Sabrina T. Heijkoop

Plan-of-the-Day Adaptive Radiotherapy for Locally Advanced Cervical Cancer

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Plan-of-the-Day Adaptive Radiotherapy for Locally Advanced Cervical Cancer

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Rabobank

Chapter 1

Introduction

1.1 CERVICAL CANCER

Cervical cancer is one of the most common female malignancies worldwide. In the United States, the yearly incidence exceeds 12000 and more than 4000 women die as a result of this disease (1). In the Netherlands, per year, on average around 700 women are diagnosed with cervical cancer. For 224 of those women the disease is fatal (2).

Cervical cancer mainly spreads by tumor invasion in surrounding organs and via lymph nodes to other parts of the body. The para-aortic lymph nodes are secondary stations and are always paralleled with metastases in the pelvic lymph nodes. At the time of diagnosis, the most important prognostic factors are tumor size, local extent and spread to the lymph nodes. A higher stage of disease means a lower overall 5-year survival with a worst case scenario for survival lower than 20% (2).

Early detection through population screening programs, starting at the age of 30 years in the Netherlands, has a beneficial impact on the incidence of cervical cancer (2). The most important risk factor for cervical cancer is a persistent infection with an oncogene Human Papilloma Virus type (3). Risk factors for HPV persistence and development of cervical cancer are sexual intercourse at a young age, multiple sexual partners, smoking, and immune suppression (3).

The standard treatment for cervical cancer depends on the FIGO-stage (4). In low stage disease (tumors only localized in the cervix or with minimal spread to the proximal vagina), surgery is the first choice of treatment. In higher stages, locally advanced disease is treated with either chemo-radiation or with neoadjuvant chemotherapy followed by radiotherapy and hyperthermia. In case of metastatic disease (stage IVB), patients are treated in a palliative setting with chemotherapy.

1.2 RADIOTHERAPY

Radiotherapy is a treatment modality that uses ionizing radiation to eradicate tumor cells. An important pathway leading to cell kill is induction of lethal damage in the cell DNA.

In case radiotherapy is applied for cervical cancer, the tumor is both irradiated with X-ray beams that are directed from outside the patient towards the tumor (external beam radiotherapy, EBRT), and with a radioactive source that is temporarily placed inside the body in order to locally deliver a high dose to the tumor (Brachytherapy). Total treatment time is usually 5-7 weeks, including chemotherapy or hyperthermia (above).

In EBRT, Intensity Modulated Radiation Therapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT) are modern delivery techniques, used to increase organ at risk (OAR) sparing with more conformal dose distributions than conventional 3D conformal

radiotherapy (3DCRT) (5-8). However, in treatment of cervical cancer, large and complex geometrical day-to-day variations in the pelvic area limit the potential positive impact of IMRT and VMAT (9-12). Especially bladder filling variations have a large impact on the daily position of the fundus of the cervix-uterus in the body, and are correlated with motion in AP direction (13). Earlier research (10,11) showed that due to large anatomical variations, the cervix-uterus was underdosed when IMRT was given with a Clinical Target Volume (CTV) to Planning Target Volume (PTV) margin of 15 mm. Another analysis demonstrated that a pre-treatment established motion model, correlating bladder volume with cervix-uterus position and shape, could be used to predict the position of the cervix-uterus during treatment (5,14). Bondar et al. (15) showed that the pre-treatment cervix-uterus motion model could be used to make plan libraries containing treatment plans for several Internal Target Volumes (ITV), each linked to a different bladder volume range.

Since September 2011, the EBRT part of the treatment of advanced cervical cancer patients in our department is performed using an online adaptive Plan-of-the-Day protocol. The goal of the protocol is to irradiate the patients with patient-specific, relatively small CTV-to-PTV margins. The protocol is based on a patient-specific plan library. For each library plan, the cervix-uterus is covered with a high dose for a specific range of possible cervix-uterus positions and shapes (above). Together, these plans with relatively small PTV margins should cover the full motion range of the cervix-uterus. On top of these plans, a library always contains a motion-robust back-up plan with generous margins. Each treatment fraction, prior to dose delivery, an in-room Cone Beam CT (CBCT) scan is made of the patient on the treatment couch. This CBCT is used to select the plan that best fits the anatomy-of-the-day from the plan library. In case none of the small margin plans fit with the anatomy-of-the-day, or in case of bad image quality, the motion-robust backup plan is chosen for treatment.

1.3 THIS THESIS

In this thesis, we have investigated and further improved the Plan-of-the-Day approach for locally advanced cervical cancer patients.

In Chapter 2 we report on the clinical introduction of the first two phases of our online Plan-of-the-Day protocol, including in total 64 patients. In the first phase, a patient's treatment library consisted of two plans, an IMRT plan with an individualized CTV-to-PTV margin, and a motion-robust 3DCRT plan. In the second phase, patients with large cervix-uterus motion as a function of bladder filling (assessed in the treatment planning phase) had a library consisting of two IMRT plans (empty-to-half-full and half-full-to-full bladder plans) with relatively small margins, and the 3DCRT backup plan.

With the introduction of IMRT and adaptive approaches using smaller CTV-to-PTV margins, EBRT for cervical cancer has become more sensitive to intra-fraction uncertainties. In Chapter 3, we systematically investigated the intra-fraction motion of the cervix-uterus, assessed with pre- and post-fraction CBCT scans. Further, we evaluated to what extent changes in bladder or rectum filling during treatment had an impact on the intra-fraction cervix-uterus motion.

Almost all our cervical cancer patients were treated in prone position using a bellyboard for small bowel displacement. This setup was based on an internal study, performed prior to introduction of the online adaptive approach and showing superiority in OAR sparing compared to supine treatment (16). However, as there was no adaptive treatment, large CTV-to-PTV margins were used in that study. In chapter 4 we performed a planning study to compare prone and supine treatment for small margin adaptive radiotherapy. Small bowel sparing was the most important parameter in this study.

In Chapter 5, we prospectively investigated the Quality of Life (QoL) of our cervical cancer patients during the radiation treatment phase with the Plan-of-the-Day approach, using validated EORTC questionnaires (QLQ-C30 and CX-24), thereby covering dynamics of the acute treatment phase.

In Chapter 6, the optimal number of library plans in adaptive radiotherapy for locally advanced cervical cancer was investigated by a dosimetric evaluation.

Chapter 7 contains a general discussion on the work presented in the previous chapters, including suggestions for future research.

Chapter 2

Clinical implementation of an online adaptive Plan-of-the-Day protocol for non-rigid motion management in locally advanced cervical cancer IMRT

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ABSTRACT

Purpose

To evaluate the clinical implementation of an online adaptive Plan-of-the-Day protocol for nonrigid target motion management in locally advanced cervical cancer intensity modulated radiation therapy (IMRT).

Material & Methods

Each of the 64 patients had four markers implanted in the vaginal fornix to verify the position of the cervix during treatment. Full and empty bladder computed tomography (CT) scans were acquired pre-treatment to build a bladder volume dependent cervix-uterus motion model for establishment of the plan library. In the first phase of clinical implementation, the library consisted of one IMRT plan based on a single model-predicted internal target volume (mpITV), covering the target for the whole pre-treatment observed bladder volume range, and a 3D conformal radiation therapy (3DCRT) motion-robust backup plan based on the same mpITV. The planning target volume (PTV) combined the ITV and nodal clinical target volume (CTV), expanded with a 1-cm margin. In the second phase, for patients showing >2.5-cm bladder-induced cervix-uterus motion during planning, two IMRT plans were constructed, based on mpITVs for empty-to-half-full and half-full-to-full bladder. In both phases, a daily cone beam CT (CBCT) scan was acquired to first position the patient based on bony anatomy and nodal targets, and then select the appropriate plan. Daily post-treatment CBCT was used to verify plan selection.

Results

Twenty-four and 40 patients were included in the first and second phase, respectively. In the second phase, 11 patients had two IMRT plans. Overall, an IMRT plan was used in 82.4% of fractions. The main reasons for selecting the motion-robust backup plan were, uterus outside the PTV (27.5%), and markers outside their margin (21.3%). In patients with two IMRT plans, the half-full-to-full bladder plan was selected on average in 45% of the first 12 fractions, which was reduced to 35% in the last treatment fractions.

Conclusion

The implemented online adaptive Plan-of-the-Day protocol for locally advanced cervical cancer enables (almost) daily tissue-sparing IMRT.

2.1 INTRODUCTION

Large and complex day-to-day tissue variations in the pelvic area limit the efficacy of intensity modulated radiation therapy (IMRT) for locally advanced cervical cancer (5,15,17,18). Bladder-filling variations can have large impact on shape and position of the cervix-uterus. Drinking instructions, used to minimize bladder-filling variations, has limited efficacy (10). Previously, a dosimetric study demonstrated that in 6 of 14 patients, the cervix-uterus was underdosed when applying IMRT with a clinically recommended clinical target volume (CTV)-to-planning target volume (PTV) margin of 15 mm (9,11). To guarantee adequate coverage for a large proportion of patients, generous margins of 24-40 mm are required (12,14,15). However, those generous margins jeopardize tissue-sparing properties of IMRT. In proof-of-principle analyses, it was shown that a pre-treatment established motion model could be used to predict the position of the cervix and uterus during treatment (5,14). This concept was elaborated in a study by Bondar et al. (15), which showed that a personalized PTV, based on a pre-treatment acquired shape model improved normal tissue sparing. Furthermore, they demonstrated that the shape model could be used to make a plan library containing treatment plans that are linked to a certain bladder volume range. Based on these results, we developed a novel online adaptive protocol using daily cone beam computed tomography (CBCT) based plan selections from a plan library that explicitly accounted for patient-specific bladder volume-dependent cervix-uterus shape and position variations. This protocol is currently evaluated in a prospective clinical implementation. In this report, we describe the practical implementation of the protocol and report our experience with the first 64 patients. To our knowledge, this is the first report describing clinical experience with such a Plan-of-the-Day (PotD) approach for cervical cancer.

2.2 MATERIAL AND METHODS

Patients

In our institute, patients with an intact uterus receiving definite radiation therapy have been included in the PotD protocol since June 2011. Patients with positive para-aortic lymph nodes were not eligible. This study reports on the first 64 patients treated with this protocol. Routine pre-treatment work-up consisted of gynecologic examination under anesthesia and computed tomography (CT) scans of thorax and abdomen. During the examination under anesthesia, four polymer-based markers (PolyMark; Cortex Manufacturing Inc, Lake Stevens, WA) were implanted in the submucosa of the vaginal fornix to verify the position of the cervix during treatment. Patients with International Federation of Gynecology and Obstetrics (FIGO) cancer stages up to IIB medial were

treated with chemoradiation, and those with FIGO stage IIB lateral or higher were treated with concurrent radiation therapy and hyperthermia (4).

Fifty-seven patients were treated in prone position, using a belly board. For maximum sparing of organs at risk (OAR), daily treatment with a filled bladder was pursued by instructing patients to drink 300 ml of water two hours prior to treatment, to empty the bladder and drink an additional 300 ml of water one hour prior to treatment. Daily CBCT-based plan selection from an individualized plan library was applied to account for (large) residual interfraction bladder filling variations and the patient-specific impact of such variations. As detailed below, in the first phase of implementation, plan libraries contained a single IMRT plan plus a motion-robust 3D conformal radiation therapy (3DCRT) plan (backup plan). In the second phase, plan libraries for patients with large bladder-induced cervix-uterus motion consisted of two IMRT plans (for relatively empty and full bladders, respectively) and the backup plan. The dose prescribed to the PTV was 46 Gy in 23 daily fractions. All patients received 21 Gy in three brachytherapy sessions.

Establishment of patient-specific, model-predicted Internal Target Volumes

To model each individual patient bladder filling and subsequent impact on cervix-uterus motion, a full and an empty bladder CT scan was acquired pre-treatment with the patient in the treatment position. To obtain a sufficiently filled bladder, the same drinking protocol as that used for treatment was used (patient section). After acquisition of the full bladder CT scan, patients were asked to empty their bladder, followed directly by a second CT scan acquisition.

The two scans were aligned on the bony anatomy. In both scans, the bladder and the cervix-uterus CTV, consisting of uterus, cervix, and superior part of the vagina, were manually delineated. An in-house, nonrigid registration algorithm was then used to derive a patient-specific cervix-uterus shape model, defining for every possible bladder volume the corresponding 3D cervix-uterus structure (19). With this shape model, model-predicted internal target volumes (mpITVs) were generated for PTV construction and planning. In the first phase, a single mpITV, containing the cervix-uterus model shapes for all intermediate bladder volumes, was used for plan library generation. This mpITV was extended if the bladder in the full-bladder scan was not sufficiently full (<700ml) or empty in the empty-bladder scan (>50ml), according to the extension rule defined by Bondar et al. (15). Compared to the common use of a large population-based margin, PTV establishment based on this whole-bladder-volume range mpITV improved healthy tissue sparing for patients with small cervix-uterus motion. For patients with large cervix-uterus motion, this mpITV approach guarantees adequate CTV coverage at the cost of large volumes of healthy tissue irradiated to a high dose. Therefore, in the second phase, for patients with a cervix-uterus motion >2.5 cm (measured at the fundus of the uterus), 2 extra mpITVs were used for plan generation, 1 containing all

cervix-uterus model shapes for empty-to-half-full bladders and the other the shapes for half-full-to-full bladders. Figure 1 shows mpITVs on a full bladder CT scan for 2 second-phase patients.

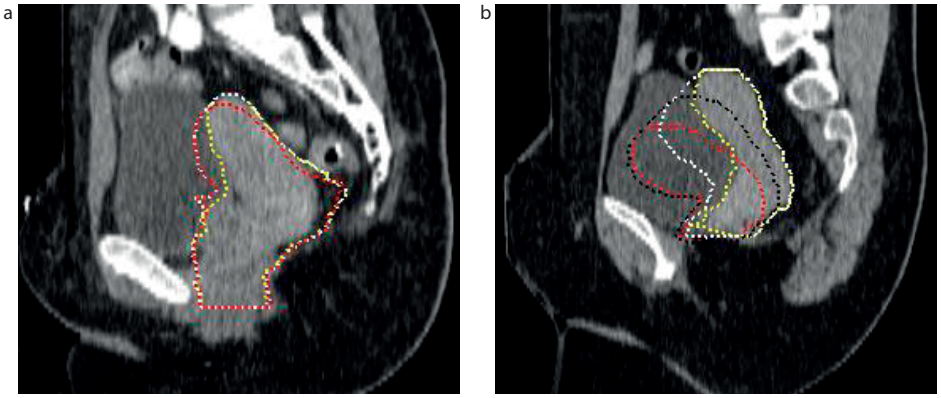


Figure 1. (a) Sagittal view of the full bladder CT scan with the corresponding cervix-uterus (yellow), cervix-uterus of the empty-bladder CT (red), and whole-bladder range mpITV (white) of a patient with small cervix-uterus motion. (b) Sagittal view of the full bladder CT for a patient with large cervix-uterus motion. Black dashed line denotes the empty-to-half-full mpITV, and the white dashed line denotes the half-full-to-full mpITV.

