) for both target volumes are addressed with robust planning. Treatment simulations are performed to test whether the combination of the margin and robustness recipe results in sufficient target coverage for motion, geometric uncertainties, and range uncertainties. These simulations also examine where underdosage and overdosage occur in the target volume so that improvements can be made to the margin and robustness recipe in future research.

METHODS

Patient data

The data of 14 LACC patients was included in this study. These patients were treated in the Leiden University Medical Center between April 2014 and March 2017 and their data was obtained for an institutional review board approved prospective study. For every patient, a full and empty bladder planning CT (pCT) scan prior to the treatment and an average of four weekly repeat CT (reCT) scans after daily fraction were available. All patients were treated with a comfortable full bladder. All scans were acquired with the Philips Brilliance Big Bore CT (installed in 2010) in supine position with a slice thickness of 3mm.

Target volumes and organs at risk

The contours of the target volumes and OARs of six patients (R06, R08, R10, R11, R13, R16) were available from a previously conducted study.[38] These contours were delineated by a radiotherapy technologist following the EMBRACE-II protocol and checked by an experienced radiation oncologist (Remi Nout (RN)).[6]

The delineation of the target volumes of the other eight patients was performed by Eva Negenman (EN) and Sander Kuipers (SK) using MiM Software (MIM Software Inc., version 7.1.6, Cleveland, OH). These delineations were checked by experienced radiation oncologists (Miranda Christianen (MC), Henrike Westerveld (HW), or RN).

The target volumes used in this study were the low-risk clinical target volume (CTV_T_LR) and the CTV_E. This CTV_T_LR included the entire uterus with a margin of 20 mm towards the vagina, the complete parametria bilaterally, any pathological lymph nodes in the parametrium, and the high-risk clinical target volume (CTV_T_HR). This CTV_T_HR consists of the initial gross tumor volume seen on MRI and the remaining cervix not infiltrated by the tumor.

The CTV_E included the nodal region with the assumed microscopic disease and included all pathological node volumes and the bilateral lymph node regions. The cranial border of the CTV_E depends on the classification of the patient based on their nodal pathology (intermediate or high risk). Patients with LACC are classified as intermediate except when they had more than one pathological node at common iliac or above, or more than three pathological lymph nodes.[6] For intermediate-risk patients, these lymph node regions consist of the common iliac, internal iliac, external iliac, obturator, and presacral regions. For high-risk patients, the para-aortic lymph node region was included in addition to these regions. The top border of this para-aortic lymph node region was at the level of renal veins and at least 3 cm cranial of the highest pathological node.[6]

The clinical delineations on the pCT of the CTV_N were used in this study. Because there was no information about the pathological lymph nodes on the reCTs, they were not delineated separately as CTV_N on the reCTs.

This study used the clinical OAR structures on the pCT. These OAR structures were reviewed by radiation oncologists for clinical treatment plans. The OAR structures included the bowel, sigmoid, bladder, rectum, and femoral heads in intermediate-risk patients. In addition to these structures, kidney structures were included in high-risk patients.

In addition, contrast and air within the GI-system, the bones, and the spinal cord were delineated on the pCT as these structures were used in treatment planning.

Generation of the ITVs

In accordance with the EMBRACE-II protocol,[6] an ITV was created to account for motion in CTV_T_LR due to bladder filling. This ITV was created using a patient-specific motion model.[9]

The full and empty bladder pCT scans were aligned on bony anatomy using rigid image registration within the clipbox. This clipbox extends from the pubic tubercle to the coccyx in the anterior-posterior direction, from the iliac crests in the left-right direction, and from the iliac crests to the lesser trochanter in the cranial-caudal direction (Figure 1 in Appendix B). This rigid image registration was used as the initial alignment for the non-rigid registration of the CTV_T_LR of the empty and full bladder pCT scan. Thin-Plate Spline was used as the non-rigid registration method that finds pairs of corresponding points between the surfaces of the structures.[39] These corresponding points were linearly fitted to create the patient-specific motion model and the cervix-uterus shape was defined from this model for every possible bladder volume.[9] This model was used as ITV and an example is shown in Figure 2. In the same way, the non-rigid registration algorithm was used to linearly fit the surface of the empty bladder to the full bladder and create a motion model for the bladder.

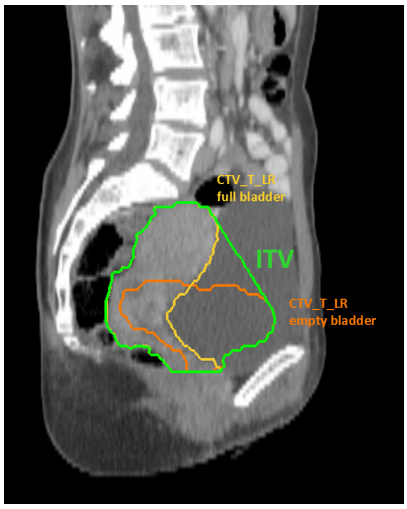

Figure 2: Sagittal view of the internal target volume (ITV) and the low-risk clinical target volume (CTV_T_LR) of the full bladder pCT and the registered empty bladder pCT of patient R06.

PART 1: UTERUS MARGIN RECIPE

This first part of the study examines the anisotropic margin recipe required around the ITV to account for interfraction target motion of the CTV_T_LR to ensure sufficient tumor coverage using the patient-specific motion model. To investigate this sufficient margin recipe, the ITV was expanded with several anisotropic margin recipes. Second, the expanded ITV was combined with the CTV_E to create the ITV45, i.e. the volume with a prescribed dose of 45 Gy. Third, the overlap of the CTV_T_LR of the reCTs by the ITV45 was determined. This ITV45 was used as a surrogate for the delivered dose. Therefore, it was assumed that if this overlap was sufficient, the target coverage would also be sufficient considering uterus motion. The steps are illustrated in Figure 3.
A previous study by Bondar *et al.* showed that an isotropic margin of 7 mm was required when using the patient-specific motion model to account for cervix-uterus motion.[40] We have chosen to test margin recipes up to about twice this 7 mm to ensure that margin recipes that provide sufficient coverage are not missed. To limit the number of options to be tested and still allow for a wide range of margin recipes, steps of 2 mm to the left, right, anterior, and posterior were used. In the cranial-caudal direction, 3 mm steps were used because the slice thickness in this direction is 3 mm. Because of this slice thickness, a smaller step size leads to the same results for intermediate values. In the caudal direction, a smaller range was tested because the interfraction motion in this direction is smaller compared to the other five directions.[41] In addition, the lateral movement was assumed to be nearly symmetrical, resulting in a symmetrical margin in the left-right direction in each margin recipe.

A total of 3430 margin recipes were tested:

- Left and right: [1, 3, 5, 7, 9, 11, 13]
- Anterior: [1, 3, 5, 7, 9, 11, 13]
- Posterior: [1, 3, 5, 7, 9, 11, 13]
- Cran: [3, 6, 9, 12]
- Cau: [0, 3]

Next, the expanded ITV and CTV_E were combined to create the ITV45 (Figure 3B). Although the anisotropic margin is only applied to expand the ITV, it is important to include the CTV_E in the overlap target volume as the CTV_E already contributes to the coverage of the CTV_T_LR in lateral directions. Therefore, a larger margin in lateral directions mainly provides a larger overlap of the ITV with the CTV_E without increasing the coverage of the CTV_T_LR.

Subsequently, the overlap of the CTV_T_LR of the reCTs by the ITV45 was calculated (Figure 3C). Rigid image registration was used to find the spatial relationship between the full bladder pCT and the reCT scan. The rigid transformation was used to register the CTV_T_LR from the reCT to the full bladder pCT.

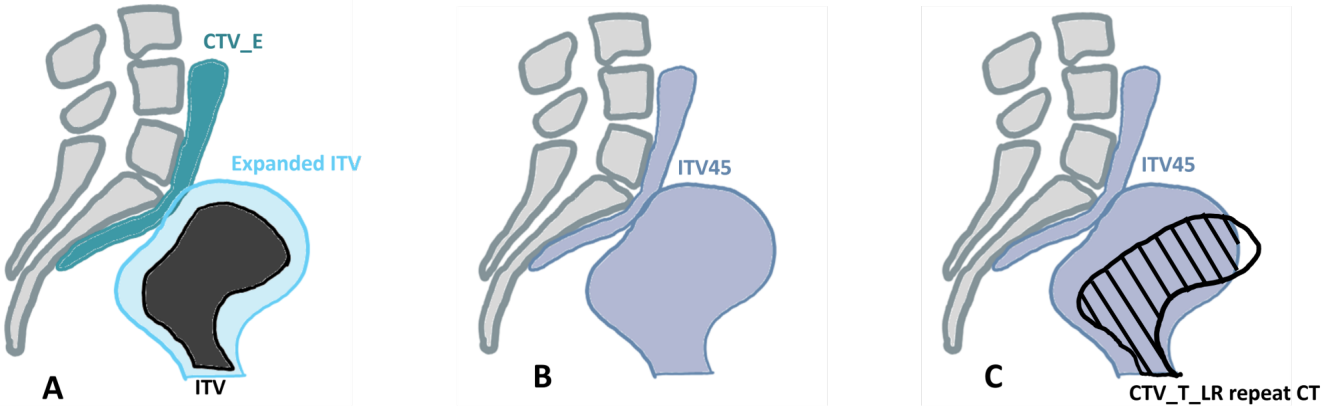

Figure 3: Schematic view of the first part of this study. A: Expand the ITV with an anisotropic margin recipe. B: Combine expanded ITV and CTV_E to create ITV45. C: Calculate the overlap (shaded area) of the CTV_T_LR of the reCTs by the ITV45.

Bladder volume of repeat CTs

The motion model of the cervix-uterus is not applicable when the bladder volume of the reCT is larger than the bladder volume of the full bladder pCT. Because the reCTs were acquired after the daily fraction (in some cases with a delay of up to one hour) without emptying the bladder, the bladder volume was sometimes much larger than the volume on the pCT. In clinical practice, the patient may be asked to empty the bladder if the bladder is foo full, followed by repositioning and irradiation. Another option in this full bladder situation could be to use a backup plan where the ITV is extrapolated to, for example, 150% of the full bladder volume. With these solutions, we see no need to consider these extreme conditions in the ITV margin. However, we do not want the above situation to occur too frequently as it increases procedure time. Therefore, only reCTs with a bladder volume greater than 133% of the bladder volume of the full bladder pCT were not considered in the margin and thus excluded from the study.

Conversely, the bladder volume of the reCT may be smaller than in empty bladder pCT. In this case, the motion model is also not valid. However, the only way to fill the bladder is to let the patient drink. Since this takes too much time in the clinical situation, the reCTs with a smaller bladder volume than the empty bladder pCT were included so that this situation is considered with the CTV-to-ITV margin.

Statistical analysis

The steps from Figure 3 were performed for all margin recipes, resulting in an overlap value for each reCT for all margin recipes. For each patient, the average overlap was calculated across the reCTs for each margin recipe. These average overlap values were analyzed and it was assumed that a margin recipe was sufficient if this overlap was at least 95% for 90% of the patients.

In addition to the average overlap, the average volume of the ITV45 (i.e. across all patients) was calculated for each margin recipe. The target volume to be irradiated (i.e. the ITV45) was attempted to be as small as possible to spare the OAR as much as possible. In the end, the margin recipe that provided sufficient tumor coverage and had the smallest ITV45 volume was selected for the second part of the study.

PART 2: ROBUST OPTIMIZATION AND TREATMENT SIMULATION

Plan library

For the treatment of LACC with photon therapy, a 2-plan library has been used in our institute since 2011 to reduce the dose to healthy tissue.[42] The dosimetric advantages of a PotD strategy encourage further development of this strategy. In 2017, Nováková *et al.* examined the optimal number of plans for individual cervical cancer patients.[43] The authors showed that patients with uterine movements (99th percentile of Hausdorff distance (HD)) greater than 20 mm benefited from the addition of an extra plan to the single plan library. A 3-plan library was advantageous when patients had large uterine motion (HD99 > 30 mm), and patients with extreme uterine motion (HD99 > 50 mm) could benefit from a library of 4 plans.[43]

In this study, the plan library proposed by Nováková *et al.* was used, except that the uterine tip movement was measured manually instead of calculating the HD99. This manual measurement was preferred to the HD99 because it is already used in the clinic in our institute. The cut-off values of Nováková *et al.* were used to determine the number of plans in the plan library and are shown in Table 1.

In addition to creating the subITVs for each patient, the corresponding bladder structures, e.g. a half-full bladder for a 2-plan library, were also created. These bladder structures were used in treatment planning.

Table 1: Number of plans in the plan library corresponding to the movement of the tip of the uterus. The last column indicates the bladder filling corresponding to the subrange ITV.

Tip of the uterus displacement	Number of subrange ITVs	Bladder filling
< 20 mm	1	0 to 100%
20 to 30 mm	2	Empty to 50% 50% to full
30 to 50 mm	3	Empty to 33% 33% to 66% 66% to full
> 50 mm	4	Empty to 25% 25% to 50% 50% to 75% 75% to full

For all 14 patients, the subITVs were generated according to Table 1. The selected margin recipe identified in the first part of this study was used to expand the subITVs. The each of the expanded subITV was combined with the CTV_E to create the ITV45 for each plan.

Treatment planning with Erasmus-iCycle

For each plan in the plan library, Erasmus-iCycle was used to create a treatment plan with robust optimization. After optimization, the plans were evaluated on the EMBRACE-II hard dose constraints using a 32 scenario evaluation method.[6] The Erasmus-iCycle algorithm, robust optimization and evaluation will be explained in the following paragraphs.

The in-house developed TPS Erasmus-iCycle,[44] which was extended with IMPT, was used to create treatment plans for all patients. Erasmus-iCycle performs multi-criteria optimization based on a so-called wish-list. In this wish-list, the clinical limits are set as constraints and the goals as prioritized objectives. These constraints are never violated, while the objectives are optimized one by one according to their priority. The next objective is optimized when the current objective is achieved and constrained. In this way, pareto-optimal plans are created taking into account the objectives in the wish-list.[44] This wish-list is defined by the user and can be used for an entire population group to automatically generate treatment plans.

In this study, pencil beam resampling was used as the planning method.[45] In this planning method, multi-criteria optimization is repeated, excluding spots with small contributions in each iteration and randomly selecting a new sample of candidate spots. In this way, more spot placements are possible than with a regular grid planning method.

Creating the Erasmus-iCycle wish-list

To enable automated treatment planning for LACC patients using Erasmus-iCycle for IMPT, a general wish-list was created for both patients with and without pathological lymph node involvement. The wish-list was created to fulfill the EMBRACE-II hard dose constraints[6] for the majority of patients.

These general wish-list was used to create treatment plans for the 14 patients and were optimized with minor adjustments when the constraints were not fulfilled in the evaluation. Two posterior oblique beams (150°and 210°) and two lateral beams (90°and 270°) were used.[26]

Treatment optimization

Robust optimization was performed with setup 5 mm SR, i.e. a vector length for the isocenter shifts was 5 mm, and 3% RR. Three percent range robustness was used in accordance with the literature and other tumor sites in our institution.[26,46,47] It was assumed that five millimeters setup robustness was sufficient to account for geometric uncertainties. Nineteen scenarios were optimized: one nominal plan, and six cardinal iso-center shifts combined with a -3%, 0%, and +3% range shift. Further optimization settings can be found in Table 1 in Appendix B.

A contrast agent was administered before the pCTs were acquired and resulted in high density values in the pCT. Therefore, the contrast in the bowel, rectum, and sigmoid was overwritten by the density of water (0 HU) during optimization. In addition to the contrast, the air pockets were overwritten with a value of -500 HU if they were larger than 1 cm in the direction of the beam. If less than 1 cm in beam direction, the air pockets were overwritten by a value of 0 HU (density of water). This air pocket overwrite was consistent with the clinical protocol used for esophagus cancer in HollandPTC. However, since all air pockets were delineated as one structure in each patient, all air pockets were overwritten with -500 HU if at least one pocket was larger than 1 cm in the beam direction.

Treatment evaluation

For the robust evaluation, a 5 mm SR was used in 14 directions (six cardinal directions and eight along the diagonal). A -3% or +3% RR in addition to the SR was used, resulting in 14 x 2 = 28 scenarios. Besides these 28 scenarios, the nominal scenario was evaluated. In these 29 scenarios, the contrast was still overwritten with the HU value of water, as in the optimization. The air pockets were overwritten similar to the treatment optimization phase. In addition to the 29 scenarios, an extra nominal scenario with original HU values for the air pockets was added to ensure that the plans were robust for air pockets.

From these 30 scenarios, the voxel-wise maximum was derived by combining the maximum dose values for each voxel in these 30 scenarios. The voxel-wise minimum was derived in the same way, but combining the minimum dose value for each voxel.[48,49] This results in 32 scenarios used in the evaluation.

The treatment plans were optimized until they reached the hard dose constraints of EMBRACE-II for the ITV, PTV, and OAR in the evaluation.[6] In addition to these constraints, the D50 (the dose received by 50% of the target volume) of the ITV45 had to be within a range of 45 ± 0.5 Gy. Since no PTV45 is used in our strategy, the EMBRACE-II constraints for the PTV45 were checked for the ITV45 in the voxel-wise maximum and voxel-wise minimum. Similarly, the PTV-N constraints were checked for the CTV_N in the voxel-wise scenarios. All constraints to be met in the evaluation are summarized in Table 2. Percentages in Table 2 are percentages of 45 Gy unless otherwise stated for lymph nodes and the Dmax and Dmin are D99.9 and D0.01, respectively.

After optimization and evaluation, the final treatment plans were scaled such that D95%= 95% of the prescribed dose (45 Gy) for the ITV45 at the voxel-wise minimum. This scaling is performed to achieve maximum OAR sparing consistent with EMBRACE-II recommendations.[6]

*Table 2: Constraints that had to be fulfilled in the evaluation of treatment plans. The PTV hard dose constraints from EMBRACE-II were transcribed into constraints for the ITV45 or CTV_N using the voxel-wise maximum and voxel-wise minimum.[6] The ITV45 consists of the expanded ITV and the CTV_E. Percentage of 45 Gy unless otherwise stated for lymph nodes. Dmax and Dmin are D99.9 and D0.01, respectively. *Not considered for intermediate-risk patients.*

		No lymph node involvement	Involved lymph nodes
Voxmin	**Target volume**	**ITV45**: V42.75 Gy > 95%	**ITV45**: V42.75 Gy > 95% **CTV_N**: D98% > 90% of prescribed LN dose
Voxmax	**Target volume**	**ITV45**: Dmax < 107%	**ITV45**: Dmax% ITV45 < 107% (for helper structure ITV45 – (PTV-N + 1 cm)) **CTV_N**: Dmax < 107% of prescribed LN dose
Nominal	**Target volume**	**ITV45**: Dmin > 95% **ITV45**: D50% = 45 ± 0.5 Gy	**ITV45**: Dmin > 95% **ITV45**: D50% = 45 ± 0.5 Gy
	OAR	**Bowel**: Dmax < 105% **Sigmoid**: Dmax < 105% **Bladder**: Dmax < 105% **Rectum**: Dmax < 105% **Spinal Cord**: Dmax < 48 Gy **Femoral heads**: Dmax < 50 Gy **Body**: Dmax < 107%	**Bowel**: Dmax < 105% in regions outside 10-15 mm from the CTV-N **Sigmoid**: Dmax < 105% in regions outside 10-15 mm from the CTV-N **Bladder**: Dmax < 105% in regions outside 10-15 mm from the CTV-N **Rectum**: Dmax < 105% in regions outside 10-15 mm from the CTV-N **Kidney**: Dmean < 15Gy* **Spinal Cord**: Dmax < 48 Gy **Femoral heads**: Dmax < 50 Gy **Body**: Dmax < 107%

Treatment simulation

In order to investigate whether the combination of the margin found in the first part of the study, the plan library, and the robustness recipe (5 mm SR and 3% RR) is sufficient taking into account geometric and range uncertainties, ten treatments per patient were simulated. Each treatment consists of 25 daily fractions, all with different daily anatomy and errors.

Treatment uncertainties

Realistic errors that may occur when treating LACC with IMPT were identified using literature and our knowledge of errors in other tumor sites treated at HollandPTC.

The systematic range underestimation arises from the conversion from the CT value to the proton stopping power using a Hounsfield look-up table. This method can not sufficiently deal with different tissues and inter-patient variability.[50] Wohlfahrt *et al.* showed that this conversion leads to a systematic underestimation of 1.7% ± 0.5% in prostate cancer using a dual-energy CT.[51] Since the tissues traversed by the beam are largely identical in prostate and cervical cancer, this 1.7% was assumed to be the systematic underestimation for our situation and the ± 0.5% the systematic uncertainty. Furthermore, an additional uncorrelated uncertainty in the prediction of stopping power of 0.7% is taken into account for the conversion from dual-energy CT to single-energy CT,[52] resulting in a total underestimation of 1.7% and a total systematic uncertainty of ±0.9%.

Geometric uncertainties mainly include organ movements and patient movements within the fraction, as well as uncertainties in patient setup, e.g. uncertainties in the couch position and isocentre offset. Variation in anatomy is accounted for by using reCTs in the treatment simulation. Intrafraction movement of prone positioned cervical cancer patients was assessed by Heijkoop *et al.* for an average time of 20.8 minutes.[53] The group mean intra-fraction movement was 0.1 ± 1.4, 1.8 ± 1.5 and -2.8 ± 1.8 mm in lateral, craniocaudal and dorsoventral directions, respectively. Since the expected treatment time in our institute is about 10 minutes, these values were divided by the square root of two. The geometric uncertainties in our institute have already been determined and it was assumed that these errors are normally distributed.[54] The range and geometric uncertainties are listed in Table 3.

Table 3: Range and geometric uncertainties considered in the treatment simulation.[51–54]

Range uncertainties (%)	**Systematic ± 1 SD**								
Stopping power prediction [51,52]	1.7 ± 0.9								
Geometric uncertainties (mm)	**Mean**			**Systematic ± 1 SD**			**Random ± 1 SD**		
	LR	**AP**	**CC**	**LR**	**AP**	**CC**	**LR**	**AP**	**CC**
CT isocenter[54]				± 0.5	± 0.5	± 0.5			
Isocenter gantry[54]							± 0.5	± 0.5	± 0.5
Couch[54]							± 0.5	± 0.5	± 0.5
Online matching[54]							± 0.5	± 0.5	± 0.5
Intra-fraction motion[53]	-0.1	0.8	0.3	± 0.9	± 0.4	± 0.3	± 1.0	± 0.8	± 0.7
Total	**-0.1**	**0.8**	**0.3**	**± 1.0**	**± 0.6**	**± 0.6**	**± 1.3**	**± 1.2**	**± 1.1**

Treatment simulation

One of the reCTs was randomly selected for each fraction to mimic the daily anatomy. A systematic range error, a random geometric error, and a systematic geometric error were sampled from the distributions created with the total values from Table 3 and were added to the reCT. The systematic errors were fixed throughout the treatment (i.e. for all 25 fractions), while the random errors varied per fraction.

After adding the errors to the reCT, the treatment plan was recalculated on this adapted reCT, resulting in a dose distribution for that fraction. These steps were repeated 25 times (25 fractions). Treatment simulation was repeated 10 times per patient, resulting in a total of 140 treatments. The flow diagram of the treatment simulation is shown in Figure 4.

Dose accumulation

The dose of both the CTV_T_LR and CTV_E was accumulated over the 25 fractions to simulate the total dose distribution administered to target volumes.

Registration was performed between the target volumes of pCTs and reCTs to be able to accumulate the dose of the 25 fractions. This registration consisted of a rigid pre-match (already performed in the first part of this study) and a non-rigid surface registration of the CTV_T_LR and CTV_E. Again, Thin-Plate Spline was used as non-rigid surface registration method.[9] With this non-rigid surface registration, both the surface points and the points within the structure were registered.