Plan library generation using mpITVs

The full-bladder CT scan, in which the nodal CTV, parametria, and OARs were contoured, was always used for treatment planning. To construct PTVs, generated mpITVs were combined with the nodal CTV and parametria and were expanded with a 1-cm margin to account for intrafractional errors and model imperfections. In the first phase, the plan library contained one IMRT plan, generated for the PTV derived from the whole-bladder-volume range mpITV. In the second phase, the library contained IMRT plans for the empty-to-half-full and half-full-to-full mpITVs. High quality IMRT plans were generated in a two-step procedure. First, Erasmus-iCycle, an in-house algorithm for fully automated multi-criteria plan generation, was used to automatically generate a 7- to 9-beam IMRT plan with optimized beam orientations and fluence profiles (20). To establish a clinical, segmented IMRT plan, an individual template with optimized beam angles and achieved plan parameters was imported into our clinical treatment planning system (Monaco; Elekta AB Stockholm, Sweden) (21). For all patients, the plan library was completed with a 3D-conformal, four-field box plan generated using the XIO planning system (Elekta AB). In both phases, the PTV for this plan was always based on the whole-bladder-volume range mpITV. Due to the large PTV and the 3D box shape of the dose distribution, 3DCRT plans were robust against uncertainties in cervix-uterus position.

Preparations for online plan selection

To facilitate plan selection, the following structures were made available in the software application used to acquire and register CBCT scans (XVI version 4.5.1b141; Elekta AB). For treatments with one IMRT plan, the PTV and marker tubes were imported. These marker tubes were created by connecting, pair-wise, the implanted markers in the aligned (patient section) empty and full bladder CT scans by a line, which was expanded with a 1-cm margin. When the library consisted of 2 IMRT plans, 2 tubes per marker pair (1 for the empty-to-half-full and 1 for the half-full-to-full plan) were imported by splitting each connecting line into 2 equal parts followed by the 1-cm margin expansion. The marker tubes were used to verify the position of implanted markers during daily plan selection (daily image-guidance section). For patients with 2 MRT plans, the marker tubes, 2 PTVs, and a constructed half-full bladder structure were imported to select between the 2 IMRT plans.

Daily image guidance and plan selection procedures

CBCT scans were acquired daily before dose delivery and registered to the planning CT scan, using intensity-based registration in XVI software. Required translational patient displacements were automatically executed by a remote couch translation (TheraView couch setup assistant; Cablon Medical, Leusden, The Netherlands). In addition, when a pelvis rotation of more than 4° around the left-right axis was observed, nodal CTV coverage was verified offline. If the nodal CTV was underdosed, the field was enlarged in the anterior-posterior direction at the cranial border. For patients with two IMRT plans, a second CBCT scan was acquired after dose delivery to verify intrafraction anatomy stability.

During the first phase, the decision was carried out semi-online. In a multidisciplinary team, it was decided to use the motion-robust backup plan for treatment and to disable the IMRT plan for the remainder of the fractions. In this phase only one IMRT plan was available. During the second phase, two IMRT plans were available for each fraction and plan selection and verification was performed online. A decision tree was used to guide the daily plan selection process. For patients with two IMRT plans, it was first determined whether the bladder was more or less than half-full using the half-full bladder structure displayed in the matched CBCT scan. This step was skipped for patients with one IMRT plan. Subsequently, the PTV and marker tubes of the chosen IMRT plan were shown in the matched CBCT scan. Then, it was verified that at least three markers were inside the marker tubes and the uterus was inside the PTV (Fig 2). If both conditions were fulfilled, the IMRT plan was selected; otherwise, the backup plan was used. In that case, for extra safety, the 95% isodose line in the backup plan was inspected to ensure target coverage. Details for how plan selection was carried out in the record and verify system (MOSAIQ version 2.3; Elekta AB), can be found in Appendix 2A.

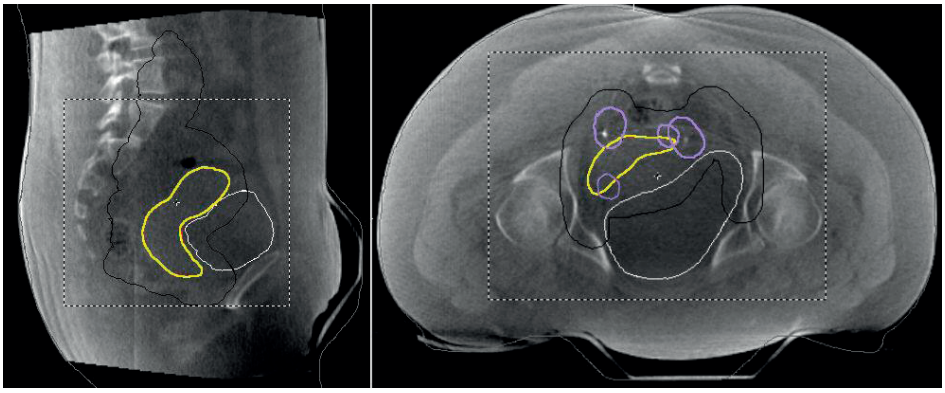


Figure 2. Sagittal view (left) of a CBCT scan made in the second implementation phase for plan selection. The yellow contour represents the cervix-uterus. The PTV for the half-full-to-full bladder plan is projected in black, and the white solid line denotes the reconstructed half-full bladder. The purple contours are the marker tubes. For this fraction, the PTV covers the uterus completely. The transversal slice (right) shows that the two markers in this slice are inside their tube.

Evaluation of the online adaptive Plan-of-the-Day protocol

For all patients, daily plan choices were recorded. In case the backup plan was selected, the reason was recorded as well. Times needed for the various steps of the plan selection procedure were assessed (phase two only). For patients with two IMRT plans, the robustness of the plan choice relative to intra-fraction anatomy changes was verified with a post-fraction CBCT scan. For all patients with two IMRT plans and a representative case with small cervix-uterus motion, we compared IMRT dose-volume-histogram (DVH) parameters with those of the backup plan (see Appendix 2B).

2.3 RESULTS

Twenty-four patients were included in the first phase (only one IMRT plan in the library, independent of cervix-uterus motion induced by bladder volume changes). In the second phase, 29 patients had a single IMRT plan in the plan library, whereas for 11 patients with large cervix-uterus motion, the library contained two IMRT plans.

During the first phase, 17 of 24 patients received IMRT in all 23 fractions. For all 24 patients in 84.3% of the treatment fractions, the IMRT plan was delivered. Figure 3 shows a continuous increase in the use of the backup plan, except for fraction 9: for two patients, the IMRT plan was available only from fractions 3 and 8 for logistic reasons. During the second phase 11 of 29 patients with one IMRT plan received IMRT for all 23 fractions (Fig. 4a). On average, in 81.1% of the treatment fractions, IMRT was selected. For patients with two IMRT plans, IMRT was selected in 81.8% of the fractions (Fig. 4b).

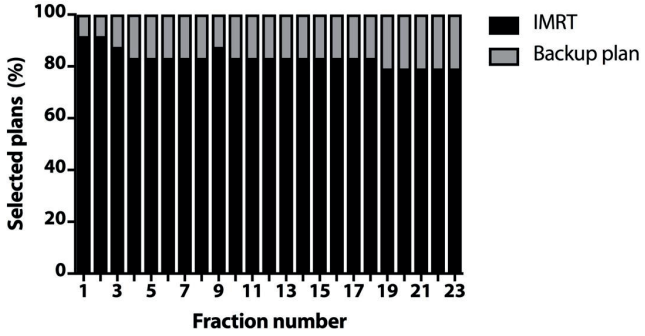


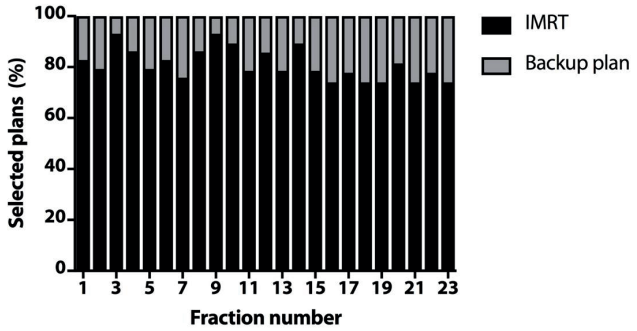
Figure 3. Selected plans across the treatment course for patients with one IMRT plan in the first phase. If the motion-robust backup plan was chosen once, this was continued for all fractions. For logistic reasons, IMRT plan was only available from fractions three and 8 for 2 patients, which explains the increase in selected IMRT plans at the ninth fraction.

Figure 4b illustrates the fact that the half-full-to-full bladder plan was mostly selected during the first half of the treatment (45%, compared to 35% for the second half). The empty-to-half-full bladder plan was selected in 51.2% during the second treatment half. For two patients, target coverage of the backup plan was still insufficient and the backup plan was adapted for subsequent fractions. For 4 fractions in 3 patients, rapid filling of the bladder as detected in the post-treatment CBCT scan would have led to selecting the half-full-to-full-bladder plan instead of the selected empty-to-half-full-bladder plan. For one fraction in one patient, urinary incontinence led to an emptier bladder at the fraction end. Projection of the delivered dose onto the post-fraction CBCT scan showed that the 1-cm margin was adequate to ensure coverage by 95% of the prescription dose in all these cases.

The potential OAR sparing was evaluated for all patients with two IMRT plans. The bowel cavity volume receiving 99% of the prescription dose was 127 cc on average for half-full-to-full IMRT compared with 172 cc for the backup plan, a reduction of 26% (range 2-79%). Similarly, for the empty-to-half-full IMRT plan the volume was 210 cc compared with 296 cc for the backup plan evaluated on the empty-bladder CT scan (reduction of 29%; range 9-89%). For further results, we refer to Appendix 2B.

The backup plan was selected in 17.5% of all fractions. The main reasons for selecting this plan was that the uterus was outside the PTV (27.5%), markers were outside their 1-cm margin (21.3%) or both (21.7%), insufficient CBCT scan quality (10.5%), pelvic rotations (5.8%), and other problems (13.2%). Visual inspection suggests that uterus outside the PTV and/or markers outside their tubes was mainly caused by differences in rectum filling compared to the planning CT scan.

a.



b.

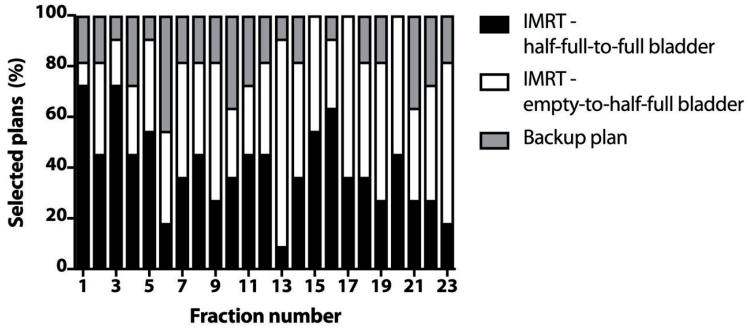


Figure 4. (a) Selected plans across the treatment course for patients with one IMRT plan in the second phase. Plan selection was carried out online. (b) Selected plans for patients with two IMRT plans in the second phase. At the end of treatment, the empty-to-half-full bladder plan was chosen more often compared to the half-full-to-full bladder plan at the start of treatment.

Treatment delivery times

Patient setup and CBCT acquisition took on average 5.0 and 2.4 minutes, respectively. In the second phase, plan selection for patients with a single or two IMRT plans took 2.2 and 2.4 minutes. The mean delivery time for IMRT was 11.3 minutes, whereas 3DCRT dose delivery took only 2.3 minutes.

2.4 DISCUSSION

In this study, we described and evaluated a two-phase clinical introduction of a novel online adaptive PotD strategy for locally advanced cervical cancer. For each fraction, a CBCT scan was used for selection of the most appropriate plan from a library containing 1 or 2 IMRT plans and a motion-robust 3DCRT backup plan. All plans were generated for established patient-specific ITVs to effectively individualize planning margins. Results

show that in most of the treatment fractions, a tissue-sparing IMRT plan could be used for treatment.

Online adaptive radiotherapy has been used and investigated previously for bladder cancer, but to our knowledge, this is the first report evaluating its clinical use for the treatment of locally advanced cervical cancer. Meijer et al reported on the clinical use of an online adaptive protocol in bladder cancer (22).

A limitation of the current approach is that the pre-treatment shape model includes only one parameter, bladder volume, whereas rectum and tumor regression may also impact the shape and position of the CTV (11,17). Furthermore, it assumes a linear relationship between bladder filling and cervix-uterus motion (5). Correctness of the mpITVs may also be compromised by uncertainties in the pre-treatment determined bladder volume range. Therefore, the model was used to expand the mpITV beyond the pre-treatment observed bladder volume range (15). Model imperfections were partly accounted for by the 1-cm ITV-to-PTV margin. In case these measures rendered insufficient, the motion-robust backup plan was used.

Further tissue-sparing could potentially be obtained by more densely populating the plan library (eg, by subdividing the bladder volume range into three or more subranges). Bondar et al (15), however, demonstrated that adding more subranges did not improve sparing as it was limited by uncertainties in the pre-treatment-established prediction model with bladder volume as the only input parameter. Therefore, future research will be focused on expanding the plan library to include rectum-filling variations and on updating the library during the treatment to account for tumor regression (23).

Plan selection was based on daily acquired online CBCT scans. The fact that the image quality of these scans is not always sufficient to visualize the relevant structures introduces another limitation. To ease plan selection, markers were implanted and margins were constructed around these markers for quick verification. Moreover, the motion-robust backup plan could be selected in case the image quality was insufficient. The latter situation occurred in 1.8% of all fractions. Daily variation in rectum filling occasionally caused the uterus and/or markers to be outside the PTV. In the future, patients may benefit from laxation before the acquisition of the planning CT scan and during treatment.

A well-trained team is mandatory to safely execute the PotD protocol within reasonable treatment times. If in doubt, on coverage by IMRT, the policy was to select the backup plan. Knowledge of the relevant anatomy and experience in interpreting CBCT images with varying image quality is necessary to give the team sufficient confidence to select IMRT. A physician (SH) always verified online the plan selection for patients with two IMRT plans. The increased planning workload could become an impediment for inclusion of more plans in the plan libraries. To avoid this, there is a definite need

for automated planning techniques. Recently, Voet et al (21,24) investigated automated planning for head and neck and prostate cancer patients.

In this study, we did not include a full dosimetric evaluation of the PotD strategy. In a previous publication of Bondar et al (15), the dosimetric benefit of PotD was already demonstrated. Part of future research is to delineate all the CBCT scans and accumulate the dose nonrigidly. To illustrate the potential benefit, we performed a DVH analysis (see Appendix 2B) that demonstrated a consistent benefit of PotD compared with the single-plan 3DCRT.

2.5 CONCLUSION

This work demonstrates that a personalized online adaptive radiation therapy strategy to manage complex deformable target motion in the treatment of locally advanced cervical cancer is feasible and requires limited extra treatment time. To ensure a safe introduction of this personalized approach, we recommend the use of a motion-robust backup plan to guarantee adequate coverage in all treatment fractions. Future research is required to expand the plan library such that more tight-fitting plans can be selected and dose to healthy tissues can be further reduced.

Chapter 3

Quantification of intra-fraction changes during radiotherapy of cervical cancer assessed with pre- and post-fraction Cone Beam CT scans

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ABSTRACT

Background & purpose

With the introduction of Intensity Modulated Radiotherapy (IMRT) and image-guided Plan-of-the-Day strategies, the treatment of cervical cancer has become more sensitive to intra-fraction uncertainties. In this study, we quantified intra-fraction changes in cervix-uterus shape, bladder and rectum filling, and patient setup using pre- and post-fraction CBCT scans.