Following non-rigid registration, random sampling was performed on the pCT target volumes (i.e. CTV_T_LR and CTV_E). The point density of these sample points was 1.0 mm and the Hammersley sequence was used as the sampling method so that the sampling was deterministic.[44,55] Corresponding points to these sample points on the

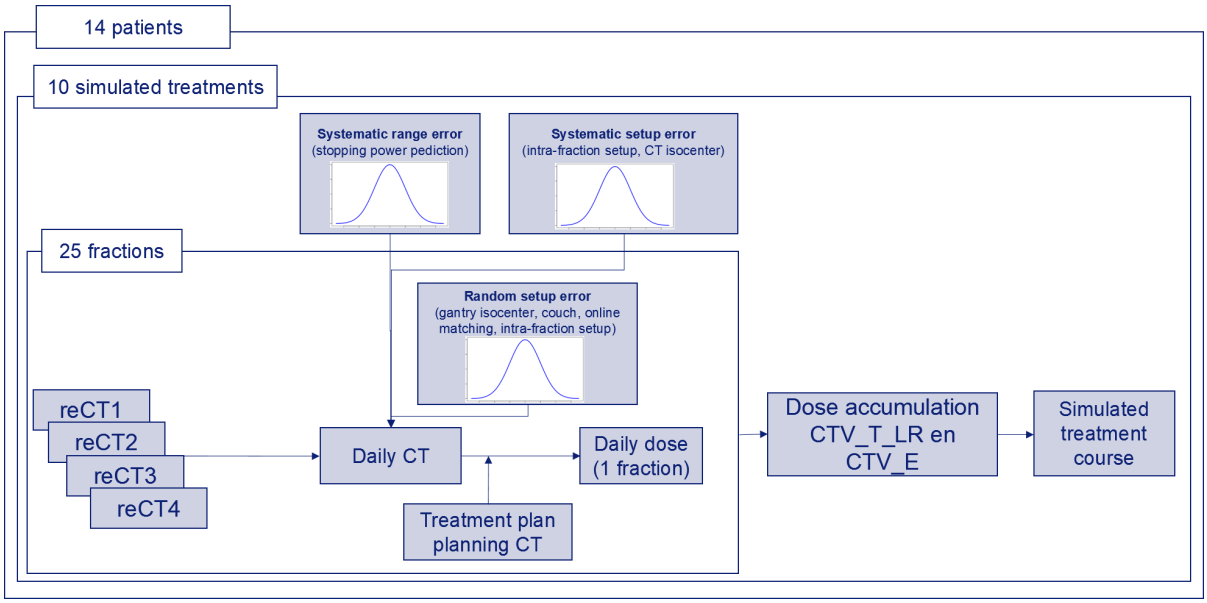

Figure 4: Flow diagram of the treatment simulations.

target volumes were found using the non-rigid registration. The recalculated dose at these corresponding points for each of the 25 fractions was mapped to the pCT sample points. These dose values were accumulated over the 25 fractions to obtain the total dose in each sample point.

The dose-volume histogram (DVH) and D95 were calculated of both target volumes for all 140 simulated treatments using this accumulated dose at all sample points. The 3D dose distribution of the two target volumes was also visualized to assess where underdosage or overdosage had occurred.

To summarize the results, the average DVH and average 3D dose visualizations of the ten treatments per patient were also examined by using the average dose at each sample point.

Statistical analysis

We assumed that the target coverage was sufficient if the ITV45 D95 on the voxel-wise minimum dose was greater than or equal to 95%. A pass rate of 90% of the patients is usually allowed for the delivered dose because the inclusion of all potential errors would result in too high robustness settings.[56] Therefore, we set D95 $\geq$ 95% of the target volume as the delivered dose criterion, which must be achieved by at least 90% of the patients.

To obtain insight into the dose distribution on the two target volumes of all simulated treatments, a population DVH was created. This population DVH consists of the mean of all treatment values for each sample point. In addition, the 10th percentile and 90th percentile of the dose values of each sample point were taken to be able to take the 90% pass rate into account.

Underdosage and overdosage in simulated treatments

The underdosage and overdosage were localized from visual inspection of the 3D dose distribution of the target volumes of the simulated treatments. Underdosage was defined as any part of the target volume receiving less than 95% of the prescribed dose, and overdosage as any part receiving more than 107% of the prescribed dose. By understanding where underdosage and overdosage occur, improvements to the margin and robustness recipe can be made to prevent these underdosages and overdosages. In addition, information on the location and identify the cause of the underdosage can help to create clinical decision tools to predict or prevent underdosage. Possible prediction tools for underdosage in the CTV_E and CTV_T_LR are described in the following sections.

Both target volumes were divided into three parts to indicate where the underdosage or overdosage occurs for cranial-caudal localization. The CTV_T_LR was divided into the cervix uteri, corpus uteri, and fundus uteri. The CTV_E was divided into low, intermediate, and high regions. This low region is the most caudal part of the CTV_E and includes the presacral, obturator, internal iliac, and external iliac regions. The intermediate part is the common iliac region up to and including the aortic bifurcation. And the high part, which is present only in high-risk patients, is the para-aortic region up to the most cranial part of the CTV_E. In addition to the cranial-caudal direction, the underdosage and overdosage localization was also determined in the anterior-posterior and left-right directions.

The severity according to the amount of dose received in the underdosage is also examined. This severity is divided into three degrees: + as it received less than 95% of the prescribed dose, ++ as it received less than 90% of the

prescribed dose, and +++ as it received less than 80% of the prescribed dose.

Prediction of underdosage CTV_E against vertebrae
From clinical experience, we know that patients can show a different relaxation of the pelvic muscles depending on their nervousness. This spine flexion results in a rotation of the pelvic bones with respect to the vertebral column. Since these pelvic bones are used for rigid matching between pCT and reCT, residual errors occur outside the pelvic region after registration. This can cause to underdosage in the CTV_E,[26] especially if the distance between the pelvic area and the target is larger.[57]

We used and compared three easy-to-use metrics to quantify this vertebral setup error, namely the error at the most cranial part of the CTV_E, at the middle of the fourth lumbar vertebra (L4), and the maximum error within the CTV_E. We expect the maximum error to best predict underdosage. However, this maximum metric is more difficult to apply clinically and is expected to be more sensitive to interobserver variability compared with the L4 metric because the L4 metric is measured at the same location in each patient. The most cranial metric was expected to be approximately equal to the maximum metric, as this point is farthest from the matched pelvic bones. We also expected less interobserver variability in the most cranial metric compared to the maximum metric, since it is clear where this metric should be measured. All metrics were measured in the sagittal slice at the middle of the vertebral column. For each metric, we count how often the value is equal to or greater than 5 mm to determine which of the metrics might predict underdosage in the CTV_E against the vertebrae.

Prediction of underdosage posterior part CTV_T_LR
Since underdosage in the posterior part of the CTV_T_LR means that there is an underdosage in the CTV_HR, it is important to prevent underdosage in this part of the CTV_T_LR. The rectum undergoes large density and volume changes between the fractions and largely overlaps with the beam path of the dose delivery to the posterior part of the CTV_T_LR. Because IMPT is sensitive to density changes along the beam path and variations in location, we expected that underdosages in this posterior part are due to differences in rectal filling between the pCT and reCTs.[35] The rectal filling is quantified by measuring the diameter of the rectum and estimating the HU value of the rectum from the pCT and reCT scans to examine the extent to which rectal density changes and rectal filling affect the target coverage. The method for these measurements is described in Appendix C.

RESULTS

Patient characteristics

For the 14 patients, full and empty bladder pCTs and reCTS were available, resulting in a total of 83 CTs included in this study. For patient R09, three CTs (two with full bladder and one with empty bladder) were acquired a few minutes apart because replanning was needed. These three replanning CT scans were included as reCTs in this study. Replanning CTs were also made for patient R05, after which three additional reCTs were acquired. These full and empty bladder replanning CTs were used as reCTs in this study, resulting in five reCTs for patient R05. For patient R08, the empty bladder CT scan was not available. Therefore, the reCT scan with the smallest volume of the bladder was used as the empty bladder CT scan.

The patients were diagnosed with FIGO 2018 (International Federation of Gynecology and Obstetrics) a stage between IB3 and IIIC2. Seven of the fourteen patients had pathological lymph nodes and six of these seven patients were classified as high-risk patients. Patient characteristics can be found in Table 4.

*Table 4: Patient characteristics of the 14 patients. HR = high risk, IR = intermediate risk. *Including the full and empty replanning CTs. ** The repeat CT scan with the smallest volume of the bladder was used as empty bladder CT scan.*

	R01	R04	R05	R06	R07	R08	R09	R10	R11	R13	R14	R15	R16	R17
Age	75	29	89	49	46	54	54	35	50	45	47	75	45	63
Histology	PCC	PCC	AC	PCC	PCC	AC	PCC	PCC	PCC	AC	ASC	PCC	ASC	PCC
Tumor size [mm]	48	40	32	30	45	63	70	44	47	45	50	75	58	30
TNM Stage (radiological)	T2BN1M0	T3bN1M0	T2bN0M0	T2bN0M0	T4N1M0	T2bN0M0	T3bN1M0	T2bN0M0	T1b3N0M0	T2a1N1M0	T4N1M0	T2bN0M0	T1b2N1M0	T2aN0M0
T-stage (clinical)	T3b	T2a2	T2b	T2a1	T2b	T2b	T3b	T2b	T1b2	T2a1	T2b	T2b	T1b2	T21
FIGO 2018	IIIC1	IIIC2	IIA2	IIA1	IIIC2	IIA2	IIIC2	IIA2	IB3	IIIC2	IIIC1	IIB	IIIC1	IIA
Nodes dose level 55 Gy	1	7	0	0	2	0	4	0	0	1	3	0	0	0
Nodes dose level 57.5 Gy	1	0	0	0	1	0	1	0	0	0	2	0	3	0
Risk group	HR	HR	IR	IR	HR	IR	HR	IR	IR	IR	HR	IR	HR	IR
Cycles of chemotherapy	6	6	5	6	6	6	6	6	6	5	5	5	5	5
# reCTs	4	4	5*	4	4	3**	3	4	4	4	4	4	4	4

Target volumes and organs at risk

The target volume delineations were improved mainly on the following points: inclusion of bone in the target volumes, inclusion of muscle in the target volumes, inclusion of the bladder in the CTV_T_LR, inclusion of the sigmoid and/or (meso)rectum in the CTV_T_LR, no inclusion of the parametria in the CTV_T_LR, inclusion of the ovaries in the CTV_T_LR, and inclusion of the ureter in the CTV_E. Three examples of delineation improvements are shown in Figure 1 of Appendix D.

PART 1: UTERUS MARGIN RECIPE

Bladder volume of repeat CTs

In 4/55 (7.3%) of the reCTs, the bladder volume was more than 133% of the bladder volume of the full bladder pCT. These four reCTs were excluded from the study. The bladder volumes of all pCTs and reCTs of all 14 patients are shown in Table 5.

Anisotropic margin recipe

A total of 3430 margin recipes were tested, of which 376 recipes had sufficient overlap, meaning that the ITV expanded with this recipe covered at least 95% of the CTV_T_LR volume (average of a patient's reCTs) in at least 90% of the patients. The five margin recipes with sufficient overlap and the smallest ITV volume (average of all patients) are listed in Table 6. Due to noise in the algorithm that calculates the overlap, the overlap can be greater than 100%.

Table 6 shows that 95% coverage was not achieved for patient R01. This is mainly due to the overlap of the second reCT (72.3% overlap for the first option). Different views of this patient are shown in Figure 2 in Appendix D. Because 95% coverage had to be achieved in at least 90% of the patients, this lower overlap was accepted for patient R01.

The margin with the smallest average ITV volume is selected and used in the second part of this study. This margin was 1, 5, 7, 3, and 3 mm in the left/right, posterior, anterior, cranial, and caudal directions, respectively.

*Table 5: Bladder volumes (ml) of the full and empty bladder pCTs and reCTs of the 14 patients. The red colors indicate that the bladder volume is larger than the full bladder pCT and the blue colors indicate that the bladder volume is smaller than the empty bladder pCT. *Volume is more than 133% of the bladder volume of the full bladder pCT.*

	R01	R04	R05	R06	R07	R08	R09	R10	R11	R13	R14	R15	R16	R17
Full bladder pCT	379	446	390	721	263	160	253	192	566	245	342	341	274	494
Empty bladder pCT	89	73	55	27	62	38	48	41	40	133	76	42	90	48
reCT1	388	200	57	458	129	-	119	389*	638	113	205	157	436*	115
reCT2	486	136	228	54	275	358*	121	137	538	218	216	375	128	256
reCT3	763*	128	391	325	130	161	56	118	506	75	183	174	242	274
reCT4	466	217	143	378	77	58	-	134	305	85	178	92	151	182
reCT5	-	-	147	-	-	-	-	-	-	-	-	-	-	

Table 6: The five margin recipes in mm with sufficient CTV_T_LR overlap and the smallest ITV volume (average of all patients) ordered by their average ITV volume. Pos = posterior, Ant = anterior, Cra = cranial, Cau = caudal. Heatmap colors: The more red the color of the percentage, the smaller the CTV_T_LR overlap.

Left /right	Pos	Ant	Cra	Cau	Volume ITV (ml)	Rel. increase in volume ITV (%)	Average overlap of CTV_T_LR volume (%)													
							R01	R04	R05	R06	R07	R08	R09	R10	R11	R13	R14	R15	R16	R17
1	5	7	3	3	472.6	0.0	88.8	97.7	97.4	98.9	99.5	99	98.5	95.3	95.9	96.4	99.2	100.5	95	98.2
1	3	9	3	3	475.6	0.6	87	95.8	97.3	98.4	99.5	99.1	99.4	95.7	95.6	97.1	99	100.5	95.2	97.4
1	5	9	3	0	479.5	1.4	85.8	96.6	96	98.5	99.4	99.1	99.4	95.7	95.3	96.9	99.3	100.2	95	96.4
3	5	7	3	3	485.6	2.8	89	97.7	97.5	99	99.7	99.1	98.5	95.5	96	96.5	99.3	100.5	95	98.5
1	7	7	3	3	485.8	2.8	90.7	99	97.8	99.3	99.7	99.1	98.5	95.5	96	96.4	99.6	100.5	95.2	98.7

PART 2: ROBUST OPTIMIZATION AND TREATMENT SIMULATION

Plan library

The PotD protocol developed by Nováková *et al.* with the adjustment of manual measurement instead of HD99 was applied to the data set of the 14 patients. Eight of the fourteen (57%) patients have uterine movement < 20mm, resulting in a 1-plan library. None of the patients have a 2-plan library, while four patients (29%) have a 3-plan library. Two patients (14%) had extreme uterine motion (>50mm), hence a 4-plan library. Table 7 shows the movement of the tip of the uterus, the corresponding plan library, and the corresponding plan for each reCT. The corresponding plan was selected by the subITV that most overlaps the CTV_T_LR.

*Table 7: Overview of the movement of the uterus per patient resulting in a number of plans in the plan library and the corresponding plan for each reCT. *Volume is more than 133% of the bladder volume of the full bladder pCT, so the reCT is excluded from the study.*

		R01	R04	R05	R06	R07	R08	R09	R10	R11	R13	R14	R15	R16	R17
Movement uterustip (mm)		13	20	35	92	62	10	12	38	42	6	4	10	20	38
Number of plans in library		1	1	3	4	4	1	1	3	3	1	1	1	1	1
Plan repeat CT	reCT1	1	1	1	4	3	1*	1	3*	3	1	1	1	1*	1
	reCT2	1	1	3	1	4	1	1	3	3	1	1	1	1	2
	reCT3	1*	1	3	3	2	1	1	1	3	1	1	1	1	3
	reCT4	1	1	2	4	1	-	-	1	2	1	1	1	1	2
	reCT5	-	-	2	-	-	-	-	-	-	-	-	-	-	-

Treatment planning with Erasmus-iCycle

Wish-list for LACC patients
The general wish-list for LACC patients with and without lymph node involvement was developed to enable treatment planning with Erasmus-iCycle. This general wish-list is shown in Table 8.

*Table 8: General wish-list for patients with lymph node involvement. *In regions outside 10 mm from the PTV-N for patients with lymph node involvement. † = constraints only for patients with lymph node involvement. ITV_shell = shell of 1 mm around the ITV45, PTV45 = ITV45 + margin of 10 mm, ITV45_ring10-15mm = ring structure around the ITV from 10 to 15 mm, CTVN_5500 = clinical target volume of all nodes with prescribed dose of 55 Gy, CTVN_5750 = clinical target volume of all nodes with prescribed dose of 57.5 Gy, PTVN_5500 = CTVN_5500 + margin of 5 mm, PTVN_5750 = CTVN_5750 + margin of 5 mm*

Constraints					
	Volume	Min/max	Type	Limit in Gy (% of pre. dose)	Robust
	ITV45*	Minimum	Linear	42.75 (95%)	Yes
	ITV_shell	Minimum	Linear	42.75 (95%)	Yes
	Bowelbag*	Maximum	Linear	46.80 (104%)	No
	Sigmoid*	Maximum	Linear	46.80 (104%)	No
	Rectum*	Maximum	Linear	46.80 (104%)	No
	Bladder*	Maximum	Linear	46.80 (104%)	No
	CTVN_5500 †	Minimum	Linear	56.1 (102%)	No
	CTVN_5750 †	Minimum	Linear	58.65 (102%)	No
	CTVN_5500 †	Minimum	Linear	50.6 (92%)	Yes
	CTVN_5750 †	Minimum	Linear	52.9 (92%)	Yes
	PTVN_5500 †	Maximum	Linear	58.6 (106%)	Yes
	PTVN_5500 †	Maximum	Linear	60.95 (106%)	Yes
Objectives					
Priority	Volume	Min/max	Type	Goal in Gy (% of pre. dose)	Robust	Parameter
1	PTV45*	Maximum	Linear	47.25 (105%)	Yes	
2	ITV45*	Maximum	QUOP	0.5	No	45.9 1
3	ITV45*	Maximum	QUOP	0.5	No	45.0 -1
4	ITV45_ring10-15mm	Maximum	Linear	45 (100%)	No	
5	Bowelbag	Maximum	Mean	5	No	
	Rectum	Maximum	Mean	10	No	
6	Sigmoid	Maximum	Mean	10	No	
	Bladder	Maximum	Mean	10	No	
7	WholeBone	Maximum	Mean	15	No	
8	Kidney_L	Maximum	Mean	0.5	No	
	Kidney_R	Maximum	Mean	0.5	No	
9	SpinalCord	Maximum	Linear	5	No	
10	Femoral heads	Maximum	Linear	10	No	
11	MU	Maximum	Linear	1	No	

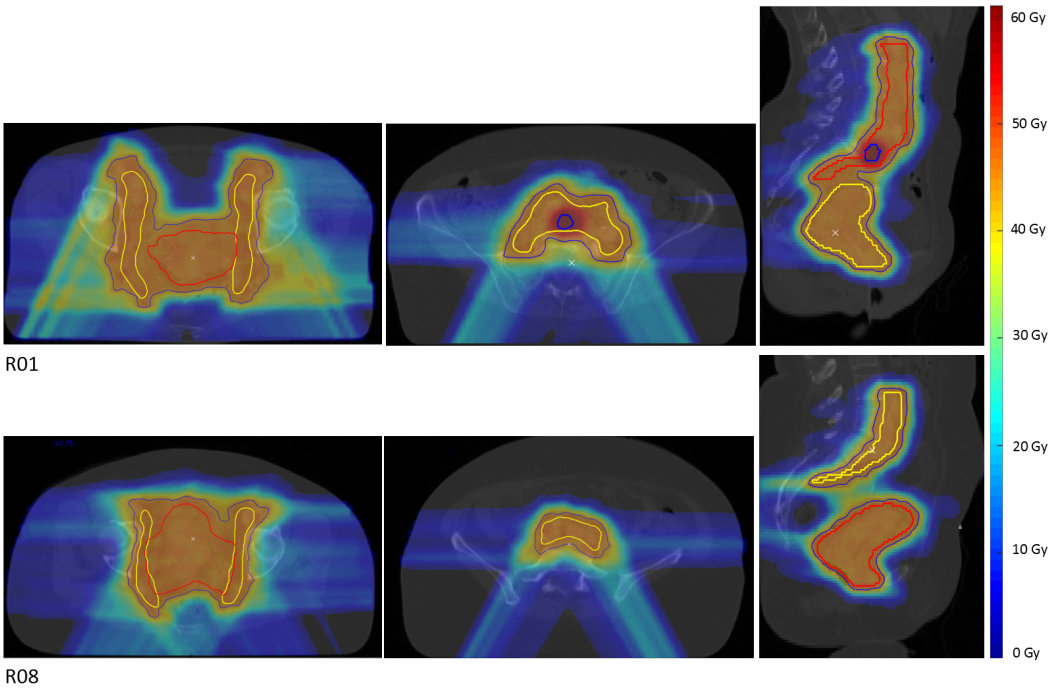

Figure 5: Example of the treatment plans for patient R01 (with lymph node involvement) and R08 (without lymph node involvement).

Treatment optimization and evaluation

All patients had an air pocket larger than 1 cm, resulting in an air override of -500 HU for all air pockets in all patients. The diameter of the air pockets ranged from 11 to 36 mm in the beam direction. The largest diameter per patient is summarized in Table 1 in Appendix D.

Treatment plans were created for each plan in the plan libraries of the 14 patients with Erasmus-iCycle. The plans were created using the general wish-list from Table 8. Minor adjustments to the general wish-list, such as a minimum dose of 96%, were required to meet the EMBRACE-II constraints from Table 2 in the robust evaluation for some patients.

The dose distributions of the nominal scenario of patient R01 (no lymph node involvement) and patient R08 (lymph node involvement) are shown in Figure 5. The dose values of the target volumes of all treatment plans are shown in Table 9, and the dose values for the OARs can be found in Table 2 in Appendix D.

*Table 9: Dose values in gray of the target volumes of the treatment plans used in the simulation. *First value is for the boost area with a prescribed dose of 55 Gy, and the second value is for the boost area with a prescribed dose of 57.5 Gy.)*

	Constraint (Gy)	Plan	R01	R04	R05	R06	R07	R08	R09	R10	R11	R13	R14	R15	R16	R17
ITV45 D95% (voxmin)	>42.75	1	42.75	42.75	42.75	42.75	42.75	42.75	42.75	42.75	42.75	42.75	42.75	42.75	42.75	42.75
		2	-	-	42.75	42.75	42.75	-	-	42.75	42.75	-	-	-	-	42.75
		3	-	-	42.75	42.75	42.75	-	-	42.75	42.75	-	-	-	-	42.75
		4	-	-	-	42.75	42.75	-	-	-	-	-	-	-	-	-
ITV45 Dmax (voxmax)	<48.15	1	47.74	47.97	47.22	47.47	48.00	47.75	47.32	47.28	47.47	47.55	47.71	47.32	48.05	47.89
		2	-	-	47.26	47.38	47.91	-	-	47.30	47.53	-	-	-	-	48.06
		3	-	-	47.23	47.31	47.77	-	-	47.29	47.21	-	-	-	-	47.78
		4	-	-	-	47.24	47.67	-	-	-	-	-	-	-	-	-
ITV45 Dmin (nominal)	>42.75	1	43.24	43.28	43.26	43.30	43.41	43.33	43.31	43.35	43.32	43.26	43.23	43.20	43.32	43.43
		2	-	-	43.28	43.27	43.36	-	-	43.35	43.34	-	-	-	-	43.40
		3	-	-	43.21	43.19	43.40	-	-	43.33	43.24	-	-	-	-	43.43
		4	-	-	-	43.26	43.33	-	-	-	-	-	-	-	-	-
ITV45 D50% (nominal)	45±0.5	1	44.85	44.94	44.82	44.91	45.02	45.03	44.79	44.87	44.90	44.81	44.88	44.87	44.98	45.12
		2	-	-	44.82	44.84	44.98	-	-	44.86	44.88	-	-	-	-	45.09
		3	-	-	44.77	44.81	44.93	-	-	44.85	44.77	-	-	-	-	45.05
		4	-	-	-	44.76	44.94	-	-	-	-	-	-	-	-	
CTVN D98% (voxmin)	>49.5 or >51.75*	1	50.35, 52.35	49.59	-	-	50.66, 51.95	-	50.17, 52.11	-	-	50.04	50.36, 51.79	-	49.77, 52.54	-
		2	-	-	-	-	50.95, 52.47	-	-	-	-	-	-	-	-	-
		3	-	-	-	-	50.47, 52.23	-	-	-	-	-	-	-	-	-
		4	-	-	-	-	50.76, 52.70	-	-	-	-	-	-	-	-	-
CTVN Dmax (voxmax)	<58.85 or <61.53*	1	58.35, 61.21	58.63	-	-	58.38, 60.88	-	58.44, 61.06	-	-	57.59	58.14, 61.13	-	58.05, 61.26	-
		2	-	-	-	-	58.17, 60.84	-	-	-	-	-	-	-	-	-
		3	-	-	-	-	58.27, 60.47	-	-	-	-	-	-	-	-	-
		4	-	-	-	-	58.14, 60.87	-	-	-	-	-	-	-	-	-
CTVN D98% (nominal)	>55 or >57.50*	1	55.38, 57.93	55.35	-	-	55.66, 58.03	-	55.58, 57.91	-	-	55.58	55.32, 57.84	-	55.58, 58.15	-
		2	-	-	-	-	55.65, 58.09	-	-	-	-	-	-	-	-	-
		3	-	-	-	-	55.55, 57.86	-	-	-	-	-	-	-	-	-
		4	-	-	-	-	55.54, 58.11	-	-	-	-	-	-	-	-	-

Treatment simulation

Ten treatments per patient were simulated, taking into account geometric uncertainties and range uncertainties. The D95 values of the 140 simulated treatments ranged from 42.7 to 44.2 Gy for the CTV_T_LR and from 38.4 to 44.1 Gy for the CTV_E. The D95 values per patient (mean, minimum, and maximum values of the ten treatments) are shown in Table 10. The D95 value for each individual simulated treatment is shown in Tables 3 and 4 in Appendix D.

In 139/140 (99%) simulated treatments, 95% of the volume of the CTV_T_LR received more than 42.75 Gy. Only in the third treatment of patient R10, the CTV_T_LR received less than 42.75 Gy (42.7 Gy). In eleven other simulated treatments, the D95 of the CTV_E was less than 42.75 Gy, namely in all treatments of patient R09 (D95 ranged from 38.4 to 40.1 Gy) and in the third treatment of patient R08 (42.7 Gy). In the other 129/140 (92%) treatments, the D95 was greater than 42.75 Gy. The dose population histograms of the simulated treatments are shown in Figure 6. As shown in Table 10 and Figure 6, the delivered dose criterion of D95 $\geq$ 95% in 90% of the patients is met for both target volumes.

Table 10: Average, minimum, and maximum D95 values of the target volumes of the simulated treatments per patient. Values below 42.75 are shown in bold.

		R01	R04	R05	R06	R07	R08	R09	R10	R11	R13	R14	R15	R16	R17	Total
CTV_T_LR	Mean (Gy)	43.5	43.5	43.9	43.6	43.8	43.8	44	43.1	43.5	43.4	43.7	43.7	43.5	44	43.6
	Min (Gy)	43.1	43.2	43.7	43.2	43.4	43.5	43.7	**42.7**	43	43	43.5	43.4	43.4	43.7	42.7
	Max (Gy)	43.7	43.7	44.1	43.8	44.1	44.1	44.2	43.4	43.6	43.6	43.8	436	43.7	44.2	44.2
	Percentages treatments D95 > 42.74	100%	100%	100%	100%	100%	100%	100%	90%	100%	100%	100%	100%	100%	100%	99.3%
CTV_E	Mean (Gy)	43.8	43.2	43.9	43.6	43.7	43.3	**39.3**	43.7	43.7	43.8	43.6	43.6	43.9	44.1	43.4
	Min (Gy)	43.7	42.8	43.7	43.4	43.4	**42.7**	**38.4**	43.3	43.4	43.6	43.4	43.3	43.6	43.9	38.4
	Max (Gy)	44	43.5	44.1	43.7	43.8	43.6	**40.1**	43.9	43.9	43.9	43.6	43.8	44.1	44.1	44.1
	Percentages treatments D95 > 42.74	100%	100%	100%	100%	100%	90%	0%	100%	100%	100%	100%	100%	100%	100%	92%

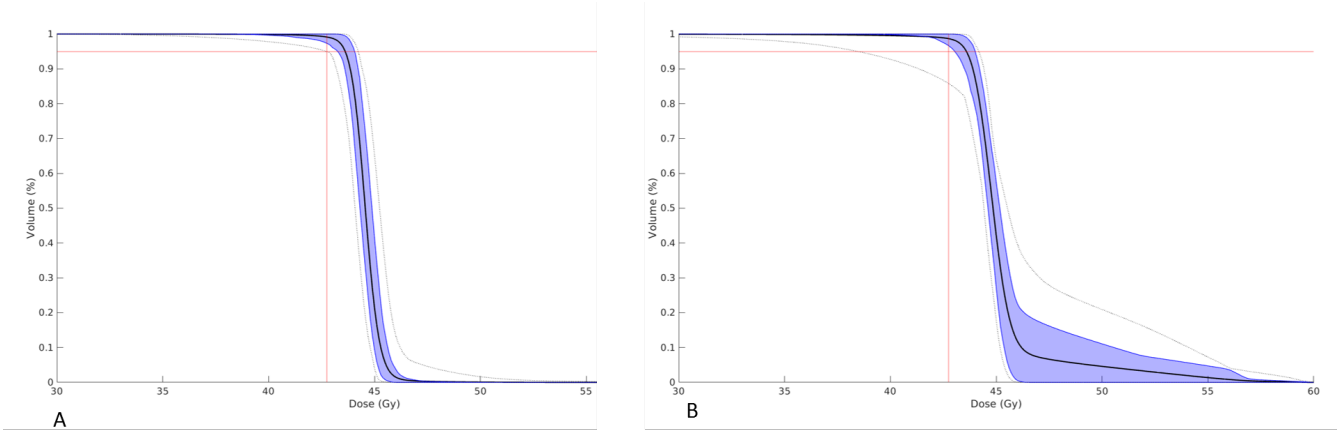

Figure 6: Population DVH for the CTV_T_LR (A) and CTV_E (B). Dotted lines indicating the lowest and highest dose value of each sample point, blue lines indicating the 10th and 90th percentile of the dose value for all sample points, black line indicating the average dose value, red horizontal line indicating 95% of the volume, red vertical line indicating 95% of the prescribed dose.

Underdosage and overdosage in simulated treatments

Although the delivered dose criterion was met for both target volumes, implying that the underdosage and overdosages were not clinically relevant, the underdosages and overdosages were identified and localized using the 3D dose distributions of the target volumes. With the identification and localization of these underdosage and overdosage, improvements to the margin and robustness recipe can be made and clinical decision tools can be created.

Underdosage occurred in 7/14 patients in the CTV_T_LR and 5/14 patients in the CTV_E. No overdosages were observed in the target volumes. The locations of the underdosages are listed in Table 11. The visualizations of the underdosages in Table 11 and an explanation for the occurrence of these underdosages can be found in Appendix E.

The posterior part of the cervix or corpus uteri received less than 42.75 Gy in three patients. Figure 7 shows the dose distribution in the target volumes of patient R06, including the underdosage in the posterior part of the cervix

uteri. Only the dose inside the target volumes were calculated. Therefore only the dose inside the target volume is visualized in this figure. So, this figure does not represent the dose distribution outside of the target volumes.

The most frequently observed underdosage in the CTV_E was underdosage against the vertebral column. In patient R09, this underdosage was so severe that part of the CTV_E received only 50% of the prescribed dose. Figure 8 shows this underdosage in patient R09. This figure also shows only the dose distribution inside the target volume.

Table 11: Location of the underdosages for the CTV_T_LR and CTV_E. + = received less than 95% of the prescribed dose. ++ = received less than 90% of the prescribed dose, +++ = received less than 80% of the prescribed dose.

		R01	R04	R05	R06	R07	R08	R09	R10	R11	R13	R14	R15	R16	R17
CTV_T_LR	Fundus									Cranial (+)					
	Corpus		Posterior (+)						Anterior (+++)		Anterior (+)			Anterior (++)	
	Cervix	Posterior (++)			Posterior (+)										
CTV_E	Risk group	HR LN	HR LN	IR LN	IR LN	HR LN	IR LN	HR LN	IR LN	IR LN	IR LN	HR LN	IR LN	HR LN	IR LN
	High		Against vertebrae (++); Coldspots (+)			Against vertebrae (++)		Against vertebrae (++)				Coldspots (+)			
	Intermediate						Coldspots (+)	Against vertebrae (+++)							
	Low						Coldspots (+)	External iliac artery (+++)							

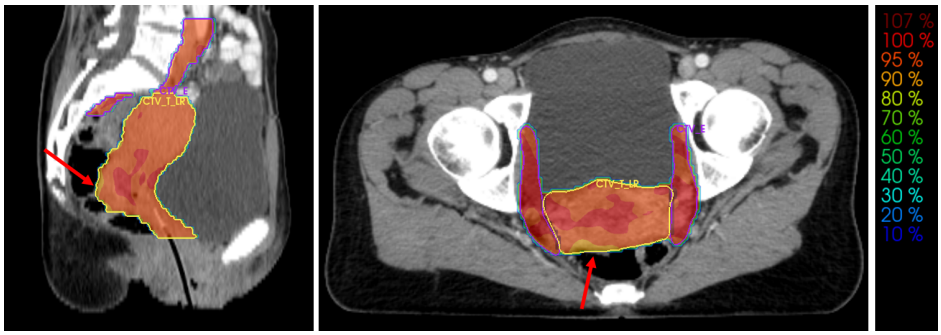

Figure 7: Underdosage in the posterior part of the cervix uteri in patient R06. Red arrow indicates the underdosages. Only the dose distribution inside the target volume is visualized and therefore this does not represent the dose distribution outside of the target volumes.

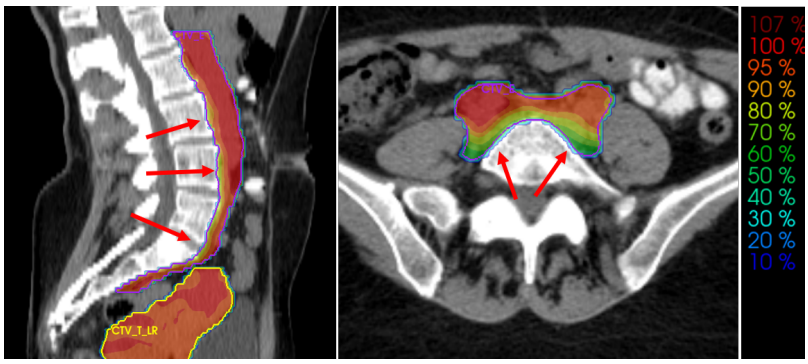

Figure 8: Underdosage in the CTV_E located against the vertebral column in patient R09. Red arrow indicates the underdosages. Only the dose distribution inside the target volume is visualized and therefore this does not represent the dose distribution outside of the target volumes.

Prediction of underdosage CTV_E against vertebrae

In the visualization of the match of the pCT and reCT, the three metrics were measured in all patients. The values of the three metrics are shown in Table 12. The values of 5 mm or more (shown in bold) are counted and listed in the bottom row.

The L4 metric and most cranial metric in patient R04 was $\geq$ 5 mm for one quarter of the reCTs, whereas the maximum error was $\geq$ 5 mm for 75% of the reCTs. In patient R07, the L4 error did not exceed 5 mm in any of the reCTs, whereas the maximum error and most cranial metric was $\geq$ 5 mm in three of the four reCTs.

All metrics showed only values $\leq$ 5 mm for all reCTs of patients R01, R05, R06, R08, R10, R15, and R17. For patients R11, R13, R14, and R16, the maximum and most cranial error were $\geq$ 5 mm in 25% or 33% of the reCTs, whereas the L4 error was $\geq$ 5 mm in none of the reCTs for patients R14 and R16.

*Table 12: Metric values of the vertebral column after bone matching. Bold = error $\geq$ 5 mm. *reCT not used in the simulation.*

		R01	R04	R05	R06	R07	R08	R09	R10	R11	R13	R14	R15	R16	R17
		HR	HR	IR	IR	HR	IR	HR	IR	IR	IR	HR	IR	HR	IR
reCT1	Error L4	0	**5**	0	2	0	*	**20**	*	0	0	2	2	*	3
	Most cranial	1	1	0	2	**5**		**7**		0	0	4	2		3
	Max error	1	**7**	0	2	**5**		**20**		0	3	4	2		3
reCT2	Error L4	0	3	0	4	1	1	**15**	0	4	3	2	4	0	4
	Most cranial	0	**12**	0	4	**6**	3	**6**	0	4	3	**5**	4	0	4
	Max error	0	**12**	0	4	**6**	3	**18**	0	4	3	**5**	4	0	4
reCT3	Error L4	*	3	0	4	0	0	**13**	3	**5**	4	0	3	4	0
	Most cranial		4	0	4	2	1	**5**	3	**5**	4	0	3	3	0
	Max error		**5**	0	4	2	1	**15**	3	**5**	4	0	3	4	0
reCT4	Error L4	0	2	1	1	0	-	-	1	0	**6**	0	2	4	3
	Most cranial	0	0	1	1	**6**			1	0	**6**	0	2	**5**	3
	Max error	0	3	1	1	**6**			1	0	**6**	0	3	**5**	3
reCT5	Error L4	-	-	0	-	-	-	-	-	-	-	-	-	-	-
	Most cranial			0											
	Max error			0											
Underdosage against vertebrae		**No**	**Yes**	**No**	**No**	**Yes**	**No**	**Yes**	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Number of reCTs with error >5 mm	Error L4	0	1	0	0	0	0	3	0	1	1	0	0	0	0
	Most cranial	0	1	0	0	3	0	3	0	1	1	1	0	1	0
	Max error	0	3	0	0	3	0	3	0	1	1	1	0	1	0

Prediction of underdosage posterior part CTV_T_LR

The rectal filling was quantified by the diameter and HU value of the rectum on the pCT and reCTs. The results can be found in Appendix C. Large air pockets (>30 mm in the beam direction) were seen in the rectum of both patients with underdosage (R01, R04, and R06) and patients without underdosage (R05, R08, R10, R11, R13, R14, R15, and R17) in the posterior part of the CTV_T_LR.

DISCUSSION

In order to develop a robust strategy for treating LACC patients with IMPT, the study was divided into two consecutive parts. The first part focused on finding an anisotropic CTV-to-ITV margin recipe to account for interfraction target motion of the uterus that provides adequate tumor coverage using a patient-specific motion model. Of the 3430 margin recipes tested, of which 376 recipes had >95% CTV_T_LR overlap for at least 90% of the patients, the margin with the smallest ITV45 volume was 1, 5, 7, 3, and 3 mm in the left/right, posterior, anterior, cranial, and caudal directions, respectively.

The range uncertainties and geometric uncertainties (including the interfraction motion of the CTV_E) were addressed in the second part of this study with a robustness recipe. A plan library was used because of the dosimetric advantages resulting from the smaller irradiated volume. The subITVs were expanded with the anisotropic margin recipe, after which robust optimization (SR 5 mm, RR 3%) and evaluation (32 scenarios) of the treatment plans were performed.

This margin and robustness recipe combination was tested for robustness to target motion, geometric uncertainties, and range uncertainties by simulating treatments. This simulation showed that this combination met the delivered dose criterion of D95 $\geq$ 95% in at least 90% of the patients for both target volumes. This means that the strategy was safe in terms of target volume dose for the LACC patient group.

The D95 was greater than 42.75 Gy in 99% and 93% of the patients for the CTV_T_LR and CTV_E, respectively. Both target volumes comfortably met the delivered dose criterion, especially the CTV_T_LR, indicating that the strategy is somewhat too conservative.

PART 1: UTERUS MARGIN RECIPE

The most favorable margin (i.e., with the smallest average ITV volume) was 1, 5, 7, 3, and 3 mm in the left/right, posterior, anterior, cranial, and caudal directions, respectively.

However, this anisotropic margin did not provide sufficient overlap in patient R01, especially in the second reCT (72.3% overlap), which is shown in Figure 1 in Appendix D. This figure shows that the CTV_T_LR of the reCT is shifted posteriorly in this reCT compared with the pCT. Figure 1 in Appendix C shows that this shift is likely due to the larger bladder volume (128% of the bladder volume of the pCT) and a less filled rectum and bowel bag in the reCT. Nevertheless, this insufficient overlap was accepted because the 95% overlap had to be achieved in only 90% of patients.

The posterior part of the uterus is prone to underdosage as shown in part 2 of our study (occurred in 3/14 patients in the posterior part of the uterus), and good coverage of this area is crucial, as this corresponds to the CTV_HR. Therefore, the fifth option in Table 6 (left/right = 1mm, posterior = 7mm, anterior = 7mm, cranial = 3mm, caudal = 3mm) could be considered to further optimize the strategy by reducing the robustness recipe while maintaining adequate tumor coverage, especially in this posterior part of the uterus.

A previous study by Bondar *et al.* showed that an isotropic margin of 7 mm was required when using the patient-specific motion model.[40] Our anisotropic margin shows that replacing an isotropic margin with an anisotropic margin reduces the margin in all directions except the anterior one. Compared with the isotropic margin of 7 mm, our margin resulted in a 25% reduction in ITV45 volume.

This large volume reduction encourages further research in this area. The margin in this study is determined in six directions. However, the movement of the CTV_T_LR in these six directions is not rigid across the structure. For example, the tip of the uterus may move caudally due to a smaller bladder volume, while the vagina remains at the same location with this smaller bladder volume. Since the movement of the CTV_T_LR is non-rigid, the required margin may vary across the structure in the six directions and thus the margin can be further optimized.

Another way to reduce our anisotropic margin would be to investigate whether steps of 1 mm instead of 2 mm lead to smaller margins.

PART 2: ROBUST OPTIMIZATION AND TREATMENT SIMULATION

The evaluation method

With the wish-list created, it was possible to use Erasmus-iCycle to create treatment plans that met the EMBRACE-II constraints for the entire LACC population. By using Erasmus-iCycle to automatically generate treatment plans, the quality of the plans is no longer dependent on the user.

These treatment plans were evaluated on 32 scenarios, including the voxel-wise minimum and voxel-wise maximum scenarios. Compared with the evaluation method used at HollandPTC, one scenario was added to the evaluation

protocol. This extra nominal scenario with the original HU values for the air pockets ensured that the treatment plans were robust against air pockets in the evaluation phase.

During optimization and evaluation, the PTV dose was prescribed to the voxel-wise minimum and maximum, in accordance with the clinical protocol of HollandPTC, which is based on the Dutch Proton Therapy Group (DUPROTON).[49] Korevaar *et al.* showed that the CTV D98 criterion on the voxel-wise minimum dose has a high correlation with the PTV D98 used in photon therapy, with a correlation slope of -0.9%. The CTV D2 on the voxelwise maximum had a high correlation with the PTV D2 with a slope of 2.3%.[49] This suggests that the simple translation of PTV constraints to CTV constraints on the voxel-wise scenario's is too conservative and that these voxel-wise minimum and maximum constraints can be relaxed.

Comparing our evaluation method with Gort *et al.*, their minimum ITV constraint (D98 $\geq$ 42.75 Gy at the voxel-wise minimum) and maximum ITV constraint (D2 $<$ 107% of the prescribed dose at the voxel-wise minimum) were stricter, whereas the D50 constraint was the same.[26] However, they did not review constraints for OAR structures. With our study, we showed that this strict evaluation method is not necessary since the delivered dose criteria was comfortably met. If we had used this stricter evaluation method, the D95 was greater than 42.75 Gy in even more patients, which is not in line with the recommendations of the EMBRACE-II protocol to achieve maximum OAR sparing.[6]

Treatment simulation

Treatment simulation was used to test the proposed strategy on the delivered dose criterion of D95 $\geq$ 95% in at least 90% of the patients. For each fraction, one of the reCTs was chosen as the daily anatomy. This results in one-third or one-fourth of the fractions having the same anatomy, whereas in the clinical situation the daily anatomy for each fraction is different. Van Herk *et al.* have shown that systematic errors have a (2.5/0.7=) 3.5 times greater impact on the required margin compared to random errors.[58] Despite the reuse of the reCTs, the results have shown that the proposed strategy is robust already considering these systematic anatomical errors.

In addition to the small number of reCT scans per patient, the generalizability of the strategy could be limited because of the relatively small number of included patients. If data from more patients had been available, a greater variation in patient anatomy would have been included in the study, increasing confidence that the strategy would work in the entire LCC patient population. However, we expect that our patient population is representative for the entire LACC population since a wide variation in the anatomy of our patients was observed. Such as the movement of the tip of the uterus from 4 to 92 mm and air pockets in the rectum ranging from 8 to 50 mm. So, although the current study is based on a small amount of included patients, we do not expect drastic changes in the results when more patients were included.

Replanning CTs were acquired in two patients (R05 and R09) because the uterus appeared to be more mobile than shown on the original pCTs. In the clinical situation, the anatomy on the replanning CT is not irradiated with the original treatment plan. Nevertheless, we used these replanning CTs in the simulation as the daily anatomy for the fractions. Achieving the delivered dose criterion of D95 $\geq$ 95% with these replanning CTs included in the simulation suggests that replanning was not necessary using our margin and robustness recipe. On the other hand, if replanning is performed in the clinic, a smaller margin and robustness recipe could possibly be allowed.

The simulation showed that the strategy is robust to inter- and intrafraction motion, range uncertainties, and geometric uncertainties. However, intrafraction bladder filling was not considered in the simulation. Since the least full plan is selected from the library when the CTV_T_LR can be treated with two plans, there is some room for movement of the CTV_T_LR resulting from the bladder filling. Furthermore, the simulation included intrafraction movements measured in patients in prone position, while our patients are treated in supine position. The intrafraction movements are smaller in patients in the supine position,[59] so these conservative intrafraction errors may partially compensate for bladder filling during treatment.

Because the pathological lymph nodes were not delineated separately as CTV_N on the reCTs, it was not possible to assess CTV_N coverage in the simulations. Therefore, it is not known whether CTV_N D95 was equal or greater than 95% of the prescribed dose considering motion, geometric uncertainties, and range uncertainties. However, since the CTV_N delineations were available on the pCT, the CTV_N constraints were evaluated in the evaluation phase. The evaluation phase showed that the CTV_N constraints were met in all 32 scenarios, suggesting a good CTV_N coverage considering the motion and uncertainties.

Underdosage in target volumes

Underdosage occurred in 7/14 patients in the CTV_T_LR and in 5/14 patients in the CTV_E.

In 3/5 patients with CTV_E, the underdosage was located against the vertebral column. As shown in Table 12, the maximal error metric showed the most distinguishable values for patients with and without underdosage in the

CTV_E against the vertebral column. The assumption that can be derived from Table 12 is that if a maximum error of 6 mm occurs in 25% of the fractions (R13) or 5 mm in less than 33% of the fractions (R11, R14, R16), underdosage is unlikely. If an error $\geq$ 5 mm occurs in 75% or more of the fractions, it is likely that underdosage is present in the CTV_E (R04, R07, R09). These observations can be used to assess when replanning is required.

The absence of underdosage in the posterior part of the uterus in patients with large air pockets (>30 mm in the beam direction) suggests that air pockets are not the main cause of this underdosage in this patient population. This result was also shown by Berger *et al.*[60] They showed that the density change due to air pockets resulted in a dose reduction for the ITV45 of 0.3% [0.1-1.3%] for D98.

However, these underdosages in the posterior part of the uterus are problematic as this is part of the CTV_HR. To compensate for these shifts, the CTV-to-ITV margin can be increased posteriorly. When the margin and robustness recipe is optimized in further research by reducing the robustness, we suggest using the fifth option in Table 6 as margin, to prevent this posterior underdosing.

The proposed strategy

As mentioned earlier, the proposed strategy proved to be robust to organ motion, geometric uncertainties, and range uncertainties. The investigated anisotropic CTV-to-ITV margin can also be used in photon therapy in LACC patients when the patient-specific motion model is applied. For example, in the Erasmus MC, the motion model is used for the treatment of LACC with photon therapy and an isotropic margin is used around this CTV to create the ITV.

In addition to a different margin, a different plan library is used in the Erasmus MC: one plan for non-movers (uterine tip displacement $<$ 2.5 cm) and two plans for movers (uterine tip displacement $\geq$ 2.5 cm). We proposed to use a library with 3 or 4 plans for patients with uterine movement of more than 30 mm. Since only a 2-plan library is used for these patients in the Erasmus MC, lower dosimetric benefit is achieved than with a 4-plan library.[43]

The planning study performed by Gort *et al.* used an anisotropic margin of 5 mm in the left-right and 10 mm in the anterior, posterior, and superior directions to expand the CTV_T_LR without using a motion model to create the ITV.[26] Since no motion model was used, they did not use a plan library. In addition to this CTV-to-ITV margin, 3% RR and 5 mm SR were used for optimization and evaluation.

Compared with our strategy, larger margins (except in the anterior direction) were used in the study by Gort *et al.* We were able to reduce the margins by using a patient-specific motion model. This shows that the motion model and PotD leads to smaller margins and target volumes which has dosimetric benefits by reducing the irradiated volume while providing sufficient target coverage.

The same robustness settings are used by Gort *et al.* which confirms that our strategy is valid even with our limited number of patients.

Future work

In this study, only one margin and robustness recipe is tested. Improvements in this recipe can be made since the delivered dose criterion was easily met in both target volumes. Because underdosage was detected in the posterior part of the uterus in three patients, we suggest increasing the CTV-to-ITV margin in the posterior direction to 7 mm while decreasing the robustness recipe to 3 mm SR and 3% RR. Further research should be undertaken to investigate if this margin and robustness recipe combination still provides sufficient target coverage taking into account the motion and uncertainties.