Materials & Methods

A total of 632 CBCT scans were analyzed for 16 patients with large tip-of-uterus displacement (>2.5cm) measured in an empty and full bladder CT scan. In all scans, the bladder, cervix-uterus, and rectum were delineated. For rectum and bladder, intra-fraction volume changes were assessed. Systematic cervix-uterus intra-fraction displacements were obtained by non-rigidly aligning the pre-fraction cervix-uterus to that in the post-fraction CBCT. Intra-fraction patient setup changes were obtained by rigidly aligning pre- and post-CBCTs using the bony anatomy.

Results

The mean time between pre- and post-fraction CBCT scan was 20.8 minutes. The group-mean intra-fraction displacements averaged over the cervix-uterus were 0.1±1.4/1.8±1.5/-2.8±1.8 (LR/CC/AP) mm. The group-mean 5^{th} and 95^{th} percentile intra-fraction displacements were -2.3,2.1/-0.8,4.9/-5.8,0.5 (LR/CC/AP) mm. There was a significant correlation between bladder inflow rate and cervix-uterus motion ($R=0.6$ and $p<0.01$). Intra-fraction changes in patient setup were 1.3/0.4/0.6 and 1.4/1.0/1.1 mm (LR/CC/AP), for systematic and random changes, respectively.

Conclusion

Intra-fraction cervix-uterus motion can be considerable and should be taken into account using appropriate PTV margins.

3.1 INTRODUCTION

Intensity Modulated Radiotherapy (IMRT) is a standard treatment technique for locally advanced cervical cancer patients and often combined with brachytherapy, chemotherapy, or hyperthermia depending on FIGO stage. IMRT improves sparing of healthy tissue as opposed to conventional 3-dimensional conformal radiotherapy due to its capacity to concavely shape the dose distribution (7,8,12,14). In our institute, IMRT is used in a library-based Plan-of-the-Day (PotD) strategy to further improve healthy-tissue sparing for patients with large, bladder-filling induced, changes in position and shape of the cervix-uterus (15,25). Each fraction, an in-room Cone Beam CT (CBCT) scan is acquired just before dose delivery, and the plan in the pre-treatment established plan library that best matches the anatomy in the CBCT scan is selected for treatment. Uncertainties from intra-fraction bladder or rectum filling or intra-fraction changes in patients' setup need to be accounted for in the Clinical-Target-Volume (CTV) to Planning-Target-Volume (PTV) margin of the library plans. As only limited data is available on intra-fraction cervix-uterus motion and intra-fraction changes in patient setup (26-28), our clinical PotD practice includes daily acquisition of a post-fraction CBCT scan to verify target coverage in the presence of the above mentioned intra-fraction uncertainties. The aim of this study is to analyze the nature and extent of the intra-fraction motion of the cervix-uterus and patient, which can be used to better estimate their contributions to the CTV-to-PTV margin. To this end, we analyzed the acquired pre- and post-fraction CBCT scans.

3.2 MATERIAL AND METHODS

Patient data

Daily pre- and post-fraction CBCT scans were analyzed for 16 cervical cancer patients with a displacement of >2.5 cm of the uterine fundus in a planning CT-scan acquired with a full bladder, compared to a planning CT scan acquired with an empty bladder. Each patient had two IMRT plans in the library, one covering the tumor for an empty to half full bladder range, the other for a half full to a full bladder range. To construct the Internal Target Volumes (ITV) for the two IMRT plans, non-rigid registration was used to build a patient-specific bladder-volume-dependent motion model from cervix-uterus contours in the full and empty bladder planning CT scans (15). To generate the two PTVs, the ITVs were combined with the nodal CTV and parametria, and expanded with a 1 cm margin. The full-bladder CT scan, in which the CTV (consisting of uterus, cervix and the superior part of the vagina), nodal CTV, parametria, and organs at risk were contoured, was used for treatment planning. Seven to nine beams were used to create step-and-shoot IMRT plans. For further details we refer to Heijkoop et al. and Sharfo et al. (25,29).

For all patients, the plan library was completed with a 3D conformal, four-field box plan. This plan, designated as the backup plan, was robust against uncertainties in the cervix-uterus shape and position but had poor healthy tissue sparing. For this backup plan the full and empty bladder ITV were combined and expanded with 1 cm. Due to the setup of the four-field technique we created a box of dose (95% isodose) around the PTV. It was selected in case neither of the two IMRT plans fitted the observed anatomy in the pre-fraction CBCT scan, or in case the CBCT-quality was insufficient for proper plan selection. To further maximize organ-at-risk (OAR) sparing, we aimed at daily treatment with a full bladder by instructing patients to drink 300 ml of water two hours prior to treatment, to empty the bladder one hour prior to treatment and drink an additional 300 ml of water. All patients were treated in prone position and received 46 Gy in 23 daily fractions.

Each fraction, the acquired pre-fraction CBCT scan was first used to position the patient's bony anatomy and nodal targets according to the planning CT scan. Next, the CBCT scan was used to select a treatment plan from the library. In case an IMRT plan was selected (in the majority of fractions), a post-fraction CBCT scan was acquired to verify whether the target was still within the PTV in spite of possible intra-fraction motion. For this study, the CTV, bladder and rectum were delineated in all pairs of pre- and post-fraction CBCT scans by a clinician (SH), and checked by an experienced radiation-oncologist (JM). To maximize consistency of the delineations automatically computed segmentations were used (30). In this process, for each patient, the first pre-fraction CBCT scan was manually delineated after which the contours were automatically propagated to all remaining pre-fraction CBCT scans and manually edited. Next, the validated contours of each pre-fraction CBCT scan were propagated automatically to the corresponding post-fraction CBCT scan and again manually edited.

Intra-fraction bladder and rectum filling changes

The volumetric meshes derived from the bladder and rectum contours were used to quantify the changes in bladder and rectum filling in ml between the pre- and post-fraction CBCT scan, as well as the inflow rate of the bladder and rectum during a treatment fraction. A Pearson correlation coefficient was calculated to determine the correlation between inflow rate of the bladder and rectum and intra-fraction cervix-uterus motion (see below for how the motion was quantified). Regression analysis was performed to relate the bladder inflow rate to the volume of the bladder at the start of a treatment fraction. All statistical analyses were performed using SPSS 20.0 and p-values less than 0.05 were considered statistically significant.

Intra-fraction motion of the cervix-uterus

In order to assess the internal organ motion of the cervix-uterus relative to the bony anatomy in a treatment fraction, the post-fraction scan was first rigidly registered to

the pre-fraction scan for all pairs of CBCT scans. Intra-fraction patient setup changes were quantified separately (see below). Next, the cervix-uterus surfaces in the pre- and post-fraction scans were non-rigidly registered using an in-house developed non-rigid registration method (31). The method simultaneously estimates the correspondence between points on two surfaces and the transformation. The result of a non-rigid registration is an intra-fraction displacement vector for each point on the cervix-uterus surface in the pre-fraction CBCT scan. In addition, for each patient, the cervix-uterus in the first pre-fraction CBCT was non-rigidly registered to the cervix-uterus shape in all remaining 22 pre-fraction CBCT scans. The obtained point correspondences allowed for calculation of the patient-specific average cervix-uterus shape over all fractions and for collection of the motion statistics from each fraction on this average shape. Next, for each patient, the mean intra-fraction displacement in all three directions was calculated for each point on the average cervix-uterus shape, where the mean was taken over all treatments fractions. The mean displacements quantify the systematic component of the intra-fraction motion for each point on the cervix-uterus shape. Then, we calculated the mean and the 5^{th} and 95^{th} percentiles of these displacements for each patient. The 5^{th} and 95^{th} percentiles are the left upper limit and the right lower limit of the 5% tail of the displacement distribution on each patient's average cervix-uterus. These values can be used to establish a margin to account for intra-fraction cervix-uterus motion. The patients' mean and the patients' 5^{th} and 95^{th} percentiles of the systematic intra-fraction motion were translated to group statistics by calculating the group-mean and standard deviation of these parameters. Positive values for LR, CC and AP pointed at motion in right, cranial and anterior directions, respectively. The accuracy of the non-rigid registration was quantified by the Hausdorff distance of the pre-fraction contours to the transformed post-fraction contours. The Hausdorff distance is a measure for the distance between two structures. It is defined as the largest minimal distance of all surface points of one structure to the points in the other structure.

Intra-fraction patient setup variation

Intra-fraction setup variation was evaluated by computing the difference in patient position after CBCT assisted patient setup (above) of the patient observed in the post-fraction CBCT scan. The pelvis bony anatomy was used as reference. For each fraction, the intra-fraction patient motion was computed by first rigidly aligning the pre- and post-fraction CBCT scans to the planning CT using grey value matching in the XVI software (version 4.5.1, Elekta, AB, Sweden). The registration clip box was defined around the bony pelvis in the planning CT scan. Rotations were converted to translations using the center of the clip box as correction reference point. The setup corrections as carried out by the Theraview Couch Setup Assistant (TCSA) (Cablon Medical, Leusden, The Netherlands) were subtracted from the calculated translations in the LR, AP, and CC directions. For

each patient, the mean intra-fraction setup change and the standard deviation were calculated for all directions. Then, the population mean (M), systematic (∑) and random changes (σ) of the intra-fraction patient setup were established. The systematic error (∑) defined the systematic population error and was calculated as the standard deviation of the distribution of the population mean (M). The random error (σ) was calculated as the root mean square of the patients' random error, i.e. the standard deviation of each patient's intra-fraction setup changes.

3.3 RESULTS

IMRT was delivered in 82.5% of the patients. Mean IMRT delivery time was 12.0 minutes. The mean time between the pre- and post-fraction CBCT scans was 20.8±3.2 minutes. In total 632 pre-and post-fraction CBCT scans were delineated.

Bladder volume increased on average by 62±55 ml over all treatment fractions and rectum volume increased on average by 5±33 ml. Bladder inflow rate was 3.0±2.7 ml/min over all treatment fractions. Figure 1 shows the pre-fraction bladder volume and bladder volume difference with the mean and SD in all patients over 23 fractions. This figure indicates that the bladder volume as well as the bladder volume change reduces during the treatment course.

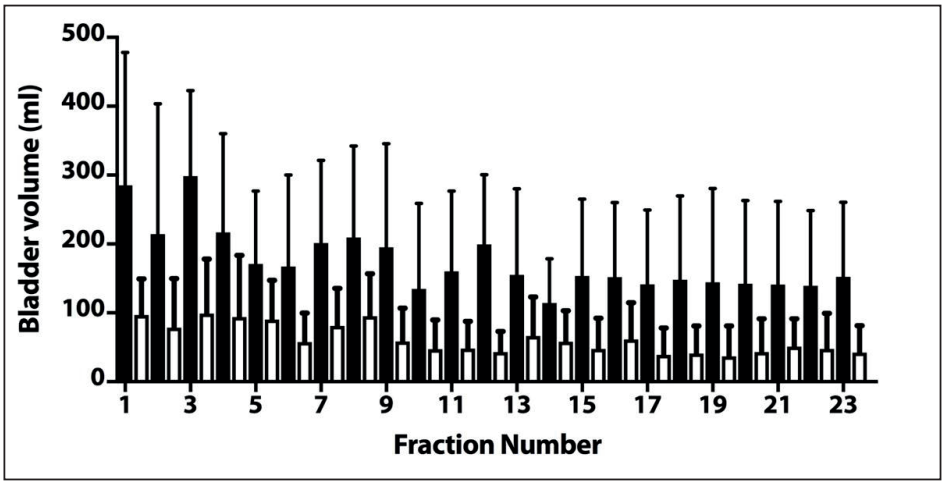

Figure 1. For each fraction, the pre-fraction bladder volume (black) and the intra-fraction bladder volume change, averaged over all patients. The error bars equal one standard deviation of the average bladder volume or bladder volume change.

A significant positive correlation was found between bladder inflow rate and volume of the bladder at the start of a fraction, as measured in the pre-fraction CBCT scan ($R=0.44$, $p<0.01$). This means that a larger bladder volume observed at the start of treatment was predictive of a higher inflow rate. Regression analysis showed a constant of 1.4 and a coefficient of 0.009, which means that for every 100 ml extra bladder volume at the start of treatment, the inflow rate increased with approximately 1 ml/min.

A significant correlation was found between bladder inflow rate and the average length of the cervix-uterus intra-fraction systematic displacement ($R=0.6$, $p<0.01$), meaning that the inflow rate could help predict cervix-uterus position during treatment. The correlation of the cervix-uterus intra-fraction displacement was evaluated separately for the LR, CC, and AP direction as well and a significant correlation was found in the CC and AP ($R=0.3$, $p<0.01$ and $R=0.6$ $p<0.01$). There was no significant correlation between rectum filling and the average length of the cervix-uterus displacement nor for the displacements in the three directions separately.

The average Hausdorff distance of the intra-fraction registration accuracy was 1.1 mm, which shows that the registration of the cervix-uterus shapes was accurate.

The mean and the 5^{th} and 95^{th} percentiles of the systematic intra-fraction displacements are depicted for each patient separately in figure 2. Table 1 summarizes these values averaged over the patient group. In the AP and CC direction the group-mean was significantly different from 0 ($p<0.05$), indicating a preferred direction for the systematic intra-fraction displacements. The filling of the bladder during the treatment fraction and the resulting cervix-uterus motion seems a plausible explanation. A similar trend was observed for the 5^{th} and 95^{th} percentiles in the AP and CC direction being asymmetrically distributed around 0 (AP: 0.5 to -5.8 mm; CC 4.9 to -0.8 mm). Figure 3 shows a color representation of the systematic intra-fraction displacements for each patient and for each direction separately. The figure demonstrates how the magnitude and direction of the systematic displacements is distributed across the cervix-uterus average shapes. Notwithstanding the inter-patient differences, the largest intra-fraction systematic displacements appear in the upper part of the uterus.

Table 2 shows the intra-fraction changes in patient setup for the patient group. Appendix 3A shows for each patient the mean and SD for each patient separately. When there was unexpectedly large motion in all directions, the image registrations were checked. Changes in bladder filling and flatulence were reasons for such patient motion. For all patients, the mean motion in CC and AP direction were smaller than 2.0 mm.