The optimal beam angle is not yet systematically studied for cervical cancer patients. In the study conducted by van der Schoot *et al.*, a 4-beam setup 30°, 90°, 270°and 330°was used.[61] These beams had been adjusted in the study by Gort *et al.* to 85°, 150-165°, 195-210°, and 275°since breathing and bowel motion are mainly in the anterior direction.[26] The beam angles used in this study originated from Gort *et al.*[26] Besides studying the optimal beam angles for LACC patients, it would be even more interesting to be able to determine these optimal beam angles easily and quickly for each individual LACC patient since we experienced that adjusting the beam angles provided better plans for some patients.

Although the proposed strategy has been shown to be robust in terms of CTV coverage, our proposed strategy can be still sensitive to large differences in daily anatomy such as large target motion and density changes along the beam path.[35,36] Online adaptation of treatment plans to this daily anatomy is proposed to ensure target coverage when the daily anatomy greatly deviates from the pretreatment anatomy.[38] However, further research is required since it is only investigated on six patients and is not yet available for patients with lymph node involvement.

CONCLUSION

By combining these two consecutive parts, a robust PotD strategy with anisotropic margin (1, 5, 7, 3, and 3 mm in the left/right, posterior, anterior, cranial, and caudal directions, respectively) and robustness recipe (SR 5mm, RR 3%) was found considering target motion, geometric uncertainties, and range uncertainties when treating LACC patients with IMPT. The D95 was greater than 42.75 Gy in 99% and 93% of the patients for the CTV_T_LR and CTV_E, respectively. This margin and robustness recipe can be further improved as the target coverage was easily achieved in both target volumes. However, attention should be paid to the posterior part of the uterus as underdosage in this part was detected in three patients. Therefore, we suggest further research to increase the CTV-to-ITV margin in the posterior direction to 7 mm while decreasing the robustness recipe to 3 mm SR and 3% RR.

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APPENDIX A: LITERATURE REVIEW

Proton and carbon ion therapy for gynecological cancers: a review

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Abstract

Background and objectives: Cervical cancer is the most common gynecological cancer diagnosed worldwide with 604,000 new patients detected in 2020. Due to chemoradiation in the treatment, many patients experience toxicities. Since the diagnosed patients are relatively young with long-term survival, the toxicities have a great impact on their quality of life. The use of particle radiation, like in proton and carbon ion therapy, instead of photon therapy may offer a solution since particle radiation allows for higher localized dose deposition with better sparing of the organs at risk. Ensuring that plans are robust to uncertainties remains a concern in particle therapy. However, there are strategies, such as margins and robust optimization, that can provide practical solutions. Due to the lack of overview of the clinical use of proton and carbon ion therapy in this field, it is unknown what margins and robustness settings dare to be applied in clinical practice to address the uncertainties in gynecological cancers. Therefore, firstly, this review aims to provide a clear worldwide overview of the institutes that use proton and carbon ion therapy for the treatment of gynecological tumors and show the time trends in this field. The second part of this review aims to clarify the margins and robustness settings the institutes dare to use for gynecological tumors.
Methods: A systematic literature search was performed in Embase, Medline, and Web of Science. Besides, the ClinicalTrials.gov database was used for ongoing clinical trials. Studies were eligible for the first part of the review when they treat gynecological cancers with proton or carbon ion radiotherapy and the publication concerned a clinical study. For the second part of this review, studies were eligible with one added criteria of explaining their strategies to address uncertainties.
Results: From the systematic search followed 14 institutes that treated gynecological tumors with carbon ion or proton therapy. Carbon ion was used in 3/14 (21%) institutes, of which one institute treated with both carbon ions and proton. Interest in proton therapy for the treatment of gynecological tumors has significantly increased over the past 10 years leading to 12 institutes using protons now in multiple European countries, Taiwan, China, and the United States. The majority of the institutes use margins around the target to address uncertainties while one institute uses robust optimization. Regarding the tumor margins, most studies used an internal target volume combined with a planned target volume (PTV) margin for whole-pelvic irradiation, while smaller margins (3 to 10 mm) were used for the primary tumor boost. As for lymph node irradiation, a 5 mm PTV margin was used in most of the studies, while the PTV margins for the positive lymph node boost ranged from 3 to 10 mm. The institutes' findings suggest that vaginal packing, filling the bladder with a catheter instead of a drinking protocol, and an endorectal balloon in situ during radiotherapy treatment may offer advantages in reducing inter- and intrafraction movement.
Conclusion: Proton and carbon ion therapy have been used in various institutes around the world since 1968 with increasing interest in the last 12 years in proton therapy. Margins are primarily used to address uncertainties in treatment planning and dose delivery in both carbon ion and proton therapy for the treatment of gynecological tumors. Institutions' experiences with, e.g., endorectal balloons, catheters, and vaginal packing may provide benefits by reducing uncertainties in subsequent studies in this field.

INTRODUCTION

Cervical cancer is the most common gynecological cancer diagnosed worldwide with 604,000 new patients detected in 2020.[1] In the Netherlands, 800 women were diagnosed in 2020.[2] About half of these women are younger than 60 years, with 25% even younger than 45 years.[2]

About 30% of women with cervical cancer are diagnosed with locally advanced cervical cancer (LACC) meaning the tumor is more than 4 cm or has grown into the tissue around the cervix, but has not spread out to any other organs. These tumors are classified as stage 1B2 to 4A.[3] Treatment for LACC consists of external beam radiotherapy (EBRT) using photons, combined with concurrent chemotherapy followed by brachytherapy.[4] This treatment has been proven effective in LACC-patients, however, many patients suffer from some degree of toxicities, mainly concerning the gastrointestinal (GI) and genitourinary (GU) tract.[5] Since the diagnosed patients are relatively young with a high long-term survival rate after treatment, the toxicities have a serious impact on their quality of life.[6,7] The combination of chemotherapy and radiotherapy also increases the risk of hematologic toxicity (HT).[5,8] HT

grade 2 or higher is seen in 69.5% of the cervical cancer patients undergoing chemoradiation.[9] A potential consequence of high-grade HT is stopping or postponing the chemotherapy.[10]

The use of particle radiation, like proton therapy, allows for higher localized dose deposition using particles' finite range with better sparing of the organs at risk (OAR) thus possibly reducing radiation-related toxicities in the treatment of cervical cancer. Several planning studies showed that proton therapy is able to cover the target while reducing the dose to the OAR in cervical cancer patients compared to new technical developments in photon therapy like intensity-modulated radiotherapy (IMRT) and volumetric arc therapy (VMAT).[11,12] The actual toxicity reduction due to OAR sparing should be examined for patients with LACC. Besides proton therapy, carbon ion therapy has also gained significant interest due to its advantageous physical and radiobiologic properties like its finite range compared to photon therapy. These unique properties of carbon ions also allow for OAR sparing while the target coverage is sufficient.[13]

The main challenge in particle therapy is the robust delivery of the dose to the target. In addition to the same sources of geometric uncertainty as in photon therapy, dose delivery in particle therapy can be more concerning due to the additional range uncertainty.[14] Ensuring that plans are robust to uncertainties remains a concern, however, there are strategies that can provide practical solutions, such as margins and robust optimization. Although many planning studies have been conducted for the treatment of gynecological cancers with proton and carbon ion therapy using these strategies, there is no clear overview of the clinical use of particle therapy in this field. Consequently, it is unknown what strategies dare to be applied in clinical practice to address the uncertainties in treatment planning and dose administration in gynecological cancers for proton and carbon ion therapy.

This review consists of two parts. First, this review aims to provide a clear worldwide overview of the institutes that use proton and carbon ion therapy for the treatment of gynecological tumors and the number of patients they treated over time to gain insights into the time trends in this field. Second, this review aims to clarify what margins and robustness settings the institutes dare to use for the treatment of gynecological tumors with protons or carbon ion therapy. All gynecological tumors are included in this review, not just cervical cancer, because all of these tumors face the same uncertainties in the pelvic region, such as bladder filling. Therefore, the inclusion of all gynecological tumors provides more insight into treatment strategies to address uncertainties.

METHODS

Search strategy

A systematic literature search was performed in the databases Embase, Medline, and Web of Science. The searches were conducted to identify all clinical articles that treated gynecological cancer with proton or carbon ion radiotherapy. Therefore, the search term for these databases consisted of three parts. The first part dealt with proton and carbon ion radiotherapy. The second part ensured that the search yielded gynecological cancers, and the third part focused on the fact that the publication concerned a clinical study. The search terms can be found in the appendix. Searches were not restricted in terms of the patient's number and publication date.

Inclusion criteria for the first part of this review, providing a global overview of the institutes that use proton or carbon ion to treat gynecological tumors, were: (1) patients with gynecological cancer, (2) patients received proton or carbon ion therapy, (3) original article (no follow-up articles or reviews), except when the original article was not found (when an article and meeting abstract were from the same group and about the same patients, the abstract was excluded in favor of the journal article), and (4) full-text was published in English. This third inclusion criterion was added to ensure that the same patient group was not included more than once to avoid biasing the number of patients who were treated at a particular institute. When the full text was not available in English or not available at all but the data needed for this part of the review was already presented in the abstract, the article was not excluded.

After removing duplicates, all remaining articles were screened for the aforementioned inclusion criteria by title and abstract. Next, full-text screening was performed and articles that did not meet the inclusion criteria were excluded. The remaining articles were included for the first part of this review.

Next, these remaining articles were again full-text screened for the second part of the review: clarifying the margins and robustness settings the institutes dare to use. The inclusion criteria for the second part were the same as for the global overview with one added criteria of explaining their strategies to address uncertainties.

In addition to the aforementioned database search, the ClinicalTrials.gov database was searched on 14 January 2022 for ongoing clinical trials. Several combinations of the following keywords were used for this search: "proton", "carbon ion", "gynecological cancer", "cervical cancer", "endometrial cancer", "vulva cancer", "vaginal cancer", "uterine cancer" and "ovarian cancer". The inclusion criteria for ongoing clinical trials were the same as for the aforementioned mentioned database search.

Finally, the reference lists of the included articles were

checked for cited articles that met the inclusion criteria of the first and the second part of the review, but were not found with the literature or ClinicalTrial.gov search.

Data extraction

For the global overview, data were collected about the institute, the city and country of the institute, the year of treatment, the type of radiation, the tumor site, and the number of patients.

Subsequently, information about the strategy to address uncertainties, such as margins and robustness settings, and information about factors that may influence the strategy e.g. immobilization strategy, bladder filling protocol, and rectal protocol was extracted for the second part of the review.

RESULTS

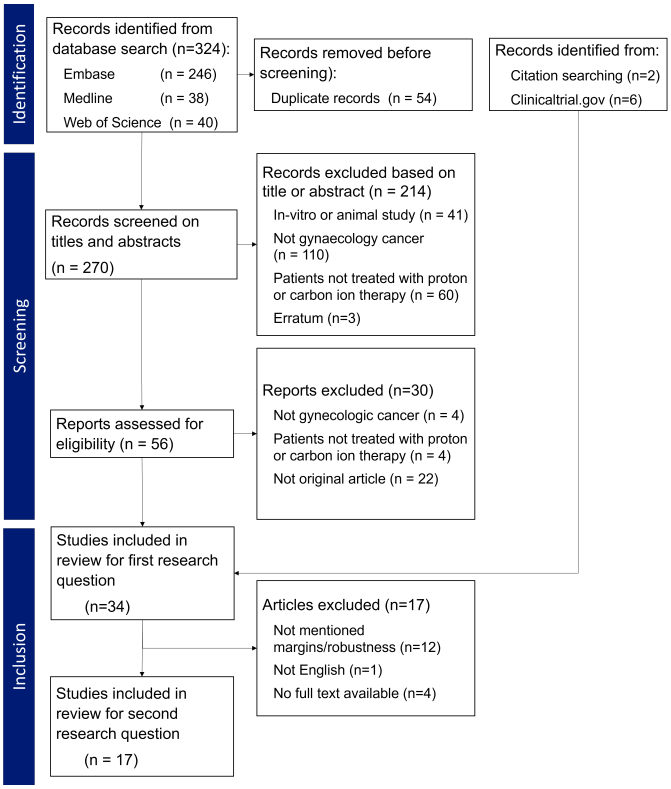

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA)-diagram of the systematic search.[15]

Eligible studies

Figure 1 shows the selection process of the studies. After applying the search terms in Embase, Medline, and Web of Science on 21 December 2021, 324 potentially eligible records were identified. After 54 duplicates were removed, 270 titles and abstracts were screened. Of the 270 records, 214 records were excluded mostly because the articles were not about gynecological cancer. In the full-text screening procedure phase, 30/56 articles did not meet the inclusion criteria for the first part of the review and were excluded. Of these 30 articles, four articles were not about gynecological cancer, four articles did not treat patients with protons or carbon ions (e.g. planning studies), and 22 articles were not the original article but described the follow-up of another record or were a review of patients mentioned in another record. In addition to the database search, the ClinicalTrial.gov search was conducted and six more clinical trials were included for the first part of the review.[16–21] Moreover, two records were identified through the reference lists that met the inclusion criteria but were not found with the search term.[22,23] In total, 34 articles were included for the first part of the review, see Table 1. One of these 34 articles describes protocols and results from two different studies.[24] These two study protocols are listed separately in Table 1.

These 34 articles were again full-text screened for the second part. It was verified whether these articles described their strategies to address uncertainties. Six articles did not describe anything about the used margins or robustness settings. The full text of five other articles was not available, and the full text of one article was not published in English, therefore information on the treatment strategies was not available, so these six articles were also excluded. In total, 17 articles were included for the second part of the review, see Table 2.

Overview of the institutes

Fourteen institutes were found in this review treating gynecological cancer with proton or carbon ion therapy. Carbon ion was used in 3/14 (21%) institutes, of which one institute treated with both carbon ions and proton. Proton therapy was used in 12/14 (86%) institutes. Figure 2 shows the time trends of the treatment of gynecological tumors with proton or carbon ion therapy at the 14 institutes.

Carbon ion therapy

Only three institutes use carbon ion therapy to treat gynecological cancers. Research into the treatment of cervical cancer with carbon ion therapy was initiated at the National Institutes for Quantum and Radiological Science and Technology (QST) hospital in Chiba, Japan, in 1995. Of the eleven protocols performed here, eight have treated squamous cell, adenosquamous cell, and adenocarcinoma of the uterine cervix. In the first of these eight protocols, women with a very advanced stage or who could not be cured with conventional radiotherapy were treated with carbon ion therapy.[25] This protocol was followed by two phase I/II studies to evaluate the toxicity and efficacy of carbon ion radiotherapy for LACC.[24] Five more protocols followed starting between 1998 and 2010[26–30] in which the latter two used concurrent chemotherapy in addition to carbon ion therapy.[29,30] A total of 252 patients were treated in these eight protocols.

Carbon ion therapy was also used for re-irradiation

*Table 1: Characteristics of the 34 articles found in this review originating from the 14 institutes treating gynecologic tumors with carbon ion and/or proton therapy. publ. = published; * Irradiated with protons or photons/chemotherapy; ** irradiated with protons and carbon ions*

Institution (City, Country)	Author Protocol	Tumor Site (No. of patients)	Year of treatment
		Carbon ion therapy	
QST Hospital (Chiba, Japan)	Nakano *et al.* [25]	Cervical cancer (squamous cell (n=42), adenosquamous cell (n=1), and adenocarcinoma (n=6))	1995 – 2000
	Kato *et al.* [24] – Protocol 9403	Locally advanced cervical cancer (squamous cell (n=27) and adenocarcinoma carcinoma (n=3))	1995 - 1997
	Kato *et al.* [24] – Protocol 9702	Locally advanced cervical cancer (squamous cell carcinoma (n=14))	1997 - 2000
	Wakatsuki *et al.* [26] – Protocol 9704	Uterine cervical adenocarcinoma (n=45) or adenosquamous (n=13) carcinoma	1998 – 2010
	Wakatsuki *et al.* [27] – Protocol 9902	Locally advanced squamous cell carcinoma of the uterine cervix (n=22)	2000 – 2006
	Wakatsuki *et al.* [28] – Protocol 0508	Locally advanced squamous cell carcinoma of the uterine cervix (n=26)	2006 – 2012
	Okonogi *et al.* [29] – Protocol 1001	Locally advanced cervical cancer (adenocarcinoma (n =26) and adenosquamous carcinoma (n=5))	2010 – 2014
	Okonogi *et al.* [30] – Protocol 1302	Locally advanced uterine cervical squamous cell carcinoma (n=22)	n.m. (publ. 2018)
	Shiba *et al.* [31]	Lymph nodes recurrence of gynecological cancers (n=16)	2008 – 2016
	Karasawa *et al.* [32]	Gynecological melanoma (vagina (n=14), vulva (n=6), cervix uteri (n=3))	2004 – 2012
	Murata *et al.* [33]	Malignant gynecological melanoma (vagina (n=22), vulva (n=12), cervix uteri (n=3))	2004 – 2017
Gunma University Heavy Ion Medical Center (Gunma, Japan)	Ohno *et al.* [34] – Protocol 1202	Locally advanced cervical cancer (squamous cell (n = 2) or adenocarcinoma (n=4))	2013 - 2018
		Proton therapy	
The Institute of Theoretical and Experimental Physics (Moscow, Russia)	Ruderman *et al.* [35]	Cervical cancer (n=35)	n.m. (publ. 1970)
	Chuvilo *et al.* [36]	Vulva (n=39) and cervical cancer (n=136)	1969 – 1981
Proton Medical Research Center (Ibaraki, Japan)	Arimoto *et al.* [37]	Advanced gynecologic malignancies (n=15)	1983 – 1987
	Kagei *et al.* [38]	Locally advanced squamous cell carcinoma of the uterine cervix (n=25)	1981 – 1991
	Tsuji *et al.* [39]	Uterine cervix carcinoma (n=19), corpus carcinoma (n=2) and vaginal carcinoma (n=2)	1983 - 1990
Mediopolis Proton Therapy and Research Center (Ibusuki, Japan)	Yanazume *et al.* [23]	Recurrent endometrial cancer in vagina (n=1)	n.m. (publ. 2015)
Roberts Proton Therapy Center (Philadelphia, United States)	Lin *et al.* [40]	Gynecologic cancers (n=10)	n.m. (publ. 2014)
	Lin *et al.* [41]	Cervix (n=7), endometrial (n=2), recurrent endometrial (n=1), vaginal (n=1)	n.m. (publ. 2015)
	Lin *et al.* [22]	Vaginal squamous cell carcinoma (n=1)	n.m. (publ. 2016)
	Taku *et al.* [42]	Uterus (n=9), cervix (n=8), vagina (n=1)*	2013 – 2014
Maryland Proton Treatment Center (Maryland, United States)	Pollock *et al.* [43]	Re-irradiation of pelvis and/or abdomen (primary tumors: endometrial (n=15), cervical (n=7), vaginal (n=3), vulva (n=2) and ovarian cancer (n=2))	2015-2020
	Yao *et al.* [44]	Gynecologic cases (n=3)	n.m. (publ. 2020)
	Mohindra *et al.* [16]	Locally advanced endometrial cancer (n=21)	2021 - 2023
Massachusetts General Hospital (Boston, United States)	Russo *et al.* [45]	Uterine (n=15) and cervical cancer (n=6)	2013 - 2018
	Russo *et al.* [21]	Cervical cancer (n=30)	2012 - 2021
Mayo Clinic (Minnesota, United States)	Petersen *et al.* [19,20]	Endometrial or cervical cancer (n=120)*	2020 – 2023
Chang Cung Memorial Hospital (Linkou, Taiwan)	Tung *et al.* [46]	Para-aortic lymph nodes of cervical adenoma (n=1) and cervical squamous cell (n=1)	2016 -2017
Shanghai Proton and Heavy Ion Center (Shanghai, China)	Zhang *et al.* [17]	Squamous cell carcinoma of cervix (n=16)**	2016 - 2021
	Guo *et al.* [18]	Locally advanced cervical cancer (n=50)*	2017 - 2020
CNAO (Pavia, Italy)	Barcellini *et al.* [47]	Squamous cell carcinoma of the vagina (n=1)	2019
Heidelberg Ion Beam Therapy Center (Heidelberg, Germany)	Arians *et al.* [48]	Cervical and endometrial cancer (n=25)	2017 - 2019
Holland PTC (Delft, The Netherlands)	Corbeau *et al.* [49]	Locally advanced cervical cancer (n=15)	2022

for recurrence of lymph nodes of gynecological cancers after definitive radiotherapy in the QST Hospital. In this protocol, 16 patients were treated between July 2008 and October 2016.[31]

Gynecological melanomas were treated with carbon ion radiotherapy in 2/11 protocols from the QST hospital. In these two protocols, 60 gynecological melanomas of the vagina, vulva, and cervix uteri were treated with carbon ions between 2004 and 2017.[32,33]

The Gunma University Heavy Ion Medical Center in Japan is the second institute treating patients with gynecological cancers with carbon ion therapy. In a phase I study, which ran from 2013 to 2018, six LACC patients were treated with carbon ion therapy combined with brachytherapy and chemotherapy.[34]

The third institute combined carbon ions with protons for the treatment of cervical cancer and is described in the proton therapy paragraph.[17]

Proton therapy

While a small number of the institutes used carbon ion therapy, 12/14 (86%) used proton therapy to treat gynecological cancers, see Table 1. However, these institutes have published only between one to three articles about gynecological tumors and two institutes have only reported a case report.

Figure 2 reveals that there is a publication gap in proton therapy between 1992 and 2012 while increasing interest in proton therapy can be seen in the last ten years in the United States, Taiwan, China, and multiple European countries. This growing interest is currently most evident in the United States, as 4/6 ongoing trials found with the ClinicalTrial.gov search are being conducted there.

The first two studies with proton therapy were conducted from 1969 at the Institute of Theoretical and Experimental Physics in Moscow, Russia. A total of 171 cervical cancer and 39 vulva cancer patients were treated in these studies.[35,36]

Proton therapy is also used at the Proton Medical

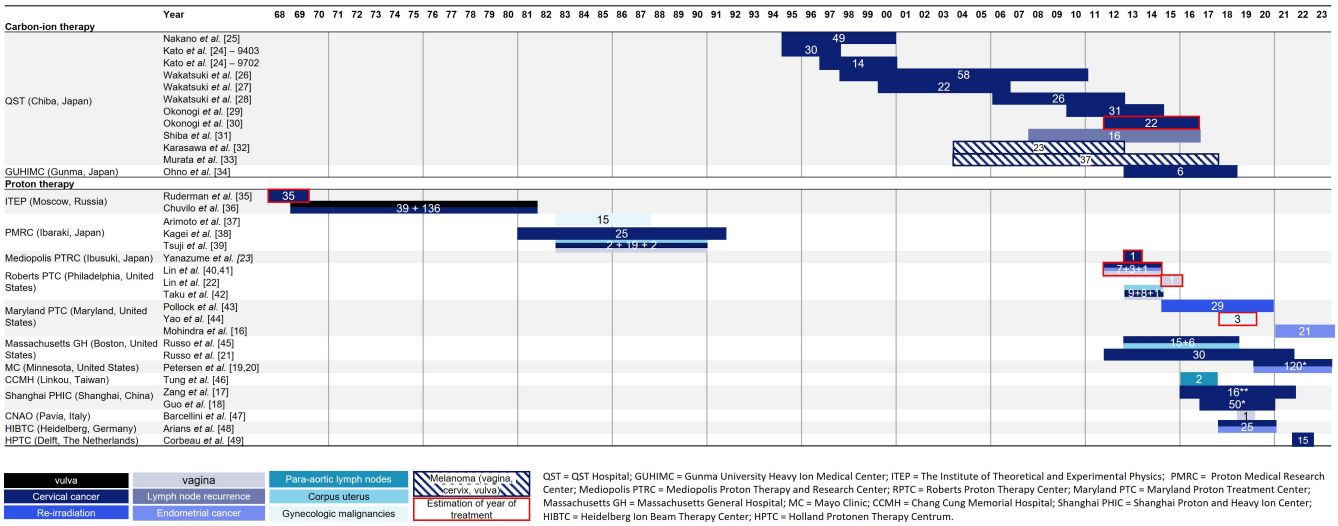

*Figure 2: Bar chart of inclusion period of all 32 included studies. The article of Kato et al. describes protocols and results from two different studies, which are visualized separately.[24] The number in the bar indicates the number of patients treated in that study. When multiple tumor sites have been treated in one study, the bar is divided into the different colors of the tumor sites. When the authors did not report when the patients were treated, an estimation was made based on the publication date and number of patients (indicated by red outline). *Irradiated with protons or photons. **Irradiated with both protons and carbon ions*

Research Center in Ibaraki, Japan, where three studies were conducted between 1981 and 1991.[37–39] In the first two studies, carbon ion therapy was used as a substitute for conventional brachytherapy.[37,38] In the third study, performed between April 1983 and September 1990, cervical cancer, uterine corpus carcinoma, and vaginal carcinomas were irradiated with protons (one patient) or in combination with photons (22 patients).[39]

After the period between 1992 and 2012 with no publications on proton therapy, the Mediopolis Proton Therapy and Research Center published on the treatment of one patient for recurrence of endometrial cancer in the vagina with proton therapy.[23]

Besides Russia and Japan, proton therapy for gynecological tumors has also been studied in the United States, namely in Philadelphia, Maryland, Boston, and Minnesota. From 2014 to 2016, four articles were published from the Roberts Proton Therapy Center in Philadelphia.[22,40–42] Two studies were published by the same authors and the ten patients with gynecological tumors treated in these publications are probably the same patient group, except that one more patient with cervical cancer was included in the last study.[40,41] Therefore, these two articles are visualized together in Figure 2. In addition to these 11 patients, a case report was published treating primary vaginal carcinoma with proton therapy almost 30 years after pelvic radiotherapy for cervical carcinoma.[22] In the fourth publication, 18 post-hysterectomy patients with gynecological cancer were irradiated with IMRT or proton therapy between January 2013 and April 2014.[42]

Three other studies in the United States were conducted at the Maryland Proton Treatment Center. Several tumors, such as endometrial, cervical, vaginal, vulva, and ovarian cancers have been irradiated with protons at this institute between 2015 and 2020.[43,44] Currently, the UPPROACH study is ongoing in which 21 patients are being treated with proton therapy and concurrent chemotherapy for postoperative treatment in locally-regionally advanced endometrial cancer.[16] The study started in February 2021 and will be completed in September 2023.

The third institute in the United States using proton therapy for gynecological tumors is the Massachusetts General Hospital in Boston where cervical and uterine cancer was treated. Six cervical cancer and fifteen uterine cancer patients were treated between October 2013 and October 2018.[45] In addition, a study is currently underway from 2012 to 2023 in which 30 post-hysterectomy patients are treated with proton therapy for cancer of the uterus or cervix.[21]

The last institute in the United States that followed from the database search was the Mayo Clinic in Minnesota. From December 2020 to December 2023 a study is ongoing in which 120 patients are treated with proton therapy or IMRT for their endometrial or cervical cancer after hysterectomy.[19] Another phase I study investigating adverse events in patients with endometrial or cervical cancer will also include 120 patients and is being conducted during the same period.[20] Since the original title of these studies is the same, they likely involved the same patients and are therefore included as one study in Table 1 and Figure 2.

In Taiwan, at Chang Cung Memorial Hospital in Linkou, proton therapy has been used for the irradiation of two gynecological patients.[46] Radiations for these two patients were performed in 2017, 2018, and 2020.

From January 2016 to October 2021, 16 patients were treated for squamous cell carcinoma of the cervix with both proton and carbon ion radiotherapy with or without chemotherapy at the Shanghai Proton and Heavy Ion Center in Shanghai, China.[17] A second study was conducted at this institute from July 2017 to September 2020 in which 50 patients were treated for LACC with proton therapy or neoadjuvant chemotherapy before radical hysterectomy, removal of pelvic lymph nodes, and abdominal aortic lymph nodes.[18]

Proton therapy is also used in Europe as a treatment for gynecological tumors, first of all at the National Center for Oncological Hadrontherapy in Pavia, Italy. One patient was treated for squamous cell carcinoma of the vagina after surgery, pelvic radiotherapy, vaginal brachytherapy, and chemotherapy for a previous endometrial adenocarcinoma.[47]

The second European country that uses proton therapy to treat gynecological cancers is Germany, at the Heidelberg Ion Beam Therapy Center. The APROVE study has included 25 patients from 2017 to 2019 to evaluate the safety and treatment tolerance of pelvic irradiation for patients with cervical or endometrial cancer after surgical resection.[48]

The Holland Proton Therapy Center in Delft, Netherlands, is the third site in Europe to report treating gynecological cancer with proton therapy. In the PROTECT study, 15 LACC patients will be included and treated with proton therapy combined with concurrent chemotherapy followed by brachytherapy[49]

Treatment strategies

Of the seven institutes that described their treatment strategies to address uncertainties, six used margins, and one used robust optimization, namely the Maryland Treatment Center in the United States. The treatment strategies are summarized in Table 2 by the clinical target volumes (CTV), internal target volume (ITV), planned target volumes (PTV), and robustness settings.

The used tumor margins for the cervix-uterus irradiation and the primary gross tumor volume (GTV) boost for squamous cell, adenosquamous, or adenocarcinoma of the cervix are visualized in Figure 3. Studies in which postoperative radiotherapy was performed are shown separately in this figure because the anatomy changed due to the surgery in such a way that the target area is not comparable to the target area of cervical cancer without surgery.

Tumor margins

Carbon ion therapy
The QST Hospital started with two CTVs for the irradiation of cervical cancer which immediately expanded to three CTVs and consequently three PTVs from the second study.[24] The standard margin for setup uncertainty was 5 mm in all studies. In addition to this 5 mm margin, a 15 mm margin around the uterus has been added for the intra- and interfraction movement from 1998 when irradiating the whole pelvic region (PTV1). This margin has been reduced to 10 mm from 2010, showing that the margins have been narrowing over time. From the protocols in 2010, concurrent chemotherapy was added. The whole-pelvic irradiation was followed by local boost irradiation on the primary tumor (PTV2 and PTV3). The margin for this PTV2 (primary site) ranged from 5 to 15 mm during the studies. The margin of the PTV3 (only GTV), also used for boost irradiation, has taken an interesting turn. The margin for the PTV3 decreased from 5 mm to 0 mm, after which a margin of 3 mm was added again from 2010. Starting in 2001, the contour of the GI tract was removed from the PTV3 because it caused too much GI toxicity.

Gynecological melanomas were treated with 5 mm CTV margins and energy-dependent PTV margins (3 mm margin (290 MeV/n energy) or 6 mm margin (350 MeV/n energy)) in the clinical trial by Karasawa *et al.*[32] In the subsequent study on melanomas by Murata *et al.*, the 5 mm CTV margin was no longer used. However, a 5 to 10 mm margin for the PTV was used. This resulted in roughly the same margin for the PTV in both studies.[33]

The major difference between the protocols of the Gunma University Heavy Ion Medical Center and the QST Hospital is that the Gunma University combined carbon ion radiotherapy with image-guided brachytherapy and chemotherapy as a treatment for LACC.[34] In this institute, carbon ion radiotherapy consisted of whole-pelvic irradiation ($iPTV_{WP}$) followed by a boost to the primary tumor (PTV_{CX}) and the positive lymph nodes (PTV_{LN}). Individual margins were added to the $iCTV_{WP}$ based on a full and empty bladder computed tomography (CT) scan for the position of the uterine body and cervix in both anatomical settings. To generate the $iPTV_{WP}$, a margin of 5 mm for positioning uncertainty was added to the $iCTV_{WP}$, see Figure 3.

The PTV_{CX} was created by adding a 3 mm margin to the CTV_{CX} and removing normal tissue structures (rectum, sigmoid, etc.) from the PTV_{CX} with a 5 mm margin, see Figure 3. This 5 mm margin around the normal tissues is not seen in other institutes. In addition to this tumor boost, the tumor was irradiated with brachytherapy.

Proton therapy
In the first few studies about proton therapy for the treatment of gynecological cancers, proton therapy was used as a substitute for intracavitary irradiation, so combined with photon therapy, for the treatment of carcinoma of the uterine cervix, corpus, and vagina.[38,39] The CTV consisted of GTV surrounded by a margin of 5 to 10 mm (Figure 3). A PTV is not mentioned in

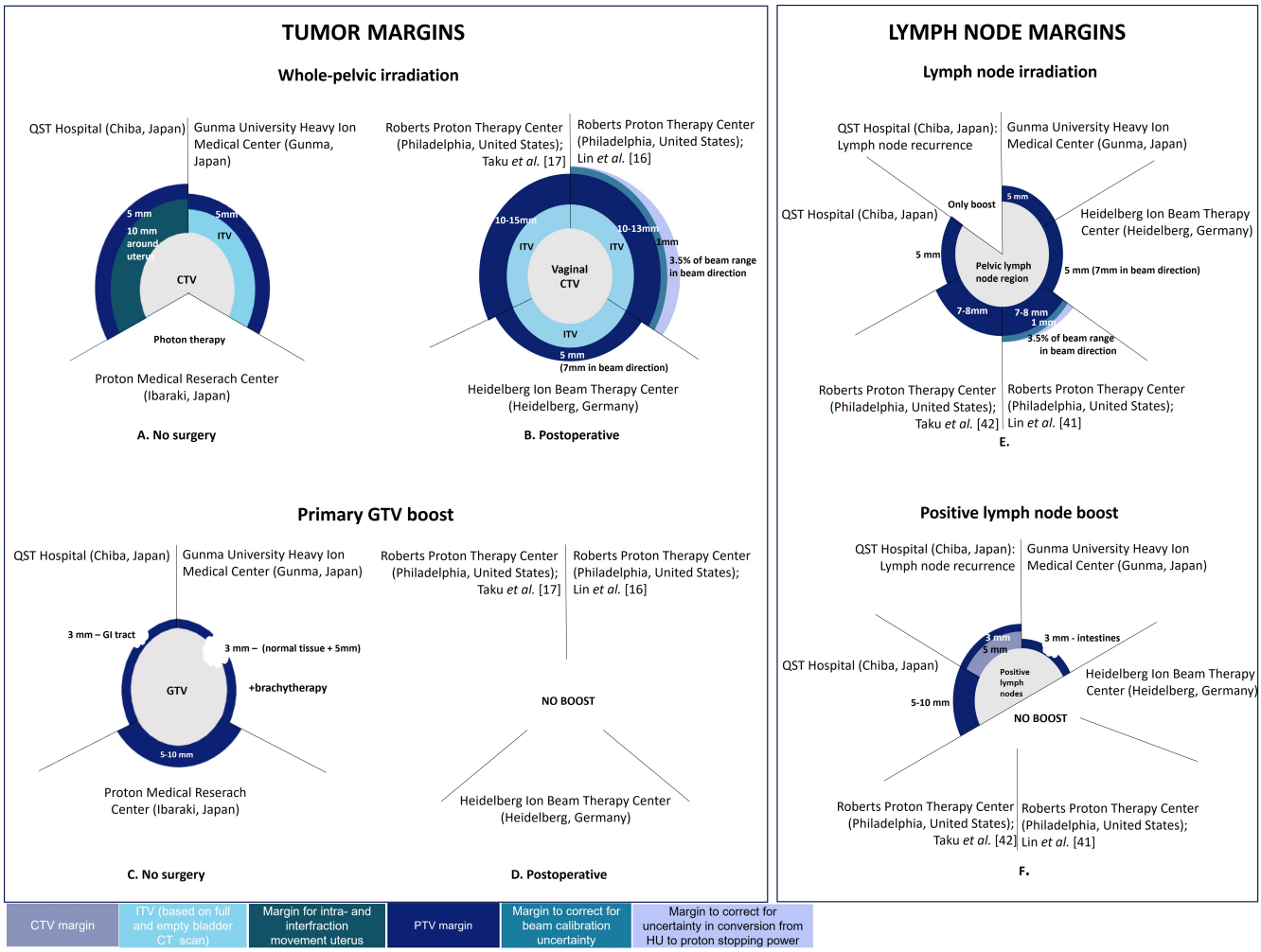

Figure 3: Margins used for the treatment of squamous cell, adenosquamous, or adenocarcinoma of the uterine cervix with proton or carbon ion therapy at the institutes. Tumor margins used for whole-pelvic irradiation without surgery (A) and postoperative (B), primary GTV boost without surgery (C) and postoperative (D) are shown separately. Lymph node margins used for lymph node irradiation (E) and positive lymph node boost (F) are also shown separately. GTV = gross tumor volume; CTV = clinical target volume; ITV = internal target volume; GI = gastrointestinal.

these articles.

After the proton publication gap until 2012, Yanazume *et al.* irradiated recurrence of endometrial cancer in the vagina at the Mediopolis Proton Therapy and Research Center.[23] The CTV consisted of the GTV with a margin of 5 mm. The PTV consisted of the CTV with a 4 mm margin for setup uncertainties and a 1 mm internal margin.

In the studies conducted by the Robertson Proton Therapy Center, different types of gynecological tumors were irradiated using an ITV.[41,42] This ITV mainly takes into account the position of the vagina and not the position of the uterus, because the patients have undergone hysterectomy. In the study of Taku *et al.*, a margin of 10 to 15 mm is applied to the vaginal ITV,[42] while in the study by Lin *et al.* a margin of 10 to 13 mm is used.[41] In addition to this 10 to 13 mm margin, Lin *et al.* applied a margin of 3.5% of the beam range in beam direction to correct for uncertainty in conversion from Hounsfield units to proton stopping power and an additional 1 mm margin to the whole PTV to address uncertainties in beam calibration. After planning, Lin *et al.* used robust evaluation. Recalculations were made in six scenarios (shift of the isocenter of ±5 mm in anteroposterior, craniocaudal, and lateral directions) showing that the plans were robust enough.[41]

The Heidelberg Ion Beam Therapy Center in Germany also includes the movement of the vagina due to bladder filling in its treatment strategy using an ITV after surgery.[48] A margin of 5 mm and 7 mm in beam direction is applied around the ITV to create the PTV.

Creation ITV

The first institute that used an ITV was the Gunma University Heavy Ion Medical Center. Individual margins were added to the CTV1 based on a full and empty bladder CT scan for the position of the uterine body and cervix in both anatomical settings ($iCTV_{WP}$). To generate the PTV for the whole-pelvic irradiation ($iPTV_{WP}$), a margin of 5 mm for positioning uncertainty

was added to this $iCTV_{WP}$.

After the proton publication gap, all institutes that treated primary gynecological cancer used full and empty bladder CT scans to account for anatomical changes in their target volumes due to bladder filling. In the studies performed at the Robertson Proton Therapy Center, the ITV mainly takes into account the position of the vagina and not the position of the uterus, because the patients have undergone hysterectomy.[41,42] According to the RTOG consensus guidelines used in this institute, an ITV should be created from the registration of the empty and full bladder CT scan to account for the maximum movement of the vaginal target tissue due to bladder filling.[50] The study by Taku *et al.* shows that in 89% of the patients this ITV is not sufficient to represent the entire range and therefore a margin is needed for the ITV.[42] In this study, a margin of 10 to 15 mm is applied to the vaginal ITV, while in the study by Lin *et al.* a margin of 10 to 13 mm is used. In addition to this 10 to 13 mm margin, a margin of 3.5% of the beam range in beam direction and a 1 mm margin to the whole PTV was applied.

The second proton institute that includes bladder filling in its treatment plan is the Heidelberg Ion Beam Therapy Center in Germany. In the APROVE study performed in this institute, the ITV does include the parametrial tissue which was not included in the studies from the Robertson Proton Therapy Center.[48] A margin of 5 mm and 7 mm in beam direction is applied around the entire CTV (CTV_nodal + ITV) to create the PTV.

Lymph nodes margins

The margins for the lymph node irradiation and the positive lymph node boost of the most recent studies are visualized in Figure 3. In this figure, the studies that irradiate after surgery are visualized in the same illustration, because the surgery does not affect the lymph node area significantly and so these margins are comparable to the studies that did not perform surgery.

Carbon ion therapy
At the QST Hospital, the pelvic lymph node region was irradiated in the whole-pelvic irradiation (CTV1). A 5 mm margin for setup uncertainty was used for the CTV1 to create the PTV1. The whole-pelvic irradiation was followed by local boost irradiation on the CTV2 including the swollen lymph nodes. The margin used for this CTV2 ranged from 5 to 15 mm in the different protocols for the treatment of cervical cancer, with a margin of 5 to 10 mm in the most recent protocol.

The setup margin was smaller for irradiation of lymph nodes recurrence after definitive radiotherapy at the QST hospital, namely 3 mm.[31] However, already a margin of 5 mm was added to the CTV site, so in total 8 mm margin (Figure 3F).

At the Gunma University Heavy Ion Medical Center, lymph nodes were first irradiated in the whole-pelvic irradiation ($iCTV_{WP}$). A margin of 5 mm for positioning uncertainty was added to this $iCTV_{WP}$ to create the $iPTV_{WP}$. The whole-pelvic irradiation was followed by a boost to the positive lymph nodes (CTV_{LN}) with a margin of 3 mm and the contour of the intestines removed from this target volume.[34]

Proton therapy
No irradiation of the lymph nodes was performed at the Proton Medical Research Center in Ibaraki,[39,41] nor in the case report in which recurrent endometrial cancer in the vagina was treated.[23]

Regarding the margins around the lymph nodes at the Roberts Proton Therapy Center, both studies used a smaller margin for the CTV of the lymph nodes than for the tumor, namely 7 to 8 mm.[39,41] In addition to this margin, a margin of 3.5% of the beam range in beam direction to correct for uncertainty in the conversion of Hounsfield units to proton stopping power and an additional margin of 1 mm to correct for uncertainties in beam calibration was added in the study by Lin *et al.*[41] No boost was given to the positive lymph nodes in these studies.

In the APROVE study at the Heidelberg Ion Beam Therapy Center, a margin of 5 mm and 7 mm in beam direction is applied around the entire CTV, including the lymph nodes, to create the PTV.[48] No positive lymph node boost was given in this study.

Robust optimization

A 3.5% range robustness and 5 mm set-up robustness were used at the Maryland Proton Treatment Center in the United States.[44] In addition to the planning CT set, the density of fillings in bowels and rectum was overridden with air and muscle to create two virtual CT sets which were used in robust planning. Unfortunately, it is unclear what type of gynecological cancers were treated and what structures and margins the CTV and PTV contained.

Influencing factors

Information on factors that may have influenced the aforementioned margins and robustness settings e.g. the immobilization strategy, bladder filling protocol, rectal protocol, and (neo-) adjuvant treatment are summarized in Table 2.

Immobilization

Patients were immobilized with customized cradles and low-temperature thermoplastic sheets during planning CT and daily treatments in all studies performed in the QST Hospital and the study from the Gunma University Heavy Ion Medical Center.[24,34]

Some studies at the QST Hospital (protocol 9704, 9902, 1001, 1302, and the gynecological melanomas

studies) used vaginal packing at each treatment session to counteract the internal motion of the cervix.[26,27,29,32,33] In addition, with a contrast medium in the vaginal packing the surface of the cervix was visualized on X-ray images. In this way, the internal position of the cervix was determined before each treatment session.

For the primary tumor boost in the study by Ohno *et al.*, a new planning CT was made in which an immobilization device was placed in the vagina.[34] This immobilization device fixed the upper vaginal position and displaced the rectum from the cervical tumor. Besides fixation, the device was used for daily position verification using three tungsten markers at the cranial side of the device.

The patients in the studies of the Roberts Proton Therapy Center were immobilized with a knee-foot lock device.[41,42]

A ProSTEP (ITV, Innsbruck, Austria) was used to immobilize patients during planning CT and daily treatments in the APROVE-study.[48]

Bladder filling protocol

At the QST Hospital in Japan, the bladder was filled through a catheter during treatments in all studies, except for the study by Shiba *et al.*[31] The amount of normal saline infused into the bladder ranged from 100 to 150 ml. In the study by Okonogi *et al.*, the infusion of normal saline was only done for the boost irradiations.[30]

At the Gunma University Heavy Ion Medical Center, the bladder was filled by the insertion of 100 ml of normal saline into the bladder for the "bladder partially full" CT scan.[34] The "bladder empty" CT scan was performed immediately after urination. During each treatment session of the whole-pelvic irradiation, the patient setup was done immediately after urination. During the boost irradiations, the bladder was filled with 100 ml of normal saline using a catheter.

At the Roberts Proton Therapy Center, the patients drank approximately 500 ml of fluid 30 minutes before the planning CT and each treatment to fill the bladder.[41,42]

Bladder filling before the daily treatment sessions was not described in the study protocol of the APROVE study at Heidelberg Ion Beam Therapy Center, even though an ITV was used.[48] The studies from Ibaraki, Ibusuki, and Maryland did not describe their protocol for bladder filling either.[23,38,39,44]

Rectal protocol

Constipation was prevented at QST Hospital and the Gunma University Heavy Ion Medical Center by prescribing laxatives when needed. In addition, enemas to clear any gas or stool were used in Protocol 1001, 1302, and the second melanoma study of the QST Hospital.[29,30,33,34] In contrast with these studies, however, no protocol was described to counteract rectal filling in the first melanoma study.[32]

At the Roberts Proton Therapy Center, additional steps were taken to ensure an empty rectum. The rectal protocol consisted of the initiation of simethicone with each meal one week before the planning CT until the end of the treatment and at least one enema two hours before the planning CT.[41,42] Additionally, during the planning CT, an endorectal balloon containing 50 to 100 ml of water was inserted. In the study of Taku *et al.*, an endorectal balloon filled with the same amount as during the planning CT was inserted during daily treatments.[42] The authors stated that the use of this endorectal balloon resulted in a smaller maximal range of movement in the anterior posterior (AP) direction of the vaginal cuff and therefore smaller CTV-PTV margins could be used with the endorectal balloon in situ. In the study of Lin *et al.*, the patients also followed a liquid diet from 12 PM the day before the planning CT.[41]

In contrast to this comprehensive rectal protocol, the studies conducted at the Proton Medical Research Center, Mediopolis Proton Therapy and Research Center, Maryland Proton Treatment Center, and Heidelberg Ion Beam Therapy Center described nothing about preventing constipation or emptying the rectum before treatment.

Adaptive treatment planning

By applying adaptive treatment planning by regularly monitoring the changes in anatomy by CT scans, the target volumes can be reduced, as the tumor usually shrinks during treatment. Adaptive treatment was described in many of the articles from the QST Hospital, the study from Gunma for the local boost irradiation and the study by Yao *et al.*[24,27,28,34,44]

In Protocol 9403, 9702, 9902, and 0508 at the QST Hospital, new planning CTs were made after whole-pelvic irradiation and before the local boost irradiation (CTV2 and CTV3) to adjust the CTV in accordance with tumor shrinkage during the treatment.[24,27,28]

Similarly, at the Gunma University Heavy Ion Medical Center, a new planning CT was made for the subsequent boost irradiation after whole-pelvic irradiation.[34]

In the study of Yao *et al.*, Quality assurance CTs (QACT) were performed regularly to monitor changes in anatomy.[44] Deformable image registration was used to transform the contours (both the targets and OARs) from the planning CTs to the QACTs. A new plan was used when the dose deviation was outside the tolerance range.

(Neo-) adjuvant treatment

In the studies conducted at the QST Hospital before 2010 in which cervical cancer was treated (Protocol 9403, 9702, 9704, and 0508), no treatment other than carbon

ion therapy was used.[24,26–28] With the extended-field carbon ion radiotherapy in Protocol 0508, still 26.9% of the patients developed distant failure exclusive of para-aortic lymph node failure.[28] To increase survival rates, concurrent chemotherapy was given from 2010 in addition to carbon ion radiotherapy to improve local control. Chemotherapy consisted of five weekly courses of cisplatin (40 mg/m^2) starting on the first day of radiotherapy treatment.

In contrast, carbon ion radiotherapy was combined with image-guided brachytherapy and chemotherapy as treatment for LACC in the Gunma University Heavy Ion Medical Center.[34] After the local boost, image-guided brachytherapy treatment sessions were performed using tandem and ovoid applicators with or without interstitial needles. Similar to the chemotherapy courses at the QST hospital, five courses of weekly cisplatin (40 mg/m^2) were given throughout the radiation treatment period.

In the proton studies before 2000 conducted at the Proton Medical Research Center, a proton boost on the GTV was given as a substitute for intracavitary irradiation, so the boost was combined with photon therapy.[38,39] However, one patient in the study of Tsujii *et al.* was treated with protons alone.[39]

The patient from the case report treated in the Mediopolis Proton Therapy and Research Center received treatment for her endometrial cancer (abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic lymph node dissection, and adjuvant systemic chemotherapy).[23] However, proton therapy alone was used for the recurrence in the vagina.