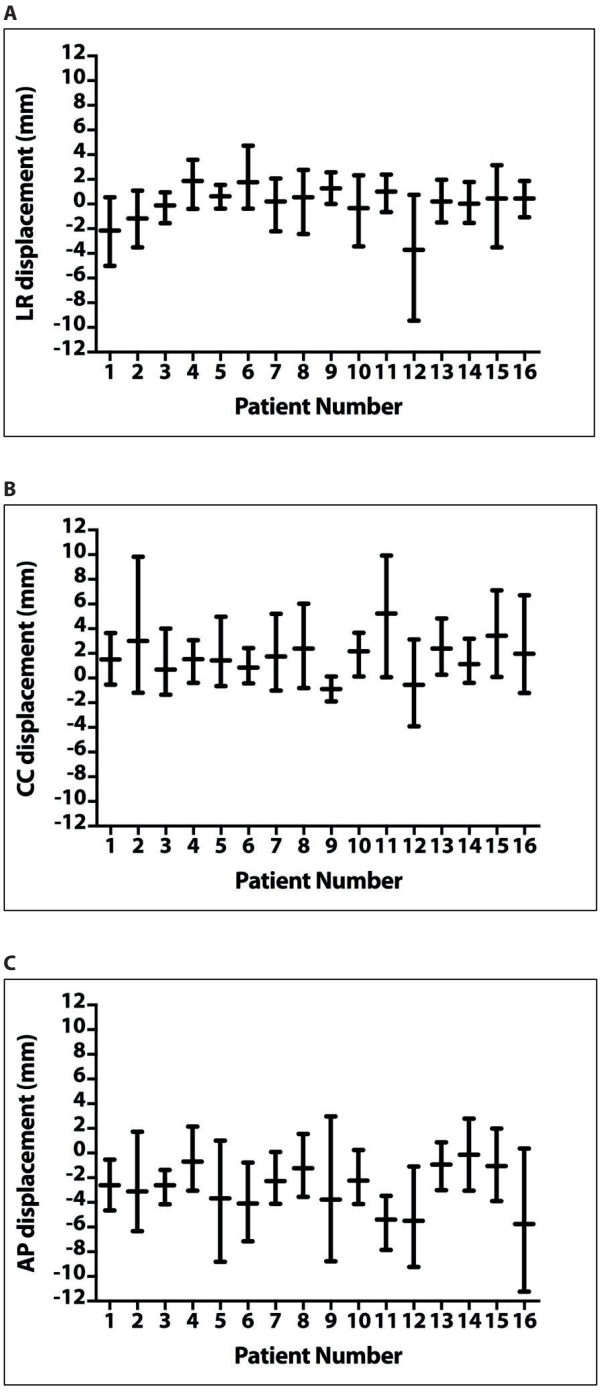

Figure 2. The mean, 5th and 95th percentiles (error bars) intra-fraction cervix-uterus displacement for each patient in the a) Left-right, b) Cranial-caudal and c) Anterior-posterior directions. Positive values for LR, CC and AP pointed at motion in right, cranial and anterior directions, respectively. Some patients had due to bladder filling a large displacement in the LR, CC and AP direction, respectively.

Table 1. Group-mean and standard deviation of the patients' mean and the mean patients' 5th and 95th percentiles of the systematic intra-fraction motion.

Cervix-uterus motion	LR (mm)	CC (mm)	AP (mm)
Mean±SD	0.1±1.4	1.8±1.5	-2.8±1.8
95th percentile±SD	2.1±1.1	4.9±2.6	0.5±1.7
5th percentile±SD	-2.3±2.4	-0.8±1.0	-5.8±2.7

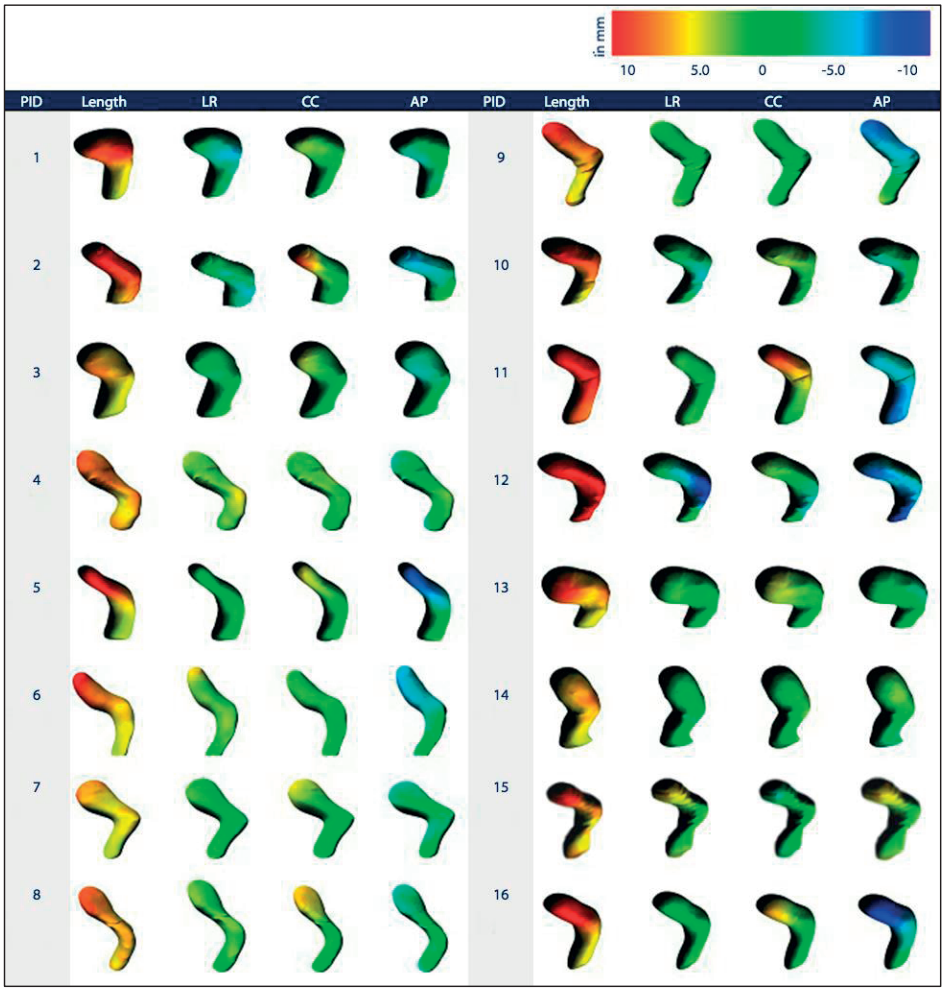

Figure 3. A color representation of the systematic intra-fraction displacements in mm projected on each patient's average cervix-uterus shape. The first shape shows the average length of the intra-fraction systematic displacements and the others show the systematic displacements in the LR, CC, and AP direction. The largest intra-fraction displacements often appear in the upper part of the uterus.

Table 2. The overall mean (M), systematic error (Σ), and random error (σ) of the intra-fraction changes in patient setup over the entire patient group .

Patient motion	LR (mm)	CC (mm)	AP (mm)
M	-0.1	0.4	1.1
Σ	1.3	0.4	0.6
σ	1.4	1.0	1.1

3.4 DISCUSSION

To the best of our knowledge, this is the first study investigating the intra-fraction motion of the cervix-uterus of cervical cancer patients, using daily acquired pre- and post-fraction CBCT scans. Results showed that intra-fraction cervix-uterus motion is considerable in our treatment time frame of 20.4 minutes with group-mean systematic intra-fraction displacements of up to 5.8 mm to posterior and up to 4.9 mm to cranial (Table 1, 5th and 95th percentiles). Individual systematic displacements could even be larger and extend beyond 10 mm (Figure 2). From our previous studies, we learned that bladder filling has an impact on the position of the uterus (10,15). In this study, we also observed a significant correlation between bladder volume difference and intra-fraction cervix-uterus displacement ($R=0.63$, $p<0.01$). Rectum filling difference had no correlation with the intra-fraction motion, which could be explained by the limited change in rectum filling during the treatment fraction.

In this study, the intra-fraction displacements were measured between the time points of the pre-fraction and post-fraction CBCT scan not knowing the actual displacement during dose delivery. An analysis to halfway through the dose delivery time of a fraction should give a more clinically relevant estimate of the intra-fraction motion. Bondar et al. demonstrated that cervix-uterus motion could be approximated by a linear function of the bladder filling (15). Furthermore, we assume that the filling of the bladder is linear in time as well. From our previous study, we learnt that the time needed for to match the CBCT to the planning CT scan is 1 minute, the time needed for plan selection and verification is on average 2.4 minutes. If we would start measuring at halfway the CBCT scan acquisition and we would add the time needed to match the CBCT scan and for plan selection, and determine the motion at the halfway mark of the average dose delivery time of IMRT (at 10.6 minutes), then the group-mean 5th and 95th percentiles will decrease from -2.3, 2.1 to -1.2, 1.1 mm in the LR direction, from -0.8, 4.9 to -0.4, 2.5 mm in the CC direction, and from -5.8, 0.5 to -3.0, 0.3 mm in the AP direction. Similarly, we calculated the 5th and 95th percentiles covering at least 90% of the patients at 10.6 minutes. These values (LR: -3.2, 2.0 mm; CC: -1.3, 5.0 mm; AP: -5.0, 1.5 mm) could be used as margins to account for the systematic intra-fraction motion. Note that in particular the margins in

the AP and CC directions are asymmetric. From October 2014 onwards, cervical cancer patients are treated in our institute by Volumetric Modulated Arc Therapy (VMAT) using the fully automated planning system Erasmus-iCycle (29). Consequently, average dose delivery time has been reduced from 12.0 minutes to 4.8 minutes. For VMAT treatments, following the same computation (at 7.0 minutes), the group-mean of the 5^{th} and 95^{th} percentiles would decrease to -0.8, 0.7 mm in LR, to -0.3, 1.6 mm in CC, and to -2.0, 0.2 mm in AP direction, halfway through the dose delivery. The values covering at least 90% of the patients are LR: -2.1, 1.3 mm, CC: -0.8, 3.3 mm, and AP: -3.3, 1.0 mm.

For most patients, the largest motion was found at the uterine fundus. Therefore, if the fundus would be excluded from the clinical target volume, the margins to account for intra-fraction motion can be reduced. This is subject to future research.

As part of our current protocol we verified whether after the delivery of the selected IMRT plan, the CTV was still inside the PTV by inspecting each post-fraction CBCT. For all patients and all fractions, the CTV was observed inside the PTV (25). Hence, the ITVs combined with the 1-cm margin were sufficient to account for the intra-fraction motion.

This study extends on other research on this topic. Haripotepornkul et al. investigated the intra-fraction motion for cervical cancer patients with daily kV imaging throughout a course of IMRT using markers implanted into the cervix. A median marker displacement of 2-4 mm was observed in any given direction, which is smaller than we analyzed, specifically in the AP direction. However, this could be explained because the markers represented the location of the cervix only, which is less affected by bladder filling changes than the uterus (27). Kerkhof et al. studied intra-fraction motion with and without registration of the bony anatomy using two or three offline MRI exams pre-treatment and in week 1 and week 4 of the treatment. Four sagittal and four axial MRI scans were acquired over a time period of 16 minutes. They found that the midsagittal primary CTV could move more than 10 mm within a 16 minute time frame. They found a weak but significant correlation between bladder filling and CTV motion (26). This study was limited by the number of scans (2-3) per patient and by the analysis of the motion only in the midsagittal plane. Chan et al. also studied the intra-fraction motion of the cervix-uterus using three points of interest (cervical os, uterine canal, and uterine fundus). The largest motion was found at the fundus of the uterus with a mean of -1.1 mm in AP direction and -3.1 mm in CC direction in a time frame of 31 minutes. This is smaller than we found, however, this could be explained by the fact that we included only patients with a large tip-of-uterus displacement measured pre-treatment in a full and empty bladder CT scan (28).

In bladder cancer patients, the intra-fraction motion has been investigated in several studies (32,33). Our study can be compared to the Dees et al. paper (32). They also used pairs of CBCT scans to analyze the intra-fraction motion. As opposed to our study, in this study two bladder filling protocols were used, one aiming at a full and one at an

empty bladder, i.e. patients were divided into two groups. They found a median bladder inflow rate over the whole patient population of 1.94 ml/min. Our results show that the bladder inflow rate was 3.0 ml/min over all treatment fractions. A more intensive drinking protocol applied in our study may explain, besides other differences between the patient groups, the higher inflow rate seen for our patients.

A limitation of this study is that observer variability in contouring the cervix-uterus in CBCT scans may impact the results. To minimize this impact, the first author consistently delineated all pairs of CBCT scans. Contouring variability was further reduced using an automatic segmentation method as contouring aid (30). Furthermore, we would like to point out that we analyzed the scans pairwise, i.e. the pre-fraction and post-fraction CBCT scans for each fraction were compared. In this way, the impact reduced mainly to interpretation differences between a pre-fraction and a post-fraction CBCT scan. Also, the accuracy of the non-rigid registration of measuring the intra-fraction motion could be a potential source of error. However, we have seen that this error was small (<1.1 mm) and thereby it had limited influence on the observed intra-fraction motion.

In this study, we quantified the intra-fraction changes in cervix-uterus shape, bladder and rectum filling, and patient setup using pre- and post-fraction acquired CBCT scans. Intra-fraction changes in patient setup motion were small. Intra-fraction cervix-uterus motion was considerably larger and correlated with the intra-fraction filling of the bladder. Intra-fraction cervix-uterus motion should not be ignored, in particular in the design of Plan-of-the-Day strategies.

Chapter 4

Optimal patient positioning (prone versus supine) for VMAT in gynecological cancer: a dosimetric study on the effect of different margins

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ABSTRACT

Background & purpose

It is unknown whether the historically found dosimetric advantages of treating gynecologic cancer with the patient in a prone position with use of a small-bowel displacement device (belly-board) remain when volumetric arc therapy (VMAT) is used and whether these advantages depend on the necessary margin between clinical target volume (CTV) and planning target volume (PTV). The aim of this study is to determine the best patient position (prone or supine) in terms of sparing organs at risk (OAR) for various CTV-to-PTV margins and VMAT dose delivery.

Material & Methods

In an institutional review board approved study, 26 patients with gynecologic cancer scheduled for primary (9) or postoperative (17) radiation therapy were scanned in a prone position on a belly-board and in a supine position on the same day. The primary tumor CTV, nodal CTV, bladder, bowel and rectum were delineated on both scans. The PTVs were created each with a different margin for the primary tumor and nodal CTV. The VMAT plans were generated using our in-house system for automated treatment planning. For all margin combinations, the supine and prone plans were compared with consideration of all OAR dose-volume parameters but with highest priority given to bowel cavity V_{45Gy} (cm^3).

Results

For both groups, the prone position reduced the bowel cavity V_{45Gy}, in particular for nodal margins ≥10 mm (ΔV_{45Gy}=23.9±10.6 cm^3). However, for smaller margins, the advantage was much less pronounced (ΔV_{45Gy}=6.5±3.0 cm^3) and did not reach statistical significance. The rectum mean dose (D_{mean}) was significantly lower (ΔD_{mean}=2.5±0.3 Gy) in the prone position for both patient groups and for all margins, and the bladder D_{mean} was significantly lower in the supine position (ΔD_{mean}=2.6±0.4 Gy) only for the postoperative group. The advantage of the prone position was not present if it needed a larger margin than the supine position.

Conclusion

For patients with gynecologic cancer, the historically found dosimetric advantages for the prone position remain for modern dose delivery techniques if large margins are needed. However, the advantage is lost for small margins and if the prone position needs a larger margin than the supine position.