The proton irradiations at the Roberts Proton Therapy Center and Heidelberg Ion Beam Therapy Center were performed after surgery.[41,42,48] Besides surgery, a vaginal brachytherapy boost is given to every patient with an indication for percutaneous pelvic radiotherapy in Heidelberg.[48]

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Table 2: Characteristics of the seven institutes treating gynecologic tumors with carbon ion or proton therapy using margins or robustness to address uncertainties.

*GTV = gross target volume; CTV = clinical target volume; ITV = internal target volume; PTV = planned target volume; n.m. = not mentioned; kV = kilovoltage; GI = Gastrointestinal; CT = computerized tomography; CBCT = cone-beam computerized tomography; pCT = planning CT; publ. = published; pt = patients; RT = radiotherapy * Irradiated with protons or photons/chemotherapy; ** In cervical cancer or endometrial cancer with cervical stromal invasion*

Institution (City, Country)	Author - Protocol	Tumor Site (No. of patients)	Year of treatment	CTV	PTV	Robust planning	(Neo-)adjuvant treatment	Immobilization	Rectal/bladder filling protocol
Carbon ion therapy									
QST Hospital (Chiba, Japan)	Kato et al. [24] – Protocol 9403	Locally advanced cervical cancer (squamous cell (n=27) and adenocarcinoma carcinoma (n=3))	1995 - 1997	CTV1 = tumor + uterus + parametrium + at least upper half of vagina + pelvic node region (pelvic vessels with 5-10 mm margin) CTV2 (new pCT) = tumor + parametrial involvement + remainder of the uterus + rest of the upper vagina + gross lymph node involvement	PTV1 = CTV1 + 5 mm margin PTV2 = CTV2 + 5 mm margin	No	No	Customized cradles and thermoplastic sheets	Laxatives if necessary 100 mL of normal saline infused into bladder
	Kato et al. [24] – Protocol 9702	Locally advanced cervical cancer (squamous cell carcinoma (n=14))	1997 - 2000	*First 7 patients same as protocol 9403* CTV1 = tumor + uterus + parametrium + at least upper half of vagina + pelvic node region (pelvic vessels with 5-10 mm margin) CTV2 (new pCT) = GTV + surrounding tissues CTV3 (new pCT) = GTV	*First 7 patients same as protocol 9403* PTV1 = CTV1 + 5 mm margin PTV2 = CTV2 + 5 mm margin PTV3 = CTV3 – GI tract	No	No	Customized cradles and thermoplastic sheets Vaginal packing.	Laxatives if necessary 100 mL of normal saline infused into bladder
	Wakatsuki et al. [26] – Protocol 9704	Uterine cervical adenocarcinoma (n=45) or adenosquamous (n=13) carcinoma	1998 – 2010	CTV1 = GTV + uterus + parametrium + at least upper half of vagina + ovaries + pelvic node region (common, internal, and external iliac, obturator, and presacral node regions) CTV2 = primary site + enlarged lymph nodes CTV3 = GTV	PTV1 = CTV1 + 5 mm margin + 15 mm margin around uterus PTV2 = CTV2 + 5 or 15 mm margin PTV3 = CTV3 – GI tract	No	No	Customized cradles and thermoplastic sheets Vaginal packing	Laxatives if necessary 100-150 mL of normal saline infused into bladder
	Wakatsuki et al. [27] – Protocol 9902	Locally advanced squamous cell carcinoma of the uterine cervix (n=22)	2000 – 2006	CTV1 = GTV + uterus + ovaries + parametrium + at least upper half of vagina + pelvic node region (common iliac, internal iliac, external iliac, obturator, and presacral node regions) CTV2 (new pCT)= primary site + enlarged lymph nodes CTV3 (new pCT) = GTV	PTV1 = CTV1 + 5 mm margin + 15 mm margin around uterus PTV2 = CTV2 + 5 or 15 mm margin PTV3 = CTV3 – GI tract	No	No	Customized cradles and thermoplastic sheets Vaginal packing	Laxatives if necessary 100-150 mL of normal saline infused into the bladder
	Wakatsuki et al. [28] – Protocol 0508	Locally advanced squamous cell carcinoma of the uterine cervix (n=26)	2006 – 2012	CTV1 = tumor + uterus + ovaries + parametrium + at least upper half of vagina + paraaortic lymph nodes + pelvic lymph nodes (common iliac, internal iliac, external iliac, obturator and presacral lymph nodes) CTV2 (new pCT) = GTV + cervix + uterine corpus + parametrium + upper half of vagina + ovaries and swelling lymph nodes CTV3 (new pCT) = GTV	PTV1 = CTV1 + 5 mm margin PTV2 = CTV2 + 5 mm margin PTV3 = CTV3 – GI tract	No	No	Customized cradles and thermoplastic sheets	Laxatives if necessary 100-150 mL of normal saline infused into the bladder
	Okonogi et al. [29] – Protocol 1001	Locally advanced cervical cancer (adenocarcinoma (n =26) and adenosquamous carcinoma (n=5))	2010 – 2014	CTV1 = GTV + uterus + ovaries + parametrium + at least upper half of vagina + whole pelvic lymph node region (common, internal iliac and external iliac, obturator and presacral lymph nodes) CTV2 = primary site + swollen lymph nodes CTV3 = GTV	PTV1 = CTV1 + 5 mm margin + 10 mm margin around uterus PTV2 = CTV2 + 5 to 10 mm margin PTV3 = CTV3 + 3 mm margin – GI tract	No	Five courses of weekly cisplatin (40 mg/m²) during C-ion treatment period	Customized cradles and thermoplastic sheets Vaginal packing	Enemas to clear stool Laxatives if necessary 100-150 mL of normal saline infused into the bladder
	Okonogi et al. [30] – Protocol 1302	Locally advanced uterine cervical squamous cell carcinoma (n=22)	n.m. (publ. August 2018)	CTV1 = GTV + uterus + ovaries + parametrium + at least upper half of vagina + whole pelvic lymph node region (common, internal iliac and external iliac, obturator and presacral lymph nodes) CTV2 = primary site + swollen lymph nodes CTV3 = GTV	PTV1 = CTV1 + 5mm margin + 10 mm margin around uterus PTV2 = CTV2 + 5 to 10 mm margin PTV3 = CTV3 + 3 mm margin – GI tract	No	Five courses of weekly cisplatin (40 mg/m²) during C-ion treatment period	Customized cradles and thermoplastic sheets Vaginal packing	Enemas to clear stool Laxatives if necessary 100-150 mL of normal saline infused into the bladder (only last 7 fractions for boost irradiation.
	Shiba et al. [31]	Lymph nodes recurrence of gynecological cancers (n=16)	2008 – 2016	CTV = GTV + 5 mm margin	PTV = CTV + 3 mm margin	No	After definitive RT for gynecologic cancers	Customized cradles and thermoplastic sheets	-
	Karasawa et al. [32]	Gynecological melanoma (vagina (n=14), vulva (n=6), cervix uteri (n=3))	2004 – 2012	CTV1 = uterus + vagina and/or vulva + pelvic lymph nodes (internal iliac, external iliac, obturator) + inguinal lymph nodes + 5 mm margin CTV2 = GTV + GTV node + minimal 5 mm margin	PTV1 = CTV1 + 3 mm margin (290 MeV/n energy) OR 6 mm margin (350 MeV/n energy) PTV2 = CTV2 + 3 mm margin (290 MeV/n energy) OR 6 mm margin (350 MeV/n energy)	No	Two pt adjuvant chemotherapy; Three pt neoadjuvant chemotherapy; Four pt after surgery	Custom-made immobilization device Vaginal packing	100-150 mL of normal saline infused into the bladder

	Murata et al. [33]	Malignant gynecological melanoma (vagina (n=22), vulva (n=12), cervix uteri (n=3))	2004 – 2017	CTV1 = uterus + vagina and/or vulva +pelvic lymph nodes (internal iliac, external iliac and obturator) + inguinal lymph nodes CTV2 = GTV + GTV node CTV3 = GTV	PTV1 = CTV1 + 5 to 10 mm margin PTV2 = CTV2 + minimal 5 mm margin PTV3 = CTV3 + 3 mm margin	No	Nine pt post-surgical recurrence; three pt neoadjuvant chemotherapy	Customized cradles and thermoplastic sheets Vaginal packing	Enemas to clear stool Laxatives if necessary 100-150 mL of normal saline infused into the bladder
Gunma University Heavy Ion Medical Center (Gunma, Japan)	Ohno et al. [34] – Protocol 1202	Locally advanced cervical cancer (squamous cell (n = 2) or adenocarcinoma (n=4))	2013 - 2018	CTV1 = GTV + uterus + parametrium + ovaries + at least upper half of vagina + whole pelvic node region (enlarged lymph nodes, common iliac, internal iliac, external iliac, obturator, and presacral node regions) iCTV_WP = CTV1 + individual internal margins uterus and cervix (based on full and empty bladder CT scan) CTV_CX (new pCT)= GTV + cervix CTV_LN (new pCT)= positive lymph nodes	iPTV_WP = iCTV_WP + 5 mm margin PTV_CX = CTV_CX + 3 mm margin – normal tissues with 5 mm margin PTV_LN = PTV_LN + 3 mm margin – intestines	No	Five courses of weekly cisplatin (40 mg/m^2) during C-ion RT treatment period Image guided brachytherapy after C-ion RT treatment period	*Both:* Customized cradles and thermoplastic shell *Local boost:* vaginal immobilization device to fix upper vagina position	Laxatives if necessary *Whole-pelvic irradiation:* irradiation after urination *Local boost:* 100 mL of normal saline infused into bladder
				Proton therapy					
Proton Medical Research Center (Ibaraki, Japan)	Kagei et al. [38]	Locally advanced squamous cell carcinoma of the uterine cervix (n=25)	1981 – 1991	CTV = GTV + 5 to 10 mm margin	N.m.	No	External photon RT to pelvis followed by proton RT to tumor	N.m.	N.m.
	Tsuji et al. [39]	Uterine cervix carcinoma (n=19), corpus carcinoma (n=2) and vaginal carcinoma (n=2)	1983 - 1990	CTV = GTV + 5 to 10 mm margin	N.m.	No	External photon RT to pelvis followed by proton RT to tumor	Polyurethane cradle during CT	N.m.
Mediopolis Proton Therapy and Research Center (Ibusuki, Japan)	Yanazume et al. [23]	Recurrent endometrial cancer in vagina (n=1)	n.m. (publ. 2015)	CTV = GTV + 5 mm margin	PTV = CTV + 4 mm (set-up) margin + 1 mm (internal) margin	No	Posthysterectomy	N.m.	N.m.
Roberts Proton Therapy Center (Philadelphia, United States)	Lin et al. [41]	Cervix (n=7), endometrial (n=2), recurrent endometrial (n=1), vaginal (n=1)	n.m. (publ. Oct 2015)	CTV_nodal = pelvic lymph nodes (internal and external iliac, common iliac and obturator lymph nodes) ITV = fused vaginal target volume from empty bladder and full bladder CT scan	PTV = (ITV + 10 to 13 mm margin) + (CTV_nodal + 7 to 8 mm margin) + margin of 3.5% of beam range in beam direction + 1 mm margin	Robust evaluation	Posthysterectomy; Two pt IMRT as component; Two pt extra boost to pelvis; Ten pt chemotherapy; Five pt brachytherapy	Supine with knee-foot lock device	Enema 2 hours before pCT Simethicone with each meal Liquid diet from 12 PM the day before pCT Rectal balloon (50-100 ml) during pCT. 473 ml of fluid 30 min before pCT and treatment
	Taku et al. [42]	Uterus (n=9), cervix (n=8), vagina (n=1)*	2013 – 2014	CTV_nodal = n.m. CTV_vaginal = vagina and paravaginal tissue on both full and empty bladder CT scan ITV = CTV_vagina full and empty bladder merged	PTV = (vaginal ITV + 10 to 15 mm margin) and (nodal CTV + 7 to 8 mm margin)	No	Posthysterectomy	Knee-foot lock device	Enema 2 hours before pCT Simethicone prescribed Rectal balloon (50-100 ml) during CT and treatment. 500 ml of fluid 30 min before pCT and treatment.
Maryland Proton Treatment Center (Maryland, United States)	Yao et al. [44]	Gynecologic cases (n=3)	n.m. (publ. 2020)	N.m.	N.m.	3.5% range uncertainty + 5 mm setup uncertainty. Bowels and rectum overridden with air or muscle	N.m.	N.m.	N.m.
Heidelberg Ion Beam Therapy Center (Heidelberg, Germany)	Arians et al. [48]	Cervical and endometrial cancer (n=25)	2017 - 2019	CTV_nodal = common + external + internal iliac lymph node areas (+ presacral lymph node region**) CTV_vagina = upper 3 cm of vagina + paravaginal soft tissue lateral to the vagina ITV = CTV_vagina full and empty bladder merged	PTV = CTV_nodal + ITV + 5 mm margin and 7 mm in beam direction	No	Postoperative; vaginal brachytherapy boost if indicated; chemotherapy if indicated	ProSTEP	N.m.

DISCUSSION

From the systematic search followed 14 institutes that treated gynecological tumors with carbon ion or proton therapy. The growing interest in proton therapy can be seen in the last ten years. The majority of the institutes use margins as a treatment strategy to address uncertainties while one institute uses robust optimization. Margins have ranged from 5 mm for the PTV to 15 mm around the uterus for inter- and intrafraction movement, with a notable decrease in conservative margins seen over time.

Overview of the institutes

With respect to the first part of the review, a clear overview is given of the 14 institutes located around the world that summarizes the location, tumor type, amount of patients, the year of treatment, and the time trends in this field, see Figure 2. With this figure, the current review shows that proton therapy was first used for gynecological tumors, namely in Russia and Japan, followed by a large publication gap in which carbon ion therapy was used. As of 2012, there is a growing interest in proton therapy in multiple European countries, Taiwan, China, and the United States.

It is somewhat surprising that only 3/14 (21%) institutes used carbon ion therapy, while 13/34 (38%) articles described treatment with carbon ion therapy. The reason for this large amount of articles is that the QST hospital has performed a lot of research compared to the other institutes.

Another interesting finding was that carbon ion and proton therapy were also combined in the treatment of gynecological tumors in the study conducted by Zhang *et al.*[17] This striking combination is not seen in other studies.

Treatment strategies

In addition to this global overview, the present review was designed to clarify what margins and robustness settings the institutes dare to use for the treatment of gynecological tumors with protons or carbon ion therapy. Surprisingly, all institutes used margins except the Maryland Proton Treatment Center where robust optimization was used. Considering other tumor sites, robust optimization is commonly used in the clinic today as in anal cancer, breast cancer, and lung cancer.[51–53] However, the studies in this review are also mostly from a time when robust optimization did not yet exist. The 3.5% range robustness used at the Maryland Proton Treatment Center is similar to what is used in other tumor sites.[51–53]

It is interesting to note that the same margin was used for many different tumor types, see Table 2. For example, Lin *et al.* treated cervical, endometrial, recurrent endometrial, and vaginal carcinoma with the same margins.[41] These findings suggest that all the treatments of these tumors experience similar uncertainties, e.g., due to movements in the pelvic region.

Another important finding was that the studies that include uterus motion using an ITV did not use an adaptive strategy, such as a plan-library. By using a plan-library based on a plan-of-the-day approach, the dose on the OAR can be reduced while maintaining target coverage.[54] This plan-of-the-day approach is applied in the clinic for pelvic radiotherapy for the irradiation of cervical cancer and other tumor types.[55,56] Van de Schoot *et al.* demonstrates the feasibility and benefits of this adaptive proton therapy strategy in cervical cancer,[57] however, none of the institutes apply this approach.

Contrary to expectations, the margins for whole-pelvic irradiation are equal or greater after hysterectomy than without surgery. This result is unexpected because the movable uterus was removed during the surgery, so the tumor target after hysterectomy is only the vagina and paravaginal tissue. In addition, the uncertainties due to setup changes will be about the same.

Regarding the tumor margins, an unexpected choice was made in the study conducted at the Gunma University Heavy Ion Medical Center, namely that normal tissue was removed from the PTV with a margin of 5 mm.[34] The authors substantiate this choice with the fact that they thereby avoid intestinal irradiation. Although intestinal irradiation may cause side effects, removing normal structures with a margin of 5 mm is not a solution since part of the GTV may be removed from the PTV and therefore tumor coverage may no longer be sufficient.

A comparison of the margins used for tumor irradiation and lymph node irradiation reveal that equal (QST Hospital, the Gunma University Heavy Ion Medical Center, and the Heidelberg Ion Beam Therapy Center) or smaller (Roberts Proton Therapy Center) margins are used for the lymph nodes irradiation than for the tumor irradiation. This is surprising since the setup uncertainties for the lymph node target area are larger because the patient is positioned using bony alignment based on the pelvic bones. Therefore, rotational errors have a larger impact on the lymph node area.[58] However, lymph nodes experience less movement due to bladder and rectal filling.

Influencing factors

The studies from the QST Hospital and the Gunma University Heavy Ion Medical Center stated that immobilization of the vagina provided less intrafraction movement, allowing them to irradiate with smaller margins. The visualization of the surface of the vagina by this vaginal packing or immobilization device may allow for better positioning of the patient and thus a smaller interfraction movement. Immobilization and visualization of the vagina may be a valuable addition for

further work, however, the benefits must outweigh the additional stress to the patient caused by the insertion of the packing and immobilization device.

Regarding bladder filling, most of the institutes used a catheter to fill the bladder. This method may provide a more consistent bladder volume rather than having the patient drink, which results in a smaller interfraction organ motion. Similar to vaginal packing, the insertion of a catheter is stressful for the patient and therefore the benefit of this catheter should be investigated before it is recommended for further studies. It is noteworthy that in the study of Ohno *et al.* the pelvic irradiation does include individual internal margins based on a full and empty bladder CT scan, while the pelvic irradiation is performed immediately after urination.[34] Irradiating with an empty bladder makes the internal margins to account for bladder filling redundant. In this situation, adding internal margins only harms the patient by delivering more dose to the OAR due to the larger target volume, without the benefits of addressing uncertainties. A possible reason for irradiating after urination is that the researchers chose a more consistent bladder volume, namely empty.

Another factor considered in this review was the rectal protocol. The most notable result was that an extensive rectal protocol including enemas, a liquid diet, and a rectal balloon was used at the Roberts Proton Therapy Center. The authors recommend treatment with an endorectal balloon in situ because it provides benefits by counteracting the movement of the vaginal cuff in the AP direction.[42] Although narrower AP margins can be achieved with the endorectal balloon in situ, the insertion of an endorectal balloon, like a bladder catheter, is stressful for the patient.

It is interesting to note that in three of the seven institutes new planning CTs were performed during the radiotherapy treatment period to account for the shrinking volume of the target. Making new planning CTs after several irradiations could be a good addition for subsequent research. However, making a new treatment plan is time-consuming, and making an additional CT plan involves extra costs.

Limitations

There are three limitations of this review. First, it is possible that institutions are missing from the overview, for example, because not all studies were found with the literature search.

Second, the value of the comparison between the margins is limited since the pelvic anatomy of Asian women is different from that of European women which may result in less or more intra- and interfraction movement in the pelvic region.[59]

Finally, all gynecological tumors are compared while their treatment experiences just different uncertainties due to, for example, the tumor location in the pelvis.

Conclusion

The review revealed that 14 institutes used carbon ion or proton therapy to treat many different gynecological tumors. Interest in proton therapy for the treatment of gynecological tumors has significantly increased over the past 10 years leading to 12 institutes using protons now.

The second aim of this study was to clarify the margins and robustness settings used in these institutes. Six institutes used margins to address uncertainties in treatment planning and dose delivery, while one institute used robust optimization. Regarding the tumor margins, most studies used an ITV combined with a PTV margin for whole-pelvic irradiation, while smaller margins (3 to 10 mm) were used for the primary tumor boost. As for lymph node irradiation, a 5 mm margin was used in most of the studies, while the margins for the positive lymph node boost also ranged from 3 to 10 mm. Although none of the institutes used a plan-of-the-day approach, the study by van de Schoot *et al.* demonstrates the dosimetric benefits, resulting in a recommendation to use this approach in a subsequent study.[54] The findings of the institutes suggest that vaginal packing, filling the bladder with a catheter instead of a drinking protocol, and an endorectal balloon in situ during radiotherapy treatment may offer advantages in reducing inter- and intrafraction movement. However, all of these procedures impose an additional burden on the patient and the benefits must outweigh the additional stress to the patient.

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APPENDIX: SEARCH TERMS

Embase

('proton radiation'/de OR 'proton therapy'/de OR 'ion therapy'/de OR 'hadron'/de OR 'fast proton radiation'/de OR (((proton* OR ion OR carbon*) NEAR/3 (radiation* OR therap* OR radiotherap* OR RT OR beam* OR irradiation* OR monotherap* OR boost*)) OR CIRT OR HIRT OR HADRON):ab,ti,kw) **AND** ('uterine cervix tumor'/exp OR ('urogenital tract tumor'/exp AND 'female'/exp) OR 'female genital tract cancer'/exp OR 'hysterectomy'/exp OR (((cervix* OR cervical* OR genital* OR urogenital* OR vulv* OR ovarian* OR ovary OR ovaries OR endometr* OR gynecol* OR gynaecol* OR uterus OR vagina*) NEAR/3 (tumor* OR tumour* OR neoplas* OR malign* OR cancer* OR carcinom* OR adenocarcin* OR melanom*)) OR hysterectom* OR (((genital* OR urogenital*) NEAR/3 (tumor* OR tumour* OR neoplas* OR malign* OR cancer* OR carcinom* OR adenocarcin* OR melanom*)) AND (female* OR woman* OR women* OR vulv* OR ovarian* OR ovary OR ovaries OR endometr* OR gynecol* OR gynaecol* OR uterus OR vagina* OR cervix* OR cervical*))):ab,ti,kw) NOT ((animal/exp OR animal*:de OR nonhuman/de) NOT ('human'/exp)) **AND** ('clinical study'/de OR 'major clinical study'/de OR 'multicenter study'/de OR 'comparative study'/de OR 'clinical trial'/exp OR 'randomization'/exp OR 'intervention study'/de OR 'controlled study'/de OR 'clinical article'/de OR (((comparativ* OR interven* OR cohort* OR longitudinal* OR correlation* OR multicenter* OR multi-center* OR clinical*) NEAR/6 (study OR studies OR research OR trial* OR articl* OR paper* OR report*)) OR ((case OR cases OR match*) NEAR/3 control*) OR (cross NEXT/1 section*)):ti,kw) NOT ([Conference Abstract]/lim OR [Conference Review]/lim) NOT (carbon-dioxide OR CO2):ti

Medline

(Proton Therapy/ OR Heavy Ion Radiotherapy/ OR (((proton* OR ion OR carbon*) ADJ3 (radiation* OR therap* OR radiotherap* OR RT OR beam* OR irradiation* OR monotherap* OR boost*)) OR CIRT OR HIRT OR HADRON).ab,ti,kf.) **AND** (exp Genital Neoplasms, Female/ OR exp Hysterectomy/ OR (((cervix* OR cervical* OR genital* OR urogenital* OR vulv* OR ovarian* OR ovary OR ovaries OR endometr* OR gynecol* OR gynaecol* OR uterus OR vagina*) ADJ3 (tumor* OR tumour* OR neoplas* OR malign* OR cancer* OR carcinom* OR adenocarcin* OR melanom*)) OR hysterectom* OR (((genital* OR urogenital*) ADJ3 (tumor* OR tumour* OR neoplas* OR malign* OR cancer* OR carcinom* OR adenocarcin* OR melanom*)) AND (female* OR woman* OR women* OR vulv* OR ovarian* OR ovary OR ovaries OR endometr* OR gynecol* OR gynaecol* OR uterus OR vagina* OR cervix* OR cervical*))).ab,ti,kf.) NOT (exp Animals/ NOT Humans/) **AND** (exp Clinical Study/ OR Multicenter Study/ OR Comparative Study/ OR Random Allocation/ OR (((comparativ* OR interven* OR cohort* OR longitudinal* OR correlation* OR multicenter* OR multi-center* OR clinical*) ADJ6 (study OR studies OR research OR trial* OR articl* OR paper* OR report*)) OR ((case OR cases OR match*) ADJ3 control*) OR (cross ADJ section*)).ti,kf.) NOT (news OR congres* OR abstract* OR book* OR chapter* OR dissertation abstract*).pt. NOT (carbon-dioxide OR CO2).ti.

Web of Science

TS=(((((proton* OR ion OR carbon*) NEAR/2 (radiation* OR therap* OR radiotherap* OR RT OR beam* OR irradiation* OR monotherap* OR boost*)) OR CIRT OR HIRT OR HADRON)) **AND** ((((cervix* OR cervical* OR genital* OR urogenital* OR vulv* OR ovarian* OR ovary OR ovaries OR endometr* OR gynecol* OR gynaecol* OR uterus OR vagina*) NEAR/2 (tumor* OR tumour* OR neoplas* OR malign* OR cancer* OR carcinom* OR adenocarcin* OR melanom*)) OR hysterectom* OR (((genital* OR urogenital*) NEAR/2 (tumor* OR tumour* OR neoplas* OR malign* OR cancer* OR carcinom* OR adenocarcin* OR melanom*)) AND (female* OR woman* OR women* OR vulv* OR ovarian* OR ovary OR ovaries OR endometr* OR gynecol* OR gynaecol* OR uterus OR vagina* OR cervix* OR cervical*))))) **AND** TI=(comparativ* OR interven* OR cohort* OR longitudinal* OR correlation* OR multicenter* OR multi-center* OR clinical* OR study OR studies OR research OR trial*) NOT TI=(carbon-dioxide OR CO2)

APPENDIX B: SUPPLEMENTARY METHODS

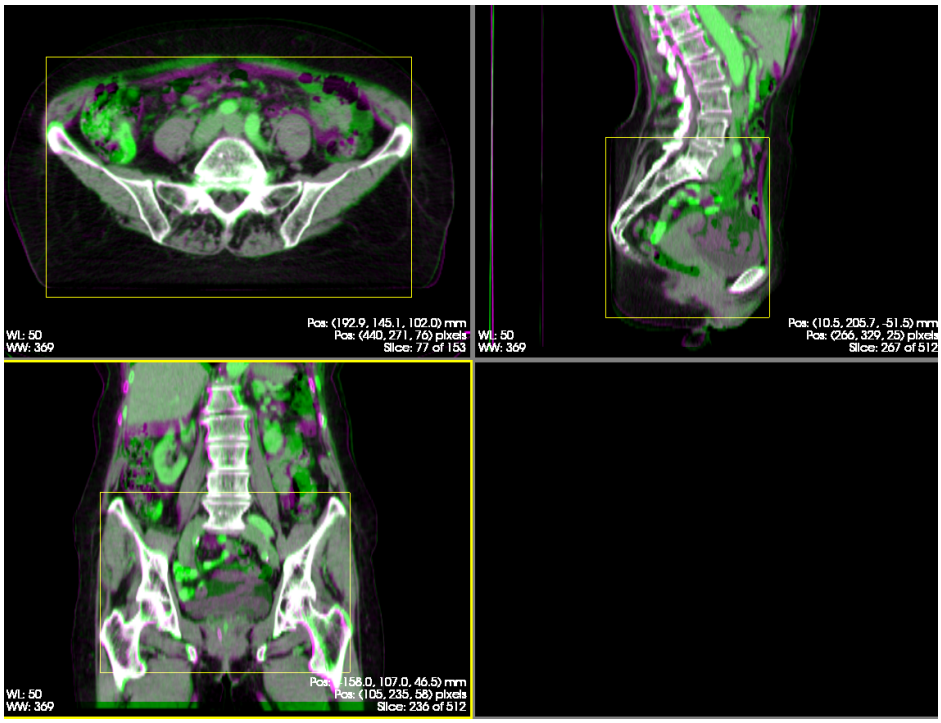

Figure 1: Clipbox used for the rigid pelvic bone registrations.

Table 1: Optimization settings used in treatment optimization.

Optimization settings	
Beam angles [degree]	90, 150, 210, 270
Setup robustness [mm]	5
Range robustness [%]	3
Number of iterations	7
Bixelgrid [mm]	2.0
Dose grid [mm]	5.0
Spot margin [mm]	5.0
Sample size	3000 (first iteration 9000)
Air override [HU]	-500
Contrast override [HU]	0

APPENDIX C: RECTAL FILLING EFFECTS AND MITIGATION

Since underdosage in the posterior part of the CTV_T_LR means that there is an underdosage in the CTV_HR, it is important to prevent underdosage in this part of the CTV_T_LR. The rectum undergoes large density and volume changes between the fractions and largely overlaps with the beam path of the dose delivery to the posterior part of the CTV_T_LR. Because IMPT is sensitive to density changes along the beam path and variations in location, we expected that underdosages in this posterior part are due to differences in rectal filling between the pCT and reCTs.[35]

Methods

The rectal filling is quantified by measuring the diameter of the rectum and estimating the HU value of the rectum from the pCT and reCT scans to examine the extent to which changes in rectal density and rectal filling affect the target coverage. Because the rectum occupies a larger cranial-caudal direction, the measurements are performed at three levels. For the caudal part of the rectum, the diameter and the average HU value are measured at the level of the caudal side of the femoral heads. The second measurement was performed at the level of the most cranial part of the femoral heads for the middle part of the rectum. For the cranial part of the rectum, the measurement is performed three slices below the sacroiliac joint.

Results

The posterior part of the cervix or corpus uteri received less than 42.75 Gy in three patients. The dose distribution of the target volumes of these patients is shown in Appendix E.

The diameter in the direction of the beam and the HU value of the rectum were measured at the three levels. The results of these measurements are shown in Table 1. When the diameter of the rectum differs by more than 20 mm from the diameter on the pCT, the value is shown in bold. In addition, if the HU value of the reCT differs by more than 200 from the HU value on the pCT, the value is shown in bold.

Large air pocket (>30 mm in the beam direction) were seen in the rectum of both patients with underdosage (R01, R04, and R06) and patients without underdosage (R05, R08, R10, R11, R13, R14, R15, and R17) in the posterior part of the CTV_T_LR.

Considering the results of the first part of this study, the overlap of the CTV_T_LR by the ITV45 was smaller in two patients with posterior underdosage than in those without posterior underdosage.

The mean overlap in the patients without underdosages was 93% (minimum 90%). Patient R01 had a average overlap of 79% and the second reCT had only 58% overlap. Patient R04 had an average overlap of 91% and only 79% on the fourth reCT. Patient R06 had an average overlap of 97%, which is more than the average of patients without underdosage. All these overlap values were calculated with an isotropic margin of 1 mm around the ITV.

The small percentages of overlap in patients R01 and R06 are due to shifts in the target volume. These shifts are the result of variation in filling of the rectum, sigmoid, bowel bag, and/or bladder. Thus, variation in the volume of these organs affects the target coverage. Figure 1 shows that the bowel bag in patient R01 has shifted the target volume anteriorly.

Discussion

Large air pockets (>30 mm in the beam direction) were detected in patients with and without underdosage in the posterior part of the CTV_T_LR. This suggests that air pockets are not the main cause of the underdosages in the posterior part of the cervix and corpus uteri in this patient population.

The CTV_T_LR of the reCTs of two patients with underdosage in the posterior part of the uterus was less overlapped by the ITV45 than in patients without underdosage in the posterior part of the uterus. These lower percentages in overlap were due to the target volume shifts caused by differences in the rectal, sigmoid, bladder, and bowel bag filling. To compensate for these shifts, the CTV-to-ITV margin can be increased in the posterior region, as in the fifth option in Table 6, to prevent this posterior underdosing.

*Table 1: Measurements of the diameter and HU value of the rectum. *reCT not used in the simulation. **Rectum not presented at this level. Bold = difference in diameter is larger than 20 mm compared to the pCT or the difference in HU value is larger than 200 compared to pCT.*

		pCT	reCT1	reCT2	reCT3	reCT4	reCT5	Underdosage CTV_T_LR
R01	Caudal femoral heads	35 (20)	35 (0)	30 (20)	*	40 **(-800)**	-	Posterior cervix uteri
	Cranial femoral heads	15 (20)	10 (-20)	19 (0)		15 (20)		
	Below SI-joint	19 (0)	30 (-30)	28 (-30)		16 (-20)		
R04	Caudal femoral heads	20 (0)	20 (0)	23 (0)	16 (20)	17 (0)	-	Posterior corpus uteri
	Cranial femoral heads	45 (-200)	30 (-200)	31 **(0)**	28 **(20)**	30 **(-500)**		
	Below SI-joint	40 (0)	28 **(-200)**	30 (0)	25 (20)	28 **(-500)**		
R05	Caudal femoral heads	23 (-100)	23 (0)	16 (0)	25 (0)	**50 (-900)**	20 (0)	
	Cranial femoral heads	8 (0)	12 (0)	16 (0)	13 (0)	15 (0)	17 (0)	
	Below SI-joint	12 (20)	10 (0)	17 (0)	12 (0)	**40 (-800)**	20 (0)	
R06	Caudal femoral heads	35 (-200)	35 (-200)	25 **(20)**	30 (-200)	50 **(-900)**	-	Posterior cervix uteri
	Cranial femoral heads	32 (-300)	24 (-150)	27 (-200)	30 (-200)	28 **(-800)**		
	Below SI-joint	38 (-200)	40 (-200)	28 (-200)	25 (-300)	26 **(-500)**		
R07	Caudal femoral heads	25 (20)	22 (20)	25 (0)	24 (20)	24 (0)	-	
	Cranial femoral heads	16 (20)	23 (25)	20 (20)	21 (20)	22 **(-300)**		
	Below SI-joint	28 (20)	30 (20)	25 (20)	23 (20)	25 (20)		
R08	Caudal femoral heads	30 (-300)	-	37 **(20)**	50 **(30)**	*	-	
	Cranial femoral heads	28 (-100)		21 (30)	26 (30)			
	Below SI-joint	30 (-100)		23 (30)	38 **(-500)**			
R09	Caudal femoral heads	20 (0)	27 (20)	29 (20)	23 (20)	*	-	
	Cranial femoral heads	17 (0)	18 (20)	18 (20)	23 (20)			
	Below SI-joint	14 (0)	23 (0)	22 (20)	20 (30)			
R10	Caudal femoral heads	26 (0)	*	27 **(-800)**	20 (20)	15 (20)	-	
	Cranial femoral heads	17 (40)		30 **(-200)**	18 (20)	27 (20)		
	Below SI-joint	17 (40)		25 (20)	20 (20)	16 (20)		
R11	Caudal femoral heads	25 (20)	40 **(-900)**	30 (0)	23 (20)	25 (20)	-	
	Cranial femoral heads	20 (20)	37 **(-300)**	40 **(-300)**	23 (20)	20 (20)		
	Below SI-joint	20 (20)	18 (20)	16 (0)	12 (20)	20 (0)		
R13	Caudal femoral heads	25 (0)	25 **(-200)**	22 **(-700)**	25 (-100)	30 **(-400)**	-	
	Cranial femoral heads	26 (-100)	25 (0)	24 (0)	30 (0)	**60** (0)		
	Below SI-joint	25 (-50)	35 (-100)	27 (0)	35 (-200)	40 (-50)		
R14	Caudal femoral heads	19 (0)	26 (20)	19 (0)	17 (0)	23 (0)	-	
	Cranial femoral heads	24 (-700)	25 **(0)**	19 **(0)**	20 **(-100)**	21 **(0)**		
	Below SI-joint	18 (20)	27 (20)	20 **(-800)**	19 (0)	23 (0)		
R15	Caudal femoral heads	23 (20)	24 **(-900)**	21 **(-700)**	23 (0)	22 (20)	-	
	Cranial femoral heads	16 (30)	24 **(-700)**	32 (-100)	33 **(-300)**	20 (30)		
	Below SI-joint	38 (0)	30 (0)	**10** (20)	20 **(-200)**	**17** (30)		
R16	Caudal femoral heads	24 (20)	*	26 (30)	30 (30)	19 (30)	-	
	Cranial femoral heads	30 (-300)		28 **(30)**	25 **(30)**	29 (-400)		
	Below SI-joint	23 (-400)		15 **(30)**	19 (-500)	22 **(-100)**		
R17	Caudal femoral heads	30 (-500)	45 (-500)	38 **(-300)**	45 **(0)**	37 (-400)	-	
	Cranial femoral heads	40 (-300)	23 (-100)	50 **(-700)**	47 (-100)	45 (-100)		
	Below SI-joint	**	**	25 (-800)	33 (-100)	**		

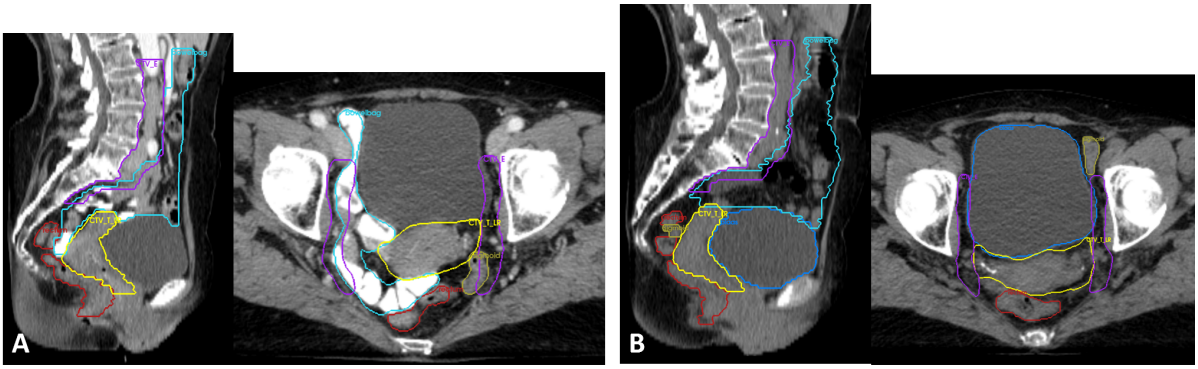

Figure 1: Shift of the target volume in patient R01. A: Sagittal and axial slice of the pCT showing the anterior shift of the target volume due to the large volume of the bowel bag. B: Sagittal and axial slice of the reCT without anterior shift. Yellow = CTV_T_LR, purple = CTV_E, red = rectum, light blue = bowel bag, dark blue = bladder.

APPENDIX D: SUPPLEMENTARY RESULTS

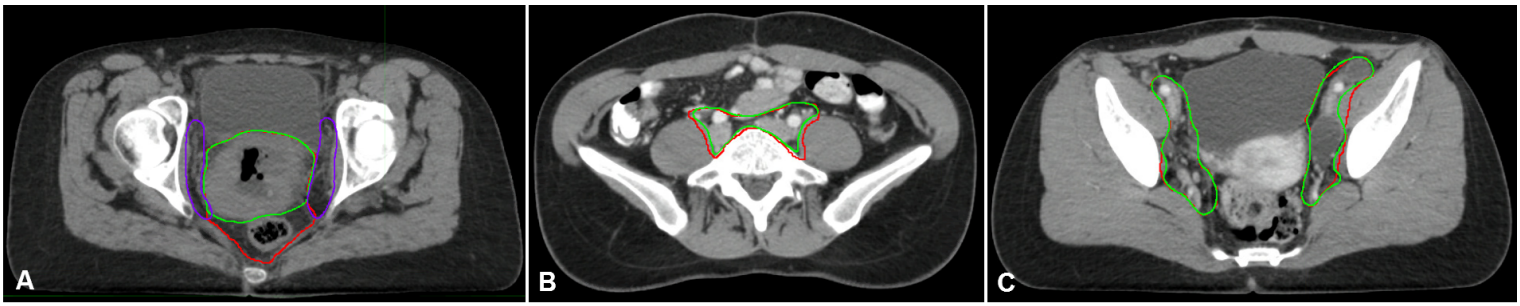

Figure 1: Improvements in the delineations of the target volumes. A: removing the rectum and mesorectum from the CTV_T_LR (red = old CTV_T_LR, green = improved CTV_T_LR) of patient R09. B: removing the psoas muscle from the CTV_E (red = old CTV_E, green = improved CTV_E) of patient R04. C: removing the iliopsoas from the CTV_E (red = old CTV_E, green = improved CTV_E) of patient R04.

Table 1: Largest diameter in mm on axial slice of the air pockets for each patient.

	R01	R04	R05	R06	R07	R08	R09	R10	R11	R13	R14	R15	R16	R17
Diameter of air pocket (mm)	16	25	23	24	36	26	32	14	11	30	28	18	20	28

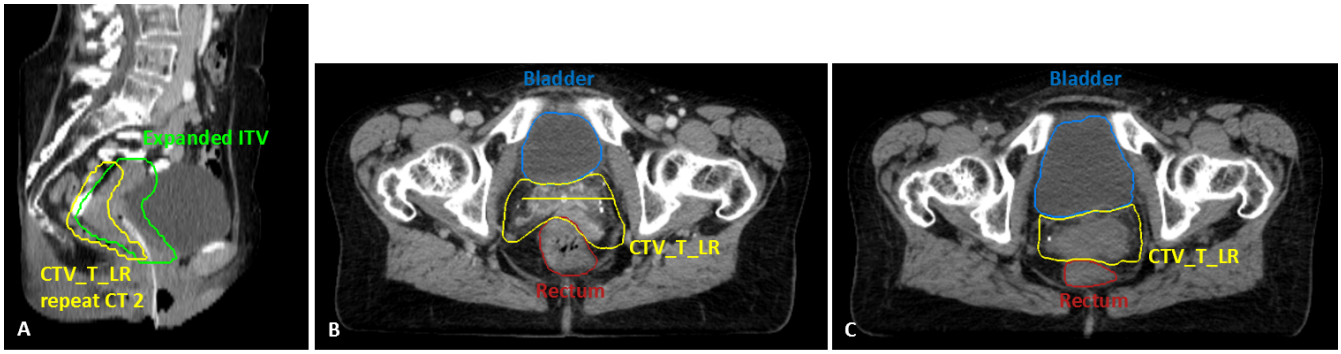

Figure 2: Multiple views of patient R01. A: Sagittal view of the full bladder pCT with the expanded ITV, and matched CTV_T_LR of reCT 2. B: Axial view of the full bladder pCT with bladder, CTV_T_LR, and rectum. C: Axial view of the second reCT with bladder, CTV_T_LR, and rectum.

Table 2: Dose values in gray of the organs at risk of the treatment plans used in the simulation.

	Constraint (Gy)		R01	R04	R05	R06	R07	R08	R09	R10	R11	R13	R14	R15	R16	R17
Bowel Dmax (nominal)	47.25	1	46.08	46.07	45.67	45.96	46.03	46.07	46.03	45.92	45.67	45.78	45.78	45.83	46.15	45.89
		2	-	-	45.63	45.98	46.04	-	-	45.88	45.68	-	-	-	-	46.10
		3	-	-	45.52	45.90	45.95	-	-	45.93	45.64	-	-	-	-	46.06
		4	-	-	-	45.95	45.98	-	-	-	-	-	-	-	-	-
Sigmoid Dmax (nominal)	47.25	1	45.73	46.09	46.02	45.92	46.38	46.14	46.03	46.05	45.98	45.85	46.03	46.06	46.32	46.14
		2	-	-	45.70	46.20	46.18	-	-	46.13	45.62	-	-	-	-	46.31
		3	-	-	45.88	45.83	46.27	-	-	46.20	45.79	-	-	-	-	46.29
		4	-	-	-	46.23	46.17	-	-	-	-	-	-	-	-	-
Bladder Dmax (nominal)	47.25	1	46.12	46.29	46.03	45.98	46.11	46.53	46.19	45.76	46.30	46.19	46.16	46.21	46.47	46.48
		2	-	-	45.96	46.00	46.34	-	-	45.98	46.05	-	-	-	-	46.24
		3	-	-	46.05	46.17	46.20	-	-	46.31	45.88	-	-	-	-	46.21
		4	-	-	-	46.11	46.38	-	-	-	-	-	-	-	-	-
Rectum Dmax (nominal)	47.25	1	46.15	46.26	45.93	45.80	46.25	46.23	45.77	45.96	45.84	45.59	45.99	46.14	46.19	45.68
		2	-	-	45.75	45.97	46.08	-	-	46.27	45.97	-	-	-	-	46.71
		3	-	-	45.75	46.04	46.06	-	-	46.18	45.64	-	-	-	-	46.40
		4	-	-	-	45.85	45.99	-	-	-	-	-	-	-	-	-
Kidney_L Dmean (nominal)	15	1	1.37	2.66	0.00	0.00	2.15	0.00	3.59	-	0.00	-	2.46	-	3.01	0.00
		2	-	-	0.00	0.00	1.23	-	-	-	0.00	-	-	-	-	0.00
		3	-	-	0.00	0.00	1.29	-	-	-	0.00	-	-	-	-	0.00
		4	-	-	-	0.00	1.92	-	-	-	-	-	-	-	-	-
Kidney_R Dmean (nominal)	15	1	1.92	2.08	0.00	0.00	1.94	0.00	5.68	-	0.00	-	6.02	-	3.79	0.00
		2	-	-	0.00	0.00	1.34	-	-	-	0.00	-	-	-	-	0.00
		3	-	-	0.00	0.01	2.00	-	-	-	0.00	-	-	-	-	0.00
		4	-	-	-	0.00	2.25	-	-	-	-	-	-	-	-	-
Spinal cord Dmax (nominal)	48	1	9.95	8.97	8.39	13.43	20.75	10.27	23.50	10.46	10.46	13.56	13.14	16.23	10.06	19.50
		2	-	-	10.48	9.85	26.07	-	-	10.79	11.02	-	-	-	-	10.54
		3	-	-	8.63	11.12	25.83	-	-	8.44	10.42	-	-	-	-	20.17
		4	-	-	-	11.54	22.14	-	-	-	-	-	-	-	-	-
Femoral heads Dmax (nominal)	50	1	41.38	30.71	16.71	29.76	24.16	23.81	33.41	22.77	30.72	38.65	32.74	23.89	30.31	38.64
		2	-	-	17.47	28.63	25.03	-	-	20.39	29.54	-	-	-	-	37.47
		3	-	-	16.06	28.72	26.67	-	-	18.55	28.93	-	-	-	-	38.46
		4	-	-	-	28.24	25.77	-	-	-	-	-	-	-	-	-
Body Dmax (nominal)	48.15	1	46.06	46.20	45.90	46.04	46.18	46.20	45.92	45.95	45.91	45.91	46.10	45.99	46.25	46.18
		2	-	-	45.89	46.01	46.08	-	-	45.95	45.89	-	-	-	-	46.18
		3	-	-	45.86	45.96	45.98	-	-	45.96	45.80	-	-	-	-	46.09
		4	-	-	-	45.93	46.01	-	-	-	-	-	-	-	-	-

Table 3: D95 values in gray for the CTV_T_LR of the 140 simulated treatments. Values below 42.75 are shown in bold.

	R01	R04	R05	R06	R07	R08	R09	R10	R11	R13	R14	R15	R16	R17
Treatment 1	43.4	43.2	44.0	43.3	44.0	43.8	44.1	43.3	43.4	43.3	43.8	43.5	43.7	44.1
Treatment 2	43.5	43.4	43.8	43.5	43.9	43.9	44.1	43.2	43.6	43.3	43.6	43.6	43.5	44.0
Treatment 3	43.3	43.4	43.7	43.2	43.6	43.5	44.0	**42.7**	43	43.6	43.7	43.7	43.4	44.0
Treatment 4	43.1	43.4	43.8	43.7	44.1	44.0	43.9	43.4	43.6	43.3	43.5	44.0	43.4	43.9
Treatment 5	43.1	43.5	43.8	43.8	43.4	43.7	43.7	42.9	43.5	43.4	43.6	43.7	43.7	44.1
Treatment 6	43.2	43.6	44.1	43.6	43.9	43.8	44.0	43.1	43.5	43.4	43.7	43.4	43.5	43.7
Treatment 7	43.6	43.6	44.0	43.8	43.8	43.7	44.0	43	43.4	43.3	43.7	43.8	43.7	43.9
Treatment 8	43.2	43.7	43.8	43.4	43.9	43.8	43.9	42.9	43.4	43.5	43.7	43.8	43.6	43.9
Treatment 9	43.7	43.3	43.8	43.5	44.0	43.8	44.0	43.1	43.6	43.5	43.7	43.7	43.5	44.0
Treatment 10	43.7	43.5	44.0	43.6	43.7	44.1	44.2	42.8	43.5	43	43.7	43.9	43.4	44.2

Table 4: D95 values in gray for the CTV_E of the 140 simulated treatments. Values below 42.75 are shown in bold.