4.1 INTRODUCTION

Radiation therapy is one of the standard modalities in gynecologic cancer treatment. Intensity modulated radiation therapy (IMRT) and volumetric arc therapy (VMAT) are both used to improve dose conformity and better spare the organs at risk (OARs) compared with 3-dimensional conformal radiation therapy (3DCRT) (5,7,8,34). More recently, IMRT or VMAT has been combined with daily adaptive treatments (eg, plan library-based Plan-of-the-Day techniques) to further reduce the planning target volume (PTV) and to spare small bowel, which is considered the most important OAR (5,25). Dose to small bowel can also be reduced by setting patients up in a prone position on a small bowel displacement device (belly-board), pushing the small bowel outside the radiation field (5). However, the prone position has the known disadvantages of reduced cone beam computed tomography (CBCT) image quality resulting from breathing artefacts and reduced rotational stability (35); these may compromise treatment accuracy and thereby the feasibility of Plan-of-the-Day adaptive strategies. Moreover, the dosimetric advantage of the prone position was mostly determined for 3DCRT or IMRT using relatively large margins (16,36-38). It is unknown to what extent those advantages remain when modern treatment planning and delivery techniques are used and how they depend on the PTV margin around the primary and nodal clinical target volume (CTV).

The aim of this work is twofold: *(1)* to determine whether the dosimetric advantages of the prone position found in the past remain for modern treatment planning and delivery techniques (ie, automatically generated dual-arc VMAT); and *(2)* to determine the impact of the CTV-to-PTV margins on OAR sparing and in particular to determine this impact on the supposed dosimetric advantage of the prone position.

4.2 MATERIAL AND METHODS

Patient data

In this prospective study, 9 primary locally advanced cervical cancer patients with intact uterus, 10 postoperative locally advanced cervical cancer patients and 7 postoperative endometrial cancer patients were included. Given that the target volume in the patients with postoperative endometrial cancer and those with postoperative locally advanced cervical cancer was the same, we merged those groups for further analysis, making a total of 17 patients with postoperative gynecologic cancer.

All patients were scanned and treated in the Amsterdam Medical Center (AMC) from 2011 to 2012 after providing written consent. The local ethics committee of the AMC approved this study.

For each patient, 2 CT scans were made on the same day: a planning CT scan in prone position using a small bowel displacement device (belly-board) and immediately thereafter a CT scan in supine position, on a flat couch with a knee roll. Before scanning, patients were instructed to drink 500 cm^3 after voiding the bladder 2 hours before the CT scan, aiming at a full bladder at the time of the scan.

In all CT scans of the patient with primary cervical cancer, the primary CTV (cervix, uterus and proximal part of the vagina) and the nodal CTV (common iliac lymph nodes, external iliac lymph nodes, internal iliac lymph nodes, presacral lymph nodes and parametrial tissue) were delineated. In addition, we delineated the bladder, rectum and bowel cavity. The latter encompassed all loops of small bowel, colon and sigmoid, including peritoneal space between the loops, starting caudally from the first bowel loop until 1 cm above the PTV in the cranial direction according to the Radiation Therapy Oncology Group consensus guidelines (39,40). In all CT scans of the postoperative patients the bladder, bowel cavity (see above), rectum, primary CTV (proximal part of the vagina and paravaginal soft tissue), and nodal CTV were delineated. The contouring was performed by SH, GW, and NB. To minimize observer variation, all contours for both positions were checked for consistency by SH and JWM.

CTV-to-PTV margins for treatment planning

The PTV was created by an expansion of the primary CTV by 5, 10, or 20 mm and of the nodal CTV by 5, 7, 10, or 15 mm (41). Four different nodal PTV margins were combined with different primary PTV margins (Table 1). Here, we supposed that in clinical practice an accurate treatment of the primary CTV using, for example, a Plan-of-the-Day adaptive approach, is usually combined with an accurate treatment of the nodal CTV. Below, we explain the rationale of the margins used.

Table 1. Nine tested CTV-to-PTV margin combinations.

Margin around nodal CTV (mm)	Margin around primary CTV (mm)
5	5
5	10
7	5
7	10
7	20
10	10
10	20
15	10
15	20

A 10 mm expansion of the nodal CTV is used in our current clinical adaptive protocol as described in Heijkoop et al (25) and was used in the AMC in 2011 and 2012. In this study we combined the 10 mm nodal CTV margin with a primary CTV margin of 10 mm and 20 mm.

Ahmad et al (42) measured residual setup errors caused by rotation and nonrigid motion in cervical cancer treated in the prone position. They found that a 15 mm nodal PTV margin was needed to account for setup errors. In this study, we combined this nodal margin with a primary CTV expansion of 10 mm and 20 mm.

Finally, we investigated a 5 mm nodal PTV margin and combined this with a 5 mm and 10 mm expansion of the primary CTV.

Automated plan generation

All VMAT plans were generated using a fully automatic method developed by Sharfo et al (29). The automated treatment plan generation was performed with our clinical treatment planning system (Monaco Version 5.0, Elekta AB, Sweden) based on an automatic pre-optimization with our in-house lexicographic multi-criterial optimizer, Erasmus-iCycle. Plan optimization with Erasmus-iCycle is based on an *a priori* defined "wish-list" containing hard constraints and prioritized objectives with assigned goal values. The wish list used in this study is clinically used at Erasmus MC. According to this wish list, patients are prescribed to receive 46 Gy in 2 Gy fractions. PTV coverage had the highest priority, followed by the sparing of the bowel cavity at V_{45Gy} (i.e. the volume receiving ≥45 Gy). The V_{15Gy} and mean dose (D_{mean}) of the bowel cavity, the rectum, and bladder were optimized with a lower priority. Pseudorings at different distances from the PTV were used to control the entrance dose in the patient and to create a conformal dose distribution. For further details on Erasmus-iCycle and automated planning we refer to Breedveld et al (20) and Sharfo et al (29). In another study from Voet et al (43), we showed that further improvements of the automatically generated VMAT plans by manually tweaking the plan objectives in Monaco led to only minor improvements in plan quality. All VMAT plans were visually checked and verified for clinical acceptability among others to ensure sufficient clearance for gantry rotation in prone position according to standardized protocols by a clinician SH and a specialized RTT RF.

Dosimetric evaluation

The primary and the postoperative patients were analyzed both combined and separately. For each patient, patient position, and for each primary/nodal margin combination, the absolute volume in cm^3 of the bowel cavity receiving at least 45 Gy (V_{45Gy}) was evaluated. We evaluated the absolute instead of the relative bowel cavity volume to reduce the impact of cranial contouring differences between the CT scans with the patient in the prone and supine position. The absolute volume was also found to be predictive for acute bowel toxicity in normal tissue complication probability models (44,45). For bladder and rectum, the D_{mean} was recorded. Because there is an inevitable time delay between the acquisition of the 2 CT scans, bladder filling may have increased in the second scan, potentially pushing the small bowel farther outside the high-dose region, or bladder filling may have decreased if the patient had to void her bladder in between the acquisitions. To verify the effect on the prone-supine comparison, we tested whether a difference in V_{45Gy} of the bowel cavity between the prone and supine position was related to the bladder volume difference between both scans. The PTV95% (volume of the PTV receiving ≥43.7 Gy) was calculated to verify PTV coverage. A paired 2-sided Wilcoxon signed rank test was used to compare both patient positions, and P-values <0.05 were considered statistically significant. SPSS Statistics 21.0 was used for

all statistical analyses. To determine the sensitivity to the needed margin, we not only compared supine with prone treatment plans, with matching margin combinations but also compared supine with prone plans for which the prone plans had a larger margin around the nodal CTV than did the supine plans. In that way, we assessed the scenario that for prone positioning a larger nodal margin is needed (ie, to compensate for uncorrected rotation errors) (42).

4.3 RESULTS

PTV coverage

The $V_{95\%}$ of the PTV was >99% for all 9 margins and for both patient positions. All treatment plans of all patients were verified and found to be clinically acceptable and deliverable.

Bowel cavity sparing and impact of margins

All patients

The mean total bowel cavity volume was 1088±397 cm^3 (1 SD) for patients in the prone position and 1601±489 cm^3 for patients in the supine position. Figure 1a shows the comparison between the supine and prone position in terms of V_{45Gy} of the bowel cavity for all patients and all matching primary/nodal margin combinations. The prone position was significantly superior for large nodal margins ≥10 mmbut not for the nodal margins of 5 and 7 mm. Table 2 lists the differences in V_{45Gy} of the bowel cavity for each matching margin combination. The significant advantage was not present if the prone position needed a larger margin than the supine position. In the latter case, the supine position was always significantly better, except for 1 margin combination (supine 20/7mm vs prone 20/10mm) (Figure 1b). Figure 2 shows the dependence of the bowel cavity V_{45Gy} on the nodal margin for both positions, where for nodal margins ≥10 mm the prone position was significantly better than the supine position. Additional data can be found for the V_{15Gy} and D_{mean} of the bowel cavity in Appendix 4A.

Primary group

The mean bowel cavity volume was 1005±351 cm^3 for patients in the prone position and 1484±521 cm^3 for patients in the supine position. Figure 3a illustrates the bowel cavity V_{45Gy} for this patient group for all matching margin combinations. This figure indicates that when small margins were used, the advantage for either prone or supine is not significant and that when larger margins were used (10/10mm, 10/15mm, and 20/15mm), the prone position was significantly better. Table 2 summarizes the differences in bowel cavity V_{45Gy} and significance between the supine and prone position for all margin com-

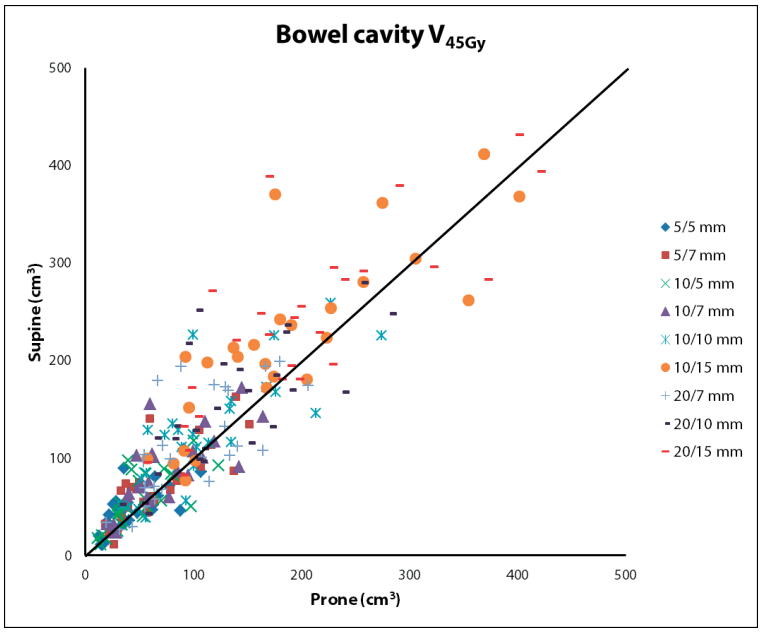

Figure 1a. Comparison of bowel cavity V_{45Gy} (cm^3) for supine and prone position for matching primary/nodal margin combinations for both groups combined. Codings for the primary/nodal margins are shown. Prone was significantly superior to supine for margin combinations ≥10/10 mm.

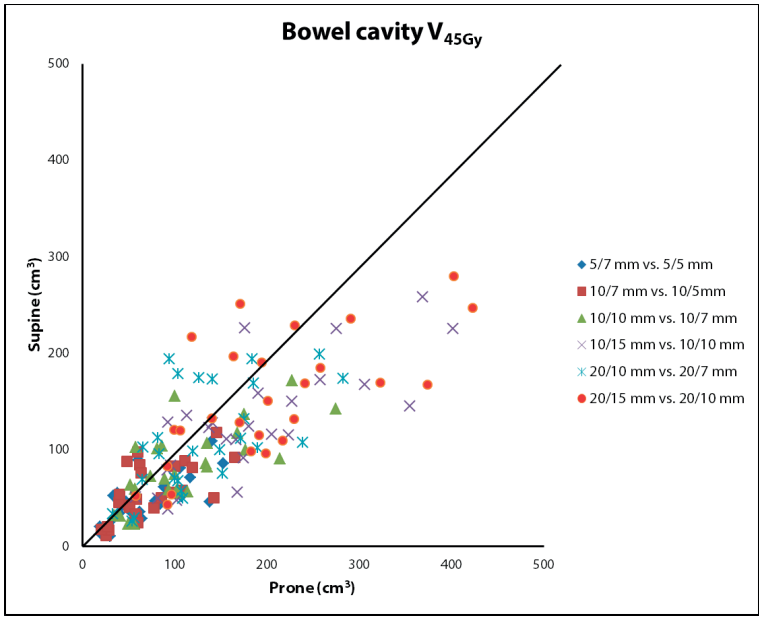

Figure 1b. For all patients, comparison of different scenarios between supine nodal margins and larger prone nodal margins in terms of bowel cavity V_{45Gy}. The first number indicates the prone margin; the second, the supine margin.

binations. Figure 3b shows again the bowel cavity V_{45Gy} but then comparing margin combinations of which the nodal margin was larger in the prone position. These results indicate that in these combinations there was no preference in patient position. For all 9 margins, we did not find any significant correlation between difference in V_{45Gy} of the bowel cavity and the difference in bladder volume.

Table 2. For both patient groups separately and combined, the dosimetric differences (OARs) between prone and supine position for matching primary/nodal margin combination. Positive values indicate that the prone position is superior.

	Bladder D_{mean} (Gy)			**Rectum D_{mean} (Gy)**			**Bowel cavity V_{45Gy} (cm^3)**		
	All	***Primary***	***Post-operative***	***All***	***Primary***	***Post-operative***	***All***	***Primary***	***Post-operative***
5/5 mm									
Mean±SD	-2.1±0.5	-1.9±1.3	-2.2±0.2	2.5± 0.3	3.3±1.2	2.1±0.4	3.8 ±1.0	5.8±2.0	2.4±0.7
P-value	<0.001*	0.05	0.001*	<0.001	0.01	0.006	0.3	0.4	0.7
5/7 mm									
Mean±SD	-2.1±0.4	-1.6±1.2	-2.4±0.1	2.5±0.2	3.3±0.8	2.0±0.4	5.9±0.8	7.6±0.1	5.1±0.6
P-value	<0.001*	0.1	0.001*	<0.001	0.008	0.02	0.3	0.4	0.5
10/5 mm									
Mean±SD	-2.2±0.4	-1.5±1.2	-2.5±0.0	2.8±0.2	3.9±0.8	2.1±1.0	5.6±0.2	12.1±3.6	2.2±1.1
P-value	<0.001*	0.1	0.001*	0.001	0.008	0.03	0.2	0.1	0.4
10/7 mm									
Mean±SD	-2.4±0.6	-1.7±1.7	-2.7±0.2	2.5±0.0	3.4±0.9	2.0±0.7	10.7±0.1	16.5±2.4	7.7±0.0
P-value	<0.001*	0.07	<0.001*	0.001	0.008	0.03	0.07	0.09	0.3
10/10 mm									
Mean±SD	-2.0±0.4	-1.4±1.3	-2.4±0.0	2.3±0.2	3.7±0.5	1.5±0.3	15.1±1.3	23.8±2.0	10.4±0.5
P-value	<0.001*	0.1	0.001*	0.02	0.008	0.08	0.05	0.04	0.3
10/15 mm									
Mean±SD	-1.9±0.4	-1.3±0.8	-2.2±0.2	2.1±0.1	2.7±0.4	1.8±0.5	33.5±2.2	40.7±4.3	29.7±2.0
P-value	0.001*	0.2	0.001*	0.001	0.01	0.02	0.04	0.03	0.04
20/7 mm									
Mean±SD	-2.9±0.7	-2.0±1.4	-3.4±0.2	2.7±0.9	2.7±0.1	2.7±1.2	13.5±4	26.2±11.5	6.7±0.9
P-value	<0.001*	0.09	<0.001*	<0.001	0.008	0.01	0.2	0.09	0.5
20/10 mm									
Mean±SD	-2.5±0.7	-1.7±1.4	-2.9±0.2	4.0±2.0	2.5±0.0	2.7±1.1	21.1±0.6	32.5±9.9	15.1±2.2
P-value	<0.001*	0.09	<0.001*	<0.001	0.008	0.004	0.04	0.07	0.1
20/15 mm									
Mean±SD	-2.1±0.5	-1.6±1.3	-2.4±0.1	2.2±0.7	1.9±0.2	2.3±0.9	36.6±3.2	46.7±8.1	31.2±4.7
P-value	<0.001*	0.1	<0.001*	<0.001	0.008	0.002	0.04	0.04	0.04

*Supine position is superior

Positive values indicate that the prone position is superior.

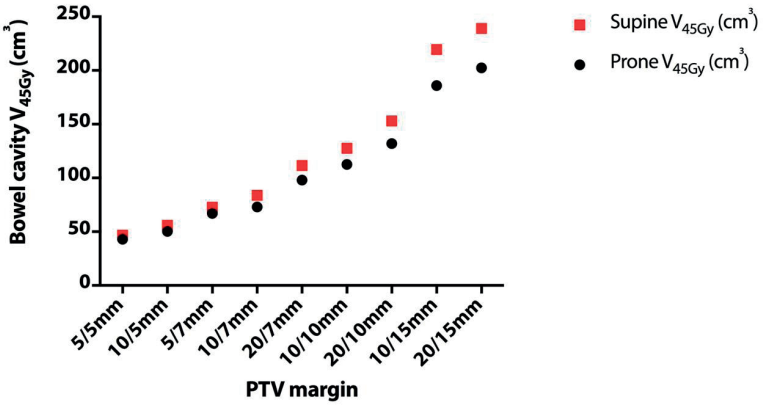

Figure 2. Dependency of the nodal margin on the bowel cavity V_{45Gy} (cm^3) for supine and prone position, for all patients. The first number indicates the primary margin; the second number indicates the nodal margin. The circles indicate the prone position; the squares indicate the supine position.

Postoperative group

The mean bowel cavity volume was 1132±423 cm^3 in the prone position and 1663±476 cm^3 in the supine position. Figure 4a shows the bowel cavity V_{45Gy} for both positions and all matching margin combinations. For this group, the prone position better spared the bowel cavity than did the supine position, in particular for large margins: 10/15mm and 20/15mm. For small margins, the advantage was less pronounced and did not reach statistical significance. Figure 4b illustrates the comparison for different nodal margins. Assuming that a smaller margin is needed in the supine position, supine is significantly better for sparing the bowel cavity.

Bladder

All patients

The mean bladder volume was 273±138 cm^3 for patients in the prone position and 313±176 cm^3 for patients in the supine position. Four patients had to void the bladders after the acquisition of the CT scan in prone position. For the other 22 patients' bladder volume increased on average by 92.2 cm^3 between the 2 scans. For all margins, the bladder D_{mean} was significantly lower in the supine position (average D_{mean} of 37.8 Gy in prone position; 35.6 Gy in supine position). In Appendix 4B the V_{40Gy} of the bladder can be found.

Primary group

The average volume was 313±136 cm^3 for patients in the prone position and 308±191 cm^3 in the supine position. There was no significant difference in D_{mean} between patients in the prone position and those in the supine position (Table 2).

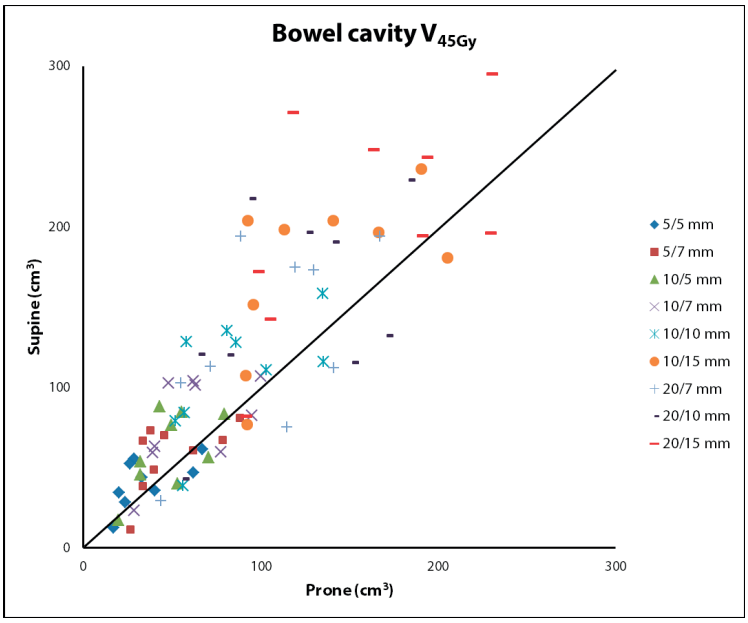

Figure 3a. Comparison of bowel cavity V_{45Gy} (cm^3) for supine and prone position for matching primary/nodal margin combinations for the primary group only. Codings for the primary/nodal margin combinations are shown. Prone was significantly superior to supine for the larger margin combinations (10/10 mm, 10/15 mm, and 20/15 mm).

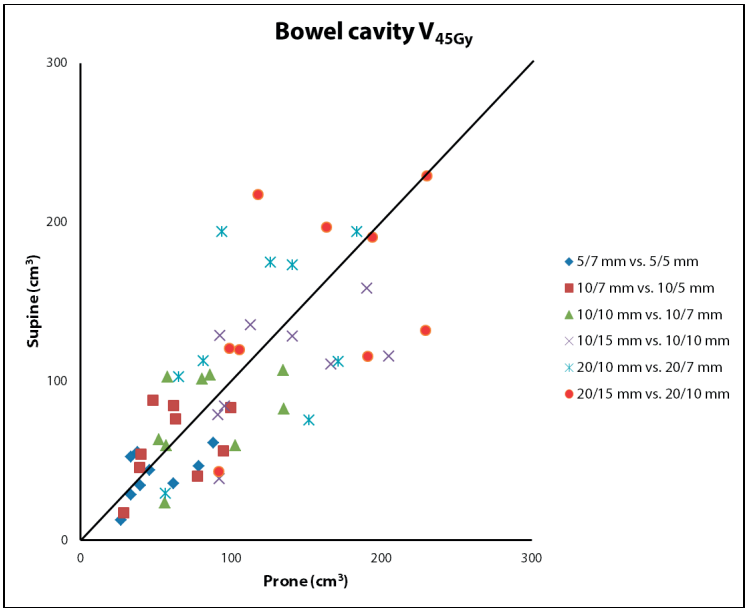

Figure 3b. For the primary group, comparison of different scenarios between supine nodal margins and larger prone nodal margins in terms of bowel cavity V_{45Gy}. The first number indicates the prone margin; the second, the supine margin.

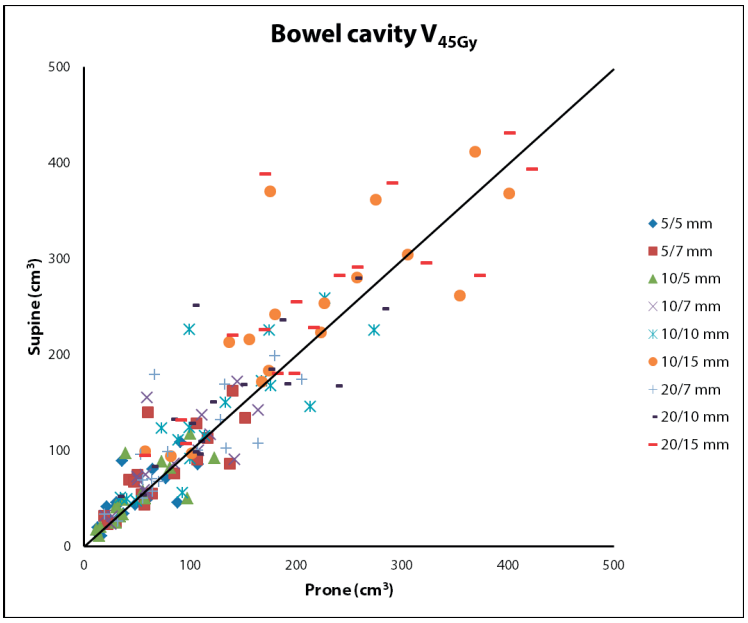

Figure 4a. Comparison of bowel cavity V_{45Gy} (cm^3) for supine and prone position for matching primary/nodal margin combinations for the postoperative group only. Codings for the primary/nodal margin combinations are shown. Prone was significantly superior to supine for the larger margin combinations (10/10 mm, 10/15 mm, and 20/15 mm).

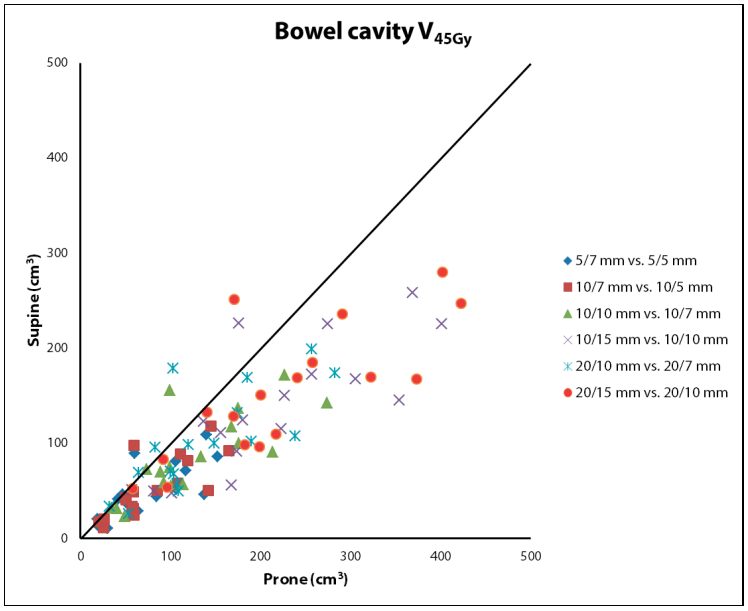

Figure 4b. For the postoperative group, comparison of different scenarios between supine nodal margins and larger prone nodal margins in terms of bowel cavity V_{45Gy}. The first number indicates the prone margin; the second, the supine margin.

Postoperative group

The average bladder volume was 251±139 cm^3 for patients in the prone position and 316±174 cm^3 in the supine position. The bladder was significantly fuller in the supine position. Table 2 shows the mean difference in bladder D_{mean} for each matching margin combination. It illustrates that the D_{mean} for patients in the supine position was significantly lower.

Rectum

All patients

The average rectum volume was 114±61 cm^3 for patients in the prone position and 93±40 cm^3 for patients in the supine position. No significant difference was found between the prone and supine position for the rectum volume. For all margin combinations, the rectum D_{mean} was significantly lower for patients in the prone position (average D_{mean} of 37.4 Gy in prone position; 39.9 Gy in supine position). In Appendix 4B the $V_{40\ Gy}$ of the rectum is given.

Primary group

The mean volume of the rectum was 143±80cm^3 for patients in the prone position and 78±28cm^3 for patients in the supine position. The D_{mean} was significantly lower for patients in the prone position (3.2±0.9 Gy) than for those in the supine for all margin combinations (Table 2).

Postoperative group

The mean rectum volume was 99±45cm^3 for patients in the prone position and 101±44cm^3 for patients in the supine position. The D_{mean} for patients in the prone position was significantly lower (2.2±0.4 Gy) than for patients in the supine position, except for the margin combination 10/10 mm (Table 2).

4.4 DISCUSSION

In this report, we present a rigorous treatment planning comparison study to determine the optimal patient position for VMAT dose delivery and for various CTV-to-PTV margins in gynecologic cancer patients. We considered the bowel cavity as the OAR that should be spared as the most needful of adequate target coverage. For the whole group and for both primary and postoperatively treated groups separately, the prone position was significantly superior in bowel cavity sparing when large margins were used around the nodal target; ≥10/10 mm (primary/nodal margin around CTV) for the whole group,

≥10/10 mm for the primary group, and ≥10/15 mm for the postoperative group (Figure 1a, 3a, and 4a). To determine the sensitivity of the dosimetric difference to the margin needed for the supine and prone position, we compared not only the prone-to-supine plans with matching margins but also the prone–to-supine plans, for which the supine plans had a smaller margin than the prone plans (Figure 1b, 3b and 4b). If in prone position a larger margin around the nodal CTV is needed due to e.g. an increased rotational instability (42,46), supine would be the preferred patient position.

For both primary and postoperative patients, the prone position was significantly better for the rectum D_{mean}. This difference could not be explained by significant anatomical differences regarding the rectum volume and CTV, which were inspected visually. A possible explanation for the difference could be that the prioritization of reducing the dose to the bowel cavity had a stronger impact on the sparing of the rectum in the supine position compared with the prone position (29). A study by Nijkamp et al(47) showed that the rectum volume also differed between the prone and supine position for rectal cancer patients . In the postoperative group, the bladder D_{mean} was significantly lower for patients in the supine position (2.6 Gy). This can be explained by the fact that in this group the bladder was significantly fuller in the CT scans of patients in the supine position.

Our results also showed that increased margins around the nodal CTV had a large effect on the V_{45Gy} of the bowel cavity. Consequently, reducing these margins could potentially reduce small bowel related side effects.

Stromberger et al (38) showed in a dosimetric study that IMRT to patients in the prone position reduces small bowel volume at doses > 20 Gy. The main differences with our study were that the relative volume for all OARs was evaluated and that only 1 margin was used for planning (ie 10 mm for the primary and nodal CTV, which is most comparable with a 15 mm margin in our study because of differences in CTV-to-GTV definition). In our study, for margin combinations ≥10/10 mm, we also found a significant difference between the prone and supine position. Pinkawa et al (37) evaluated postoperative patients only and recommended a prone patient position to protect the small bowel. However, in that study a 4-field box technique was used, which in terms of conformity could be compared with our VMAT plans with large margins. For this group we found that the prone position was also superior. Finally, Adli et al (36) showed that the prone position reduces the small bowel dose for large margins, but did not evaluate the benefit for small margins.

The question remains whether our findings based on automated treatment planning, a system unavailable to most clinics, are relevant to the rest of the world. In a validation study (43), automatically generated VMAT plans were dosimetrically compared with manually generated plans made by expert planners. Those results showed that the automatically generated treatment plans were non-inferior to the manually generated

treatment plans. Moreover, it was shown that additional manual adjustments of the automatically generated treatment plans led to only minor improvements in plan quality.

A limitation of the current study is that the bladder volume differed between the CT scans of patients in the supine and prone position. This difference is inevitable because of the time interval between the acquisition of the supine and prone CT scan. To determine the impact of the bladder volume difference, we related this to the difference in V_{45Gy} between prone and supine, but found no significant correlation. The number of primary patients was low, however, all results were found to be consistent across patients and patient groups.