	R01	R04	R05	R06	R07	R08	R09	R10	R11	R13	R14	R15	R16	R17
Treatment 1	43.9	42.8	43.9	43.4	43.8	43.2	**39.5**	43.7	43.6	43.7	43.6	43.3	43.9	44
Treatment 2	43.8	43.3	43.8	43.6	43.7	43.4	**38.4**	43.7	43.6	43.8	43.5	43.4	43.9	44
Treatment 3	43.7	43	43.7	43.4	43.6	**42.7**	**40.1**	43.8	43.6	43.8	43.6	43.6	43.9	44.1
Treatment 4	43.8	43	43.9	43.6	43.7	43.6	**40**	43.8	43.9	43.8	43.4	43.8	43.6	44
Treatment 5	43.7	42.9	43.8	43.7	43.4	43.1	**39.5**	43.6	43.5	43.9	43.4	43.6	44	44
Treatment 6	43.7	43.3	44	43.5	43.8	43.3	**38.9**	43.7	43.7	43.9	43.5	43.5	43.9	43.9
Treatment 7	43.9	43.2	44	43.6	43.7	43.2	**39**	43.5	43.7	43.7	43.5	43.8	44.1	44
Treatment 8	43.8	43.5	43.8	43.4	43.7	43.2	**38.5**	43.5	43.6	43.7	43.5	43.6	43.9	44
Treatment 9	44	43.1	44	43.5	43.7	43.3	**38.8**	43.9	43.7	43.8	43.5	43.5	43.9	44
Treatment 10	43.8	43.3	44.1	43.6	43.7	43.6	**39.2**	43.3	43.4	43.6	43.5	43.7	43.8	44.1

APPENDIX E: UNDERDOSAGE IN THE TARGET VOLUMES

The accumulated dose in the two target volumes was calculated and visualized with a 3D dose distribution for each treatment and the average of the ten treatments per patient. These visualizations provided information on the location and the severity of underdosages. No overdoses were found inside the target volumes. The dose was only calculated inside the target volume, so these figures do not represent the dose distribution outside of the target volume

CTV_T_LR

Posterior part of the cervix and corpus uteri

The posterior cervix and corpus uteri received less than 42.75 Gy in patients R01, R04, and R06. In patient R01, the CTV_T_LR of the reCT 2 is positioned more posteriorly than the CTV_T_LR of the pCT after bone matching (Figure 1B). This posterior position is due to the fact that the rectum and bowel bag are emptier on the first reCT than on the pCT and the bladder is fuller. In addition, a large rectum is seen on the fourth reCT as on the pCT, but it is filled with air rather than feces.

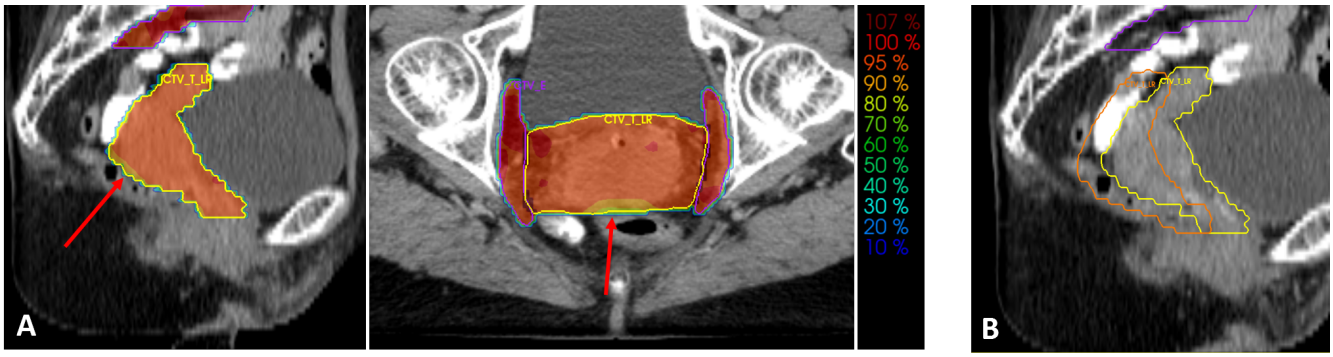

Figure 1: Underdosage in posterior part cervix uteri of patient R01. A: Sagittal and axial slice of the underdosage. The red arrow indicates the underdosage. B: CTV_T_LR of the first reCT visualized on the pCT after bone matching. Yellow = CTV_T_LR of the pCT, Orange = CTV_T_LR of the reCT.

In patients R04 and R06, a large air pocket (> 30 mm in beam direction) was seen in the rectum on three of the four reCTs, whereas this was not seen on the pCT. This suggests that the treatment plan was not robust to these large air pockets. However, such large air pockets were also present in patients R05, R10, R11, and R14, whereas these patients did not show underdosage in the posterior part of the CTV_T_LR.

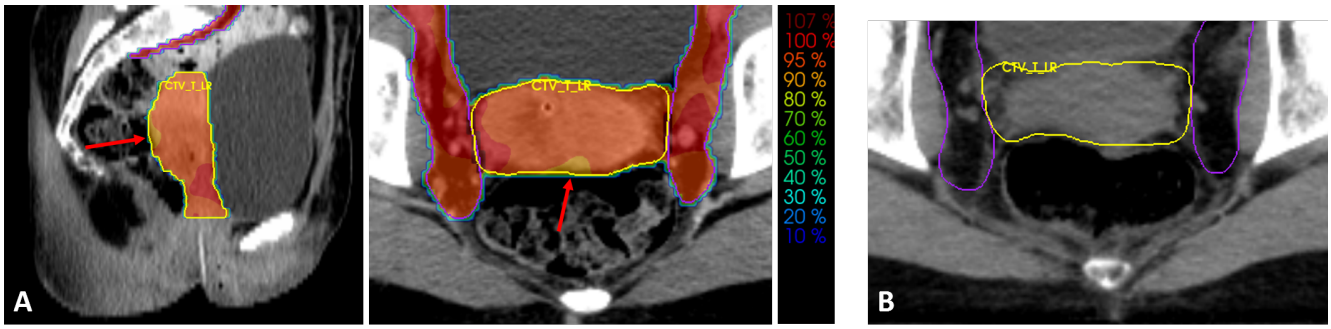

Figure 2: Underdosage in posterior part corpus uteri of patient R04. A: Sagittal and axial slice of the underdosage. The red arrow indicates the underdosage. B: Large air pocket in the rectum in the fourth reCT.

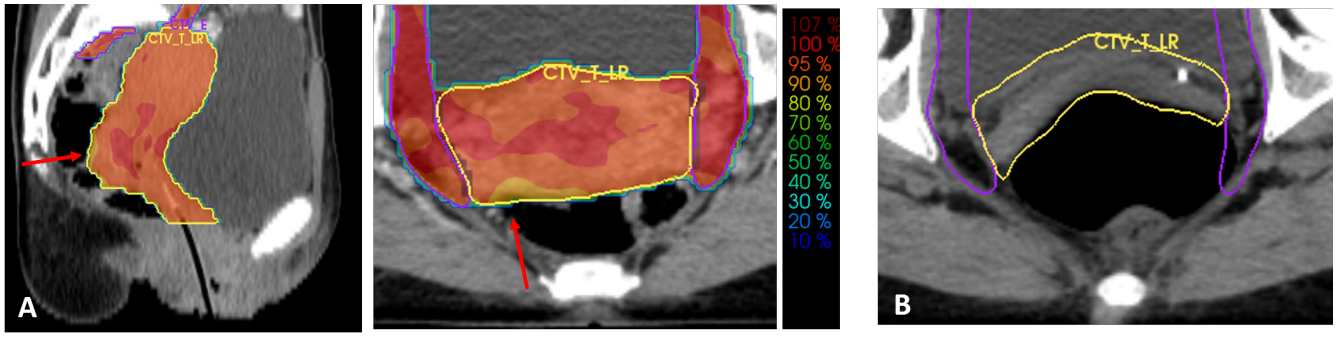

Figure 3: Underdosage in posterior part cervix uteri of patient R06. A: Sagittal and axial slice of the underdosage. The red arrow indicates the underdosage. B: Large air pocket in the rectum in the fourth reCT.

Anterior part of the corpus uteri

Underdosage in the anterior part of the corpus uteri was seen in three patients (R10, R13, R16). In patient R13, this was the result of a smaller bladder volume than on the pCT of the empty bladder in two reCTs, making the patient-specific bladder model inapplicable in half of the fractions (Figure 4).

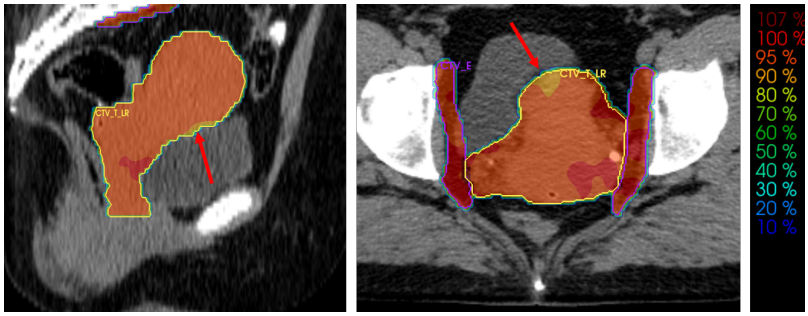

Figure 4: Underdosage in the anterior part of the corpus uteri of patient R13. Sagittal and axial slice of the underdosage. The red arrow indicates the underdosage.

The same site of underdosage was seen in patient R10, but no reCT with a smaller bladder was used in the simulation for this patient. However, there was a major difference in anatomy between the reCTs and the pCT, as shown in Figure 5. In the pCT, the bowel bag was located between the uterus and bladder, pushing the uterus cranial. Whereas, in the reCTs, the bowel bag was not located between the bladder and uterus. In the most anterior region of the underdosage, less than 70 percent of the dose was received.

The underdosage of patient R16 is visualized in Figure 6. No explanation was found for this underdosage.

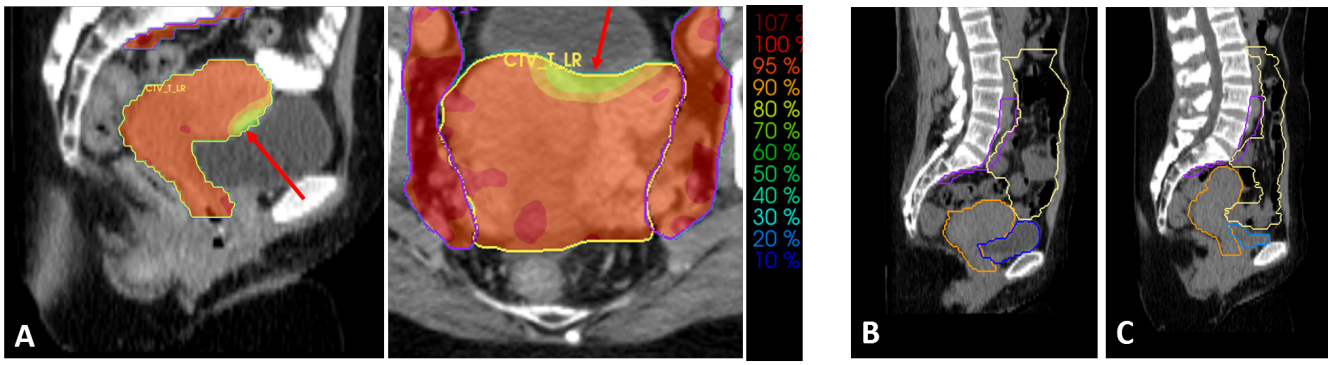

Figure 5: Underdosage in anterior part of the corpus uteri of patient R10. A: Sagittal and axial slice of the underdosage. The red arrow indicates the underdosage. B: repeat CT, bowelbag visualized in white and CTV_T_LR in orange. C: empty bladder pCT, bowelbag visualized in white and CTV_T_LR in orange.

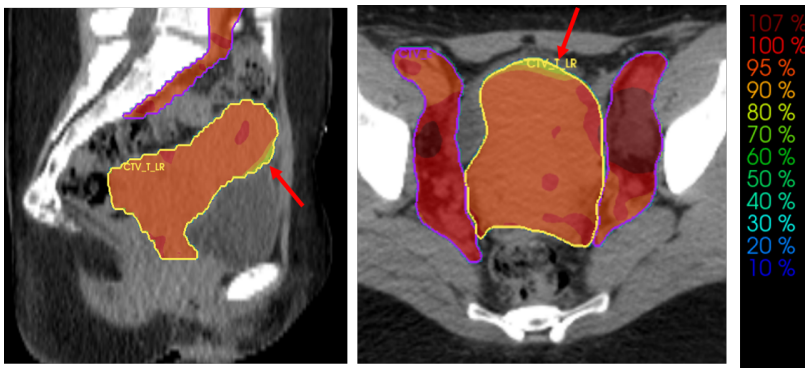

Figure 6: Underdosage in anterior part of the corpus uteri of patient R16. Sagittal and axial slice of the underdosage. The red arrow indicates the underdosage.

Cranial part of the fundus uteri
The first reCT of patient R11 shows a large rectum and bladder filling. This causes the CTV_T_LR to be flattened, i.e. smaller in the anterior-posterior direction and elongated cranially. This is probably the cause of the underdosage in the cranial part of the fundus uteri, which can be seen in Figure 7.

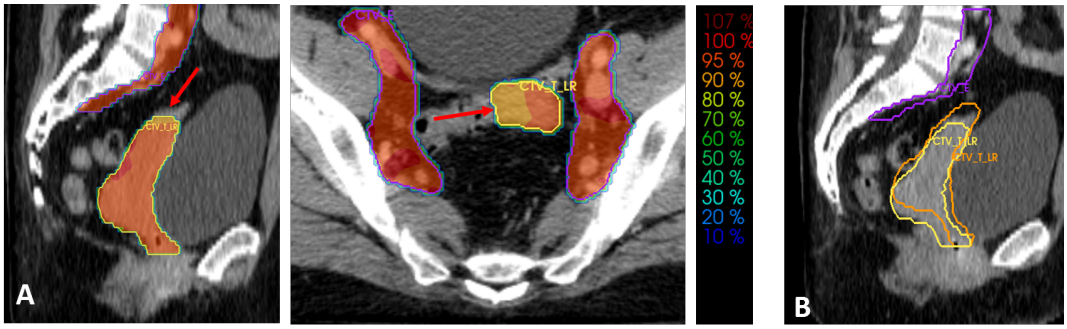

Figure 7: Underdosage in the cranial part of the fundus uteri of patient R11. A: Sagittal and axial slice of the underdosage. The red arrow indicates the underdosage. B: CTV_T_LR of the first reCT (orange) visualized on the pCT after bone matching. The CTV_T_LR is visualized in yellow.

CTV_E

Underdosage against vertebrae
In three patients (R04, R07, and R09), there was underdosage in the CTV_E located against the vertebral column. In patient R09, this underdosage was so severe that part of the CTV_E received only 50% of the prescribed dose (Figure 8). This underdosage is the result of the rotation of the pelvic bones relative to the vertebral column. Because bone matching is performed on the pelvic bones to register the reCT to the pCT, residual errors occur outside the pelvic area after registration, resulting in underdosage. The underdosages and matches of these four patients are shown in Figures 8 to 10.

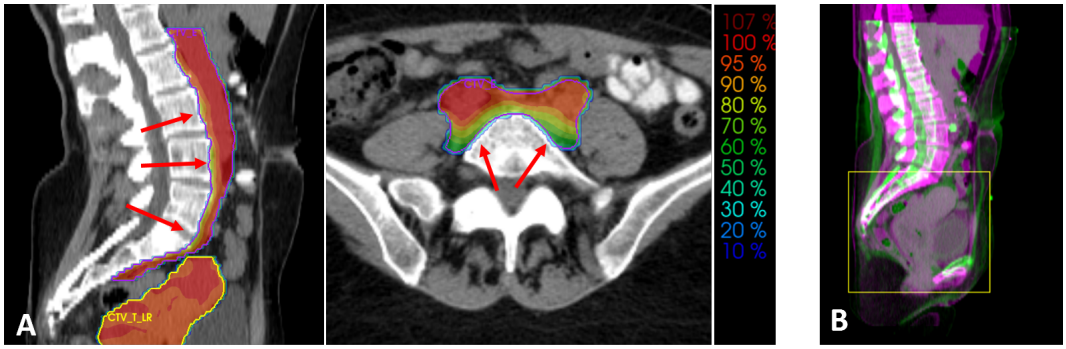

Figure 8: Underdosage in the CTV_E against the vertebral column in patient R09. A: Sagittal and axial slice of the underdosage. The red arrow indicates the underdosage. B: Pelvic bone match of the first reCTs and the pCT.

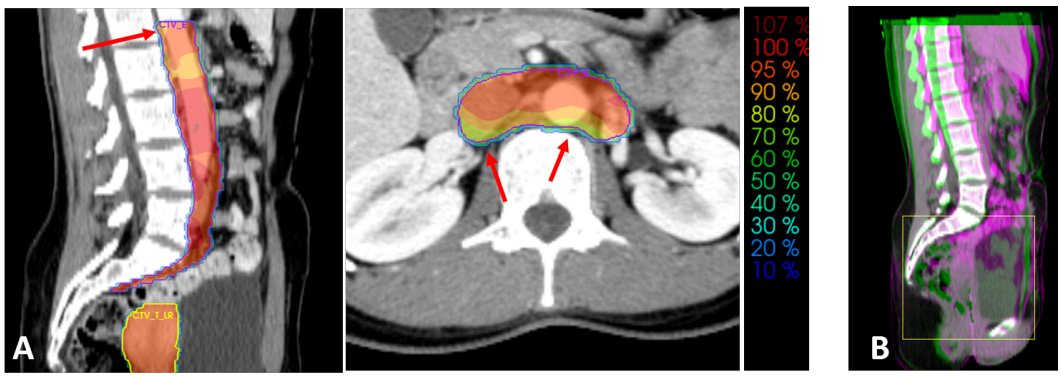

Figure 9: Underdosage in the CTV_E against the vertebral column in patient R04. A: Sagittal and axial slice of the underdosage. The red arrow indicates the underdosage. B: Pelvic bone match of the second reCTs and the pCT.

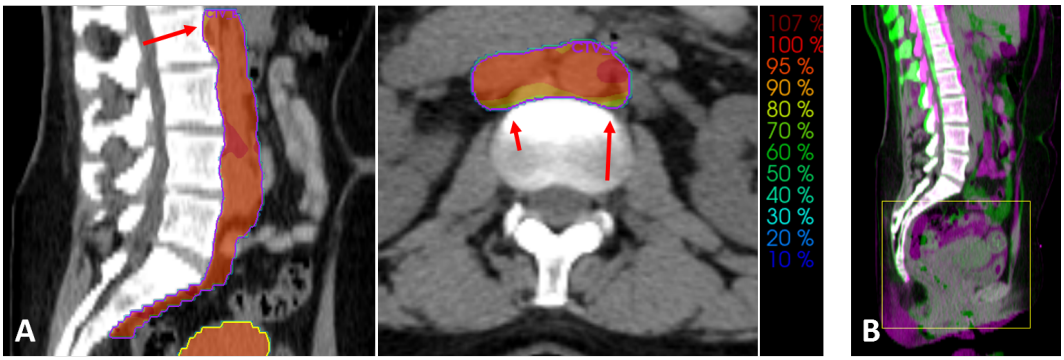

Figure 10: Underdosage in the CTV_E against the vertebral column in patient R07. A: Sagittal and axial slice of the underdosage. The red arrow indicates the underdosage. B: Pelvic bone match of the second reCTs and the pCT.

Coldspots CTV_E

In patients R04, R08 and R14 there were coldspots in the CTV_E, shown in Figures 11 to 13. A possible explanation for these coldspots is that the density in the beam path changed in one or more of the reCTs. The fractions in the simulation have the same anatomy in a quarter (R04 and R14) or half (R08) of the fractions. These systematic changes in density have a greater effect than in the clinical situation where each fraction has different density changes.

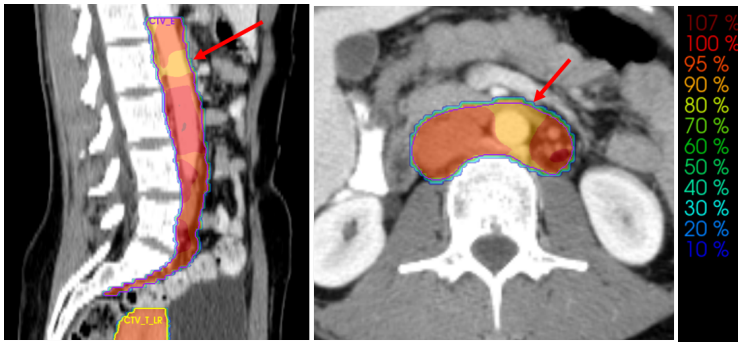

Figure 11: Coldspots the CTV_E of patient R04. Sagittal and axial slice of the underdosage. The red arrow indicates the underdosage.

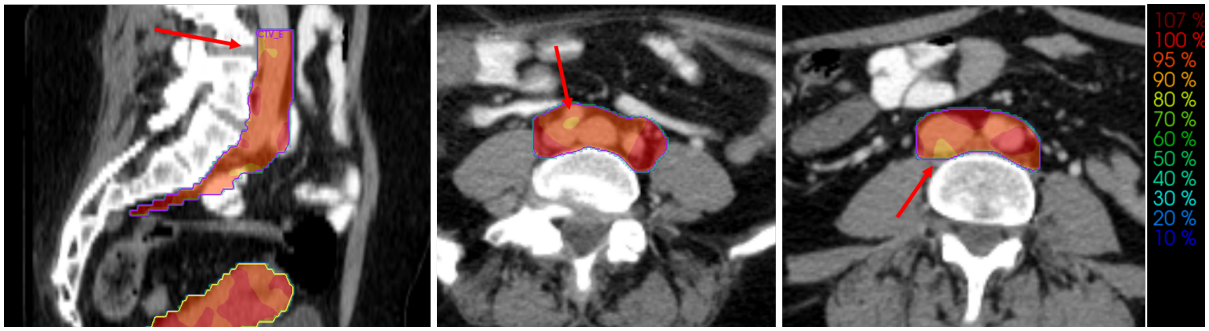

Figure 12: Coldspots the CTV_E of patient R08. Sagittal and two axial slices of the underdosage. The red arrow indicates the underdosage.

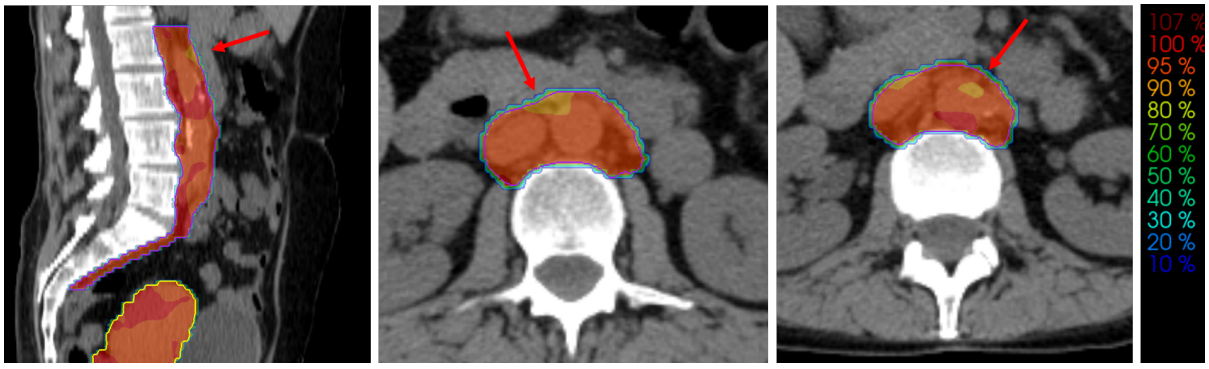

Figure 13: Coldspots the CTV_E of patient R14. Sagittal and two axial slices of the underdosage. The red arrow indicates the underdosage.

Low CTV_E: around external iliac artery

In the region of the external iliac artery in the low level of the CTV_E, there was underdosage of up to 60% of the prescribed dose in patient R09. This underdosage is shown in Figure 14. This underdosage is likely due to variations in the delineations of the reCTs compared to the pCT as the CTV_E included the external iliac artery more caudally in the delineations in the reCTs.

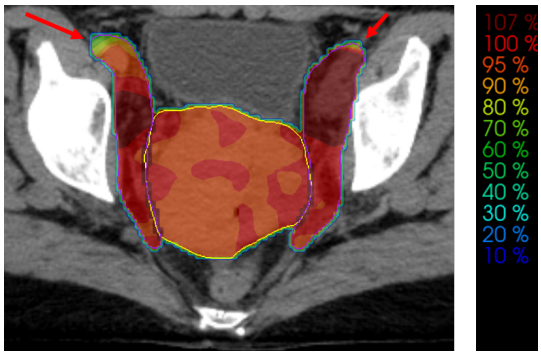

Figure 14: Underdosage around the external iliac artery in the low level CTV_E in patient R09. Axial slice of the underdosage. The red arrow indicates the underdosage.