Apart from dosimetric differences between the supine and prone position, other variables should also be taken into account in the choice of an optimal position. A belly-board, used for treatment of a patient in the prone position, usually does not fit into an MRI scanner. Therefore, MRI scans are usually acquired without a belly-board and often with the patient in a supine position. If the planning CT scan is also obtained with the patient in a supine position, image fusion will be simpler. Furthermore, with the patient in a prone position, respiratory-induced patient motion blurs the CBCT images and causes streaky artefacts. Possibly the supine position is also less susceptible to rotational errors and more comfortable for the patient (42,46). Another important factor that must be taken into account is that with the introduction of online adaptive radiation therapy techniques smaller margins can be used. This means that the potential benefit on sparing the bowel cavity when the patient is in a prone position will be lost if small margins are used. Based on the data reported in this study and for the practical purposes mentioned above, our recommendation is to treat patients in a supine position if daily image guidance enables the safe use of margins ≤10 mm. If larger margins are a prerequisite, prone positioning still remains of benefit for bowel-sparing purposes. We expect the greatest benefit from more complex techniques that enable a safe margin reduction in reducing the dose to the small bowel and consequently in reducing gastrointestinal toxicity (44). Whether the dose reductions translate into a clinically observable benefit is part of ongoing research.

It is concluded that the historically found dosimetric advantages of the prone position remain for modern dose delivery techniques with large margins. However, this advantage is lost for small margins and in case the prone position needs a larger margin than the supine position.

Chapter 5

Dynamics of patient reported quality of life and symptoms in the acute phase of online adaptive external beam radiation therapy for locally advanced cervical cancer

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ABSTRACT

Background and purpose

For locally advanced cervical cancer patients, treated with External Beam Radiotherapy (EBRT), Quality of Life (QoL) questionnaires are frequently used to evaluate treatment-related symptoms and functioning scales. Currently, it is unknown how those evolve during the radiation treatment course. In this prospective study we report on weekly-captured patient-reported QoL and symptoms during image-guided adaptive radiotherapy (IGART) of cervical cancer patients.

Material and Methods

Between January 2012 and September 2016, all locally advanced cervical cancer patients treated with IGART and brachytherapy with or without chemotherapy or hyperthermia, were eligible. QoL was assessed at baseline; weekly during the first five weeks of treatment; 1 week, 1 and 3 months after treatment, using the EORTC QLQ-C30 and the QLQ-CX24 questionnaires. Comparisons were made with an age-matched norm population.

Results

Among the 138 (70%) responders, most symptoms showed a moderate-to-large increase, reaching a maximum at the end of treatment, or first week after treatment with return to baseline value at 3 months after treatment. While most symptoms gradually increased during the first five weeks, diarrhea and bowel cramps already markedly increased within the first three weeks to reach a plateau at the 5th week of treatment. Global health and functioning were temporarily decreased and returned to a plateau at baseline level 3 months after treatment, except for cognitive functioning.

Conclusion

A profound impact on QoL was observed during the radiation treatment course, temporarily affecting functioning. The maximum impaired was reached at the end of EBRT.

5.1 INTRODUCTION

Standard treatment for locally advanced cervical cancer is external beam radiation therapy (EBRT) combined with concurrent chemotherapy and brachytherapy. Conformal dose distributions resulting from Intensity Modulated Radiation Therapy (IMRT) or Volumetric Modulated Arc Therapy (VMAT) have markedly reduced dose to organs at risks (OARs), compared to conventional 3D conformal radiotherapy (3DCRT), and less side-effects are reported (7,8,12,48). However, interfraction motion of the uterus and cervix, due to variations in bladder or bowel filling, still necessitates a considerable safety margin. This results in unwanted exposure to OARs, which may translate to more patient reported symptoms and impaired Quality of Life (QoL) (13,25,27,49).

Quality of Life questionnaires are a frequent used measurement tool in order to evaluate treatment related symptoms and functioning scales after EBRT for cervical cancer. Many studies report on QoL at baseline and 3 months – 5 years after treatment to determine long-side effects (50-55). The main conclusion in these studies is that 3 months after treatment most symptoms and functioning scales are returned to baseline value levels again, however, toxicity tends to increase again from one year after treatment. Especially gastro-intestinal, genito-urinary and vaginal/ sexual problems, that impact on the Quality of Life (QoL) are of concern (55,56). Though, despite these studies it is still unknown what the dynamics are during the acute treatment phase, and which symptoms and functioning scales are most impaired in the first 5 weeks. In order to fill this gap in current literature, the aim of this prospective analysis was to evaluate patient reported QoL and symptoms weekly during treatment to measure the dynamics of the acute phase among locally advanced cervical cancer patients treated with an image-guided online adaptive radiotherapy (IGART) technique using small margins. QoL questionnaires were used from locally advanced cervical cancer patients treated with IGART using a Plan-of-the-Day approach (25). Main goal of the PotD approach is to reduce toxicity using small margins and online image guidance. Using the QoL questionnaires of the PotD approach, a detailed analysis of the acute phase of the radiation treatment (the first 5 weeks until 3 months after treatment) is presented for locally advanced cervical cancer patients treated with a modern radiotherapy technique. Comparisons were made with an age-matched healthy (norm) population. In order to facilitate comparisons with literature, we also report our initial results up to one year after treatment.

5.2 MATERIAL AND METHODS

From January 2012 onwards, all locally advanced cervical cancer patients who were treated at the Erasmus MC Cancer Institute according to a PotD approach were asked to participate in this study and written informed consent was obtained (25). The questionnaires were part of routine clinical practice and therefore, the hospital local ethics committee granted us a waiver from needing ethical approval for using this data.

Treatment

For all patients, radiotherapy was combined with either chemotherapy or hyperthermia depending on FIGO stage (4). Patients with small tumors up to FIGO stage IB2 were treated with radiotherapy alone. Patients with higher staged disease received concurrent chemoradiation (5 cycles of cisplatin 40mg/m^2 body surface). Hyperthermia was considered if cisplatin was contra-indicated (57). Patients with very bulky tumors and/or large nodal disease or para-aortic nodal disease received neoadjuvant chemotherapy (cisplatin 70mg/m^2 body surface, given in 6 six schedules) followed by radiotherapy and hyperthermia.

The PotD approach has been previously described (25). In brief, four polymer-based markers were implanted during the gynecological examination under anesthesia, to be used for daily localization of the cervix during treatment. Before and during treatment, all patients were requested to follow a drinking protocol aiming at a moderately full bladder. Since May 2014 rectum laxation was added to the CT scan protocol. Using a full and empty bladder treatment planning CT scans, Internal Target Volumes were made of the primary target volume (consisting of GTV, cervix, uterus and proximal part of the vagina) for creation of the plan library. Patients with large cervix-uterus motion ('movers'; >2.5 cm as measured at the tip of the uterus), had two IMRT/ VMAT plans, one for an empty-to-half-full and one for a half-full-to-full bladder range. Patients with small motion ('non-movers') had one IMRT/VMAT plan, covering the whole range from empty to full. Planning Target Volumes were created using a 1-cm expansion of the combined nodal CTV and the generated ITVs. All patients had a motion robust 3D-conformal or VMAT backup plan using generous margins (25). Daily Cone Beam CT scan was used for plan selection. All patients received 46 Gy in 23 fractions or 48.6 Gy in 27 fractions in case of extended field irradiation. MRI guided high dose rate brachytherapy was given in 3 applications (7 Gy). In a minority of patients CT was used or 2 applications (8.5 Gy) were delivered using an intracavitary technique with or without combined interstitial technique. A nodal boost was given in case of pathological lymph nodes. Intention was to have the overall treatment time < 7 weeks.

Quality of Life

Patient reported QoL and symptoms were prospectively assessed at the following time points: before start of treatment (baseline); every week during treatment; 1 week and 1, 3, and 6 months after treatment and then every 6 months up to 5-years. The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and the QLQ-CX24 questionnaires were used. The QLQ-C30 questionnaire is used for all cancer sites (58), and consisted of a global health status scale, 5 functional scales (physical, role, emotional, cognitive and social functioning), 3 symptom scales (fatigue, pain, nausea and vomiting) and 5 single-item symptoms (dyspnea, loss of appetite, insomnia, constipation and diarrhea). The EORTC QLQ-CX24 questionnaire is a cervical cancer specific module consisting of 3 scales (symptom experience, body image and sexual/vaginal functioning) and 6 single-item symptoms (lymphedema, peripheral neuropathy, menopausal symptoms, sexual worry, sexual activity and sexual enjoyment) (59). Patients filled out the questionnaires using a link provided with email or on a paper version.

Statistical analysis

Patients were included as responders in this prospective study, if they had returned the baseline or the first week of treatment and at least 1 additional questionnaire. This analysis included questionnaires up to one year after treatment. Patients were censored for QoL analysis at time of progression or in case of stable disease requiring salvage hysterectomy.

Analysis of the symptoms and scales was done using the provided EORTC guidelines (59,60). All 4-7 point Likert-type response scales were linearly converted to 1-100 scores. A higher score represents either a better level of functioning or a higher level of symptoms.

Differences in scores were required to be both statistical significant (p-value <0.01, to account for multiple testing) and had to fulfill criteria of minimal clinical relevance. A non-parametric Mann-Whitney test was used to compare mean scores between different time points or between the study and norm populations. When applicable, the published consensus guidelines for small, medium and large clinically significant differences of the EORTC QLQ-C30 was used (61); otherwise the difference was considered small (5-10), medium (10-20) or large (>20) according to Osoba et al (62). Scores were compared to a Dutch female norm population (N=1424) from 2012 (sexual items in N=950 from 2011) that was matched for age using a linear regression. The Dutch norm population data was obtained with permission of the profiles registry (63). The Armitage Trend Test and Spearman Rho were used to evaluate the impact of different characteristics on single item symptoms of diarrhea and dysuria. Statistical analysis was performed using SPSS version 21.0.

5.3 RESULTS

From January 2012 until September 2016 a total of 197 locally advanced cervical cancer patients were treated with a PotD protocol, of which 138 (70%) were included as responders in this QoL analysis. Questionnaire return rates at each time point and reasons for non-response are depicted in Appendix 5A. In 97.5% of the patients the questionnaires were filled in completely; in 1.9% one question was missing and in 0.6% two or more questions were missing.

There were no significant differences in patient and treatment characteristics of responders versus non-responders. Patient and treatment characteristics are summarized in Table 1. The median age of the responders was 51.6 years (range 25 – 86) and the majority of patients had FIGO stage IIB or higher (75.4%) and received concurrent chemoradiation (53.6%). In 68.1% of the patients, the plan library contained a single IMRT/ VMAT plan ('non-movers'), and in 31.9% the plan library contained two IMRT/ VMAT plans, apart from the motion robust backup plan. Overall treatment time was < 7 weeks for 90% of the patients. The main reason for a longer treatment time was delivery of a sequential nodal boost.

Table 1. Patient, tumor and treatment characteristics (n=138 responders)

	No.	**%**
Age		
Median, years (range)	51.6	(25 – 86)
Marital status		
Married	68	48.9
Partner	27	19.4
Single	43	30.9
Children		
Yes	111	80.4
No	27	19.6
Employment		
Employed	81	58.7
Unemployed	37	26.8
Retired	20	14.5
Charlson score/ comorbidity*		
0	88	63.8
1	38	27.5
2	7	5.1
3	5	3.6

Table 1. Patient, tumor and treatment characteristics (n=138 responders) (continued)

	No.	%
FIGO stage		
1B1	17	12.3
1B2	10	7.2
IIA	7	5.1
IIB	87	63.0
IIIA	3	2.2
IIIB	10	7.2
IVA	2	1.4
IVB	2	1.4
Histological type		
Squamous cell carcinoma	119	86.2
Adenocarcinoma	14	10.1
Other	5	3.6
Brachytherapy first fraction°		
Week 4	90	65.2
Week 5	36	26.0
After EBRT	6	4.3
Nodal boost		
Yes	60	43.5
No	78	56.5
Treatment		
CT + RT	74	53.6
NACT + RT + HT	26	18.8
RT + HT	26	18.8
RT alone	12	8.7
Motion#		
Mover	44	31.9
Non mover	94	68.1
Treatment position		
Prone	94	68.1
Supine	44	31.9

*The most frequent co-morbidity was cardiovascular (31.2%) followed by chronic disease (21.7%), COPD (6.5%) and diabetes (6.0%).

#Motion: mover: tip of uterus movement of more than 2.5 cm as measured between a full and empty bladder CT scan

° 6 patients received no brachytherapy because of uterus perforation or the tumor was too large. *Abbreviations:* CT+RT=chemoradiation (5 weekly courses of cisplatin 40mg/m^2 body surface), NACT = neoadjuvant chemotherapy (6 courses of cisplatin 70mg/m^2 body surface) followed by concurrent radiotherapy and hyperthermia, RT+HT=concurrent radiotherapy and hyperthermia, RT alone = radiotherapy alone

Functioning

Scores of EORTC QLQ-C30 functioning and global health scales are shown in Table 2 and Figure 1.

The following described differences or changes in scores were both clinical relevant and statistical significant. At baseline, scores of all functional scales except global health status were lower compared to the age-matched norm population. At week five of treatment, global health, role, social and physical functioning showed a medium decrease; cognitive functioning was small decreased, while emotional functioning was stable. All functioning scores returned to a plateau at baseline level 3 months after treatment, except for cognitive functioning that after a temporary improvement at 3 months showed a small decrease again 1 year after treatment. Compared to the norm population all functioning scores, except global health showed either a small decrease or a medium decrease (cognitive functioning) 1 year after treatment.

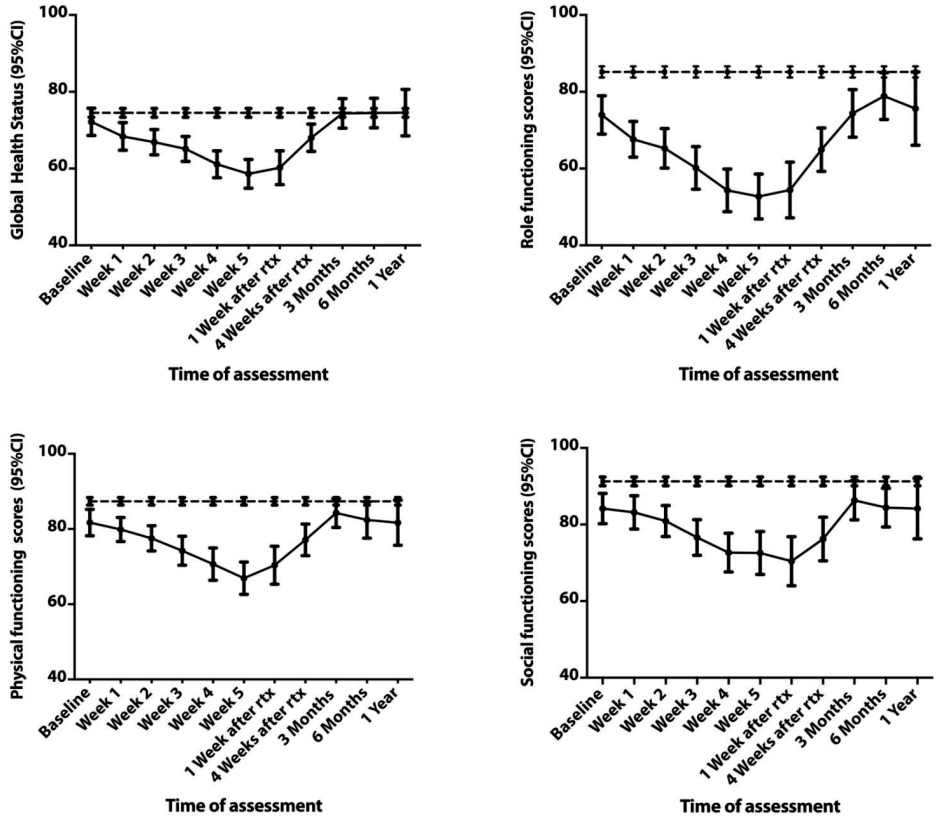

Figure 1a. Patient functioning scales (0 – 100) from European Organization for Research and Treatment of Cancer C30 questionnaire (EORTC QLQ-C30). At 3 – 6 months after treatment the global health status returns to the baseline score. Mean ± 95% confidence intervals between 40 and 100 are shown. The dotted line indicates reference values from an age-matched Dutch female population cohort.

Symptoms and sexual functioning

Scores of symptoms and sexual functioning are provided in Table 2 (QLQ-C30), Table 3 (CX-24) and Figures 2 and 3; in addition, patient responses (none, a little, quite a bit, very much) for all symptom items are provided in Appendix 5B.

At baseline, a small increase of fatigue, nausea/ vomiting, constipation, appetite loss and financial difficulties was observed compared to the norm population, while diarrhea, insomnia, dyspnea and pain symptoms were in range. During the first five weeks of treatment, a large increase was observed for bowel cramps, dysuria, irritated/sore vagina, and fatigue; a medium increase for diarrhea, nausea/vomiting, fecal leakage, difficulties voiding, menopausal symptoms and pain; a small increase for urinary frequency, tingling/numbness, appetite loss, insomnia and dyspnea; in contrast a small decrease was found for constipation.

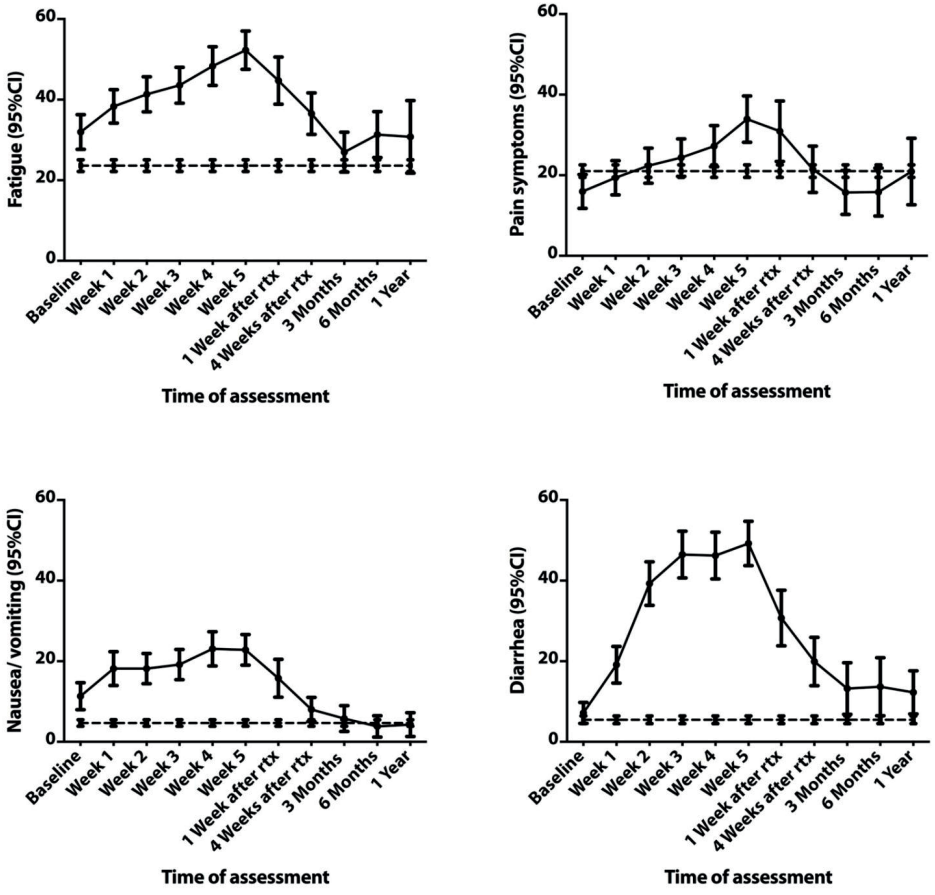

Figure 1b. Symptom scales (0 – 100) from the EORTC QLQ-C30. Mean ± 95% confidence intervals between 0 and 60 are shown. The dotted line indicates reference values from an age-matched Dutch female population cohort.

Table 2. Mean scores and standard deviations of the QLQ-C30 for each time point. The age-matched norm population value is displayed as well.

	EORTC QLQ-C30											
	Time Points											
	Week								Month			Norm
	Baseline	1	2	3	4	5	1 after	4 after	3	6	12	
	Functioning											
Global health status	72.2±19.9	68.4±20.0	66.9±18.1	65.1±18.0	61.1±19.4	58.6±19.9	60.2±19.2	68.0±16.9	74.4±16.0	74.5±15.1	74.6±18.7	*74.6±0.6*
Physical functioning	81.7±19.8#	79.9±17.9	77.5±18.6	74.2±21.2	70.7±23.8	66.9±23.0	70.4±22.3	77.1±19.7	84.3±16.1	82.4±19.0	81.7±18.6	*87.7±0.5*
Role functioning	74.0±28.0#	67.6±25.9	65.3±28.5	60.2±30.4	54.3±30.8	52.7±30.9	54.4±31.5	64.9±26.7	75.4±26.0#	78.9±23.7	75.6±29.6	*85.4±0.7*
Emotional functioning	76.9±21.0#	79.1±19.8	79.3±20.8	77.8±20.7	76.6±21.9	76.0±22.0	75.4±23.2	79.0±21.1	82.8±17.3	78.0±20.3	77.7±24.4	*83.7±0.6*
Cognitive functioning	86.1±19.0	85.4±18.3	84.5±20.0	82.1±20.1	82.5±20.5	81.5±22.3	79.6±20.8	81.0±22.5	88.0±16.8	85.8±17.4	82.1±20.0	*89.7±0.6*
Social functioning	84.2±22.1#	83.2±24.5	80.9±22.1	76.6±25.8	72.7±27.8	72.6±29.7	70.4±27.8	76.2±26.9	86.3±20.9	84.4±19.6#	84.2±24.5	*91.3±0.6*
	Symptoms											
Fatigue	32.0±24.1#	38.3±23.2	41.3±24.1	43.6±24.6	48.3±26.7	52.3±25.4	44.7±25.6	36.5±24.2	27.0±20.6	31.3±22.3#	30.8±27.4	*23.7±0.7*
Nausea / vomiting	11.3±18.7#	18.2±23.4	18.2±20.7	19.2±20.8	23.1±23.7	22.8±20.2	15.8±20.7	8.0±14.1	5.8±13.4	3.8±10.3	4.3±9.1	*4.7±0.4*
Pain	16.0±23.6	19.4±23.7	22.4±24.2	24.4±25.7	27.2±28.3	33.9±30.6	30.9±32.9	21.5±27.0	15.7±22.8	15.8±23.3	20.9±25.6	*20.8±0.8*
Dyspnoea	12.7±20.7	14.3±21.4	13.9±210	16.8±24.2	21.5±26.7	23.4±27.2	19.7±24.5	16.1±23.8	8.2±15.6	12.2±24.5	13.7±25.0	*8.1±0.5*

Table 2. Mean scores and standard deviations of the QLQ-C30 for each time point. The age-matched norm population value is displayed as well. (continued)

	EORTC QLQ-C30											
	Time Points											
	Week								Month			Norm
	Baseline	1	2	3	4	5	1 after	4 after	3	6	12	
Insomnia	21.3±25.0	24.5±28.8	20.8±24.8	22.0±27.6	28.6±32.3	27.3±29.9	27.1±31.8	23.0±28.0	23.7±30.8	25.7±30.7	30.8±33.7	*21.3±0.9*
Constipation	14.4±25.1#	16.7±26.2	11.6±20.6	11.2±21.4	8.6±18.6	8.9±17.9	9.6±21.0	6.9±17.7	2.9±11.1#	3.8±10.7#	7.9±18.1	*8.3±0.6*
Appetite loss	17.5±25.8#	20.5±25.5	24.4±30.2	25.2±29.4	26.9±32.6	31.2±31.6	23.2±28.8	18.4±26.3	11.1±22.6	10.9±20.8	9.4±21.6	*5.0±0.5*
Diarrhea	7.2±14.4	19.1±25.3	39.3±29.8	46.5±32.0	46.2±31.9	49.2±29.4	30.7±30.2	19.9±28.1	13.2±26.5	13.7±28.1	12.3±16.3	*5.5±0.5*
Financial difficulties	12.2±24.8#	10.5±23.2	9.1±23.4	8.8±21.5	11.5±26.2	10.6±23.0	11.3±24.8	11.6±23.9	12.4±24.5#	10.9±20.1	12.0±22.3	*4.3±0.5*

Clinical impact of changes over time following the method of Cocks et al.

small detoriation — small improvement

medium detoriation — medium improvment

large detoriation

Clinical and significant relevant compared to the norm population ($p<0.01$)

While most symptoms gradually increased during the first five weeks, diarrhea and bowel cramps already markedly increased within the first three weeks to reach a plateau at the 5th week of treatment. All symptoms that were increased at the end of treatment decreased again during the first 3 months after treatment. While several symptoms still remained elevated up to one year after treatment compared to baseline values (diarrhea, bowel cramps, fecal leakage, dysuria, pain, insomnia, tingling/numbness, menopausal symptoms), others decreased compared to baseline level (nausea/vomiting, constipation, appetite loss, urinary frequency). In addition, several symptoms became apparent 1 to 4 weeks after treatment and remained at a moderately increased level throughout the first year after treatment (urinary leakage, sexual/vaginal symptoms scale and components: vaginal dryness, short / tight vagina and pain during intercourse). Finally, a small decrease in vaginal discharge and abnormal blood loss became apparent during treatment and 1 to 4 weeks after treatment and remained up to one year after treatment.

The increased vaginal symptoms were paralleled by increased sexual worrying and decreased sexual enjoyment. In contrast, sexual activity gradually increased from 6 months after treatment. At baseline 21% were sexually active to any degree compared to 55% and 61% at 6 and 12 months, respectively.

Influence of treatment characteristics

Symptoms of diarrhea and dysuria showed the largest increase in the first five weeks of treatment (see above). Different patient and treatment characteristics (nodal boost, movers vs non-mover, treatment type, para-aortic irradiation, PTV volume, treatment position, use of backup plan) were evaluated for their impact on diarrhea and dysuria (see Appendix 5C). No significant prognostic factors could be found for any characteristic. The total PTV was not significantly correlated with the outcome of diarrhea ($p=0.8$) and dysuria ($p=0.6$) in the 5th week of treatment.

5.4 DISCUSSION

This prospective study reports on the dynamics of patient reported QoL and symptoms during the acute phase of treatment among 138 locally advanced cervical cancer patients, treated in an image-guided online adaptive external beam radiotherapy PotD protocol. By collecting prospectively weekly questionnaires, a total overview of patient-reported QoL and symptoms during treatment could be given filling a gap in current literature on this topic. Other studies also reported on QoL of cervical cancer patients, but to our knowledge this study is the first to report in detail QoL during the acute phase of treatment and for adaptive EBRT. During treatment symptoms were moderate to largely increased, mirrored by a moderate to large decrease in functioning and global

Table 3. Mean scores and standard deviations of the QLQ-CX24 for each time point. For each scale, the separate questions are displayed in italic. When available the age-matched norm population value is displayed as well.

	EORTC CX-24											
	Time Points											
	Week								Month			Norm
	Baseline	1	2	3	4	5	1 after	4 after	3	6	12	
	Scales											
Symptom experience	14.1±12.2	13.7±10.7	16.7±11.4	19.1±13.1	22.4±14.9	26.8±16.1	24.3±15.3	18.5±13.4	12.2±9.5	14.8±13.7	13.0±10.3	
Bowel cramps	14.8±22.8	24.4±28.4	35.0±30.6	33.3±27.7	37.9±28.7	38.8±29.2	27.6±28.5	19.8±24.9	12.3±19.0	18.6±29.9	20.2±26.3	
Fecal leakage	3.9±12.4	4.6±14.5	13.3±22.3	16.0±25.7	16.2±28.2	20.9±29.2	13.3±22.6	10.0±21.3	4.0±10.9	12.8±23.0	11.4±19.4	
Rectal bleeding	3.9±13.1	0.6±4.3	4.2±12.0	6.3±17.0	6.0±15.6	3.1±9.7	5.3±14.5	3.2±13.3	0.0±0.0	0.6±4.3	2.6±9.1	
Urinary frequency	36.2±31.7	37.6±29.4	39.8±28.7	42.2±32.1	41.4±29.8	44.5±31.4	42.7±31.3	35.8±29.5	26.8±29.9	30.0±29.2	27.0±30.3	
Dysuria	7.9±20.8	6.6±17.7	15.1±25.7	21.0±27.6	34.2±33.9	50.3±35.2	39.9±36.5	27.7±30.3	12.4±24.5	13.0±26.7	18.4±30.7	
Urinary leakage	9.3±20.4	8.1±18.5	7.7±18.8	10.1±19.3	11.5±21.6	14.8±23.7	18.9±27.4	17.1±22.4	12.9±20.9	17.8±24.1	19.3±24.1	
Difficulties voiding	7.9±18.3	7.5±18.2	10.1±22.1	11.8±22.1	14.9±23.8	21.2±28.5	20.2±27.3	17.7±27.2	9.1±17.1	13.0±25.5	7.0±15.8	
Pain lower back	18.3±26.9	19.9±25.0	19.2±25.6	19.4±28.1	23.9±29.0	21.5±27.3	24.1±27.6	19.0±23.9	21.1±27.6	18.3±27.7	17.5±25.4	
Irritated/ sore vagina	8.4±19.5	6.2±15.1	10.5±19.3	16.4±27.6	24.8±33.1	38.5±35.2	34.2±33.8	21.0±27.3	11.8±24.3	15.6±26.4	9.6±17.2	

Table 3. Mean scores and standard deviations of the QLQ-CX24 for each time point. For each scale, the separate questions are displayed in italic. When available the age-matched norm population value is displayed as well. (continued)

	EORTC CX-24											
	Time Points											
	Week								Month			Norm
	Baseline	1	2	3	4	5	1 after	4 after	3	6	12	
Vaginal discharge	30.5±29.9	24.6±28.3	21.9±22.4	22.4±24.4	22.7±24.3	30.3±27.0	33.3±27.9	28.1±27.3	21.1±22.2	18.3±25.6	10.5±20.7	
Abnormal bloodloss	13.8±24.4	9.9±22.1	8.5±20.5	10.8±21.8	12.3±22.6	10.7±20.2	8.8±19.9	3.2±9.8	2.9±9.5	4.0±12.5	0.0±0.0	
Body image	18.8±24.4	17.9±24.7	19.2±25.2	21.1±27.3	22.3±27.2	23.3±26.6	22.4±24.9	21.3±23.2	18.2±21.6	17.6±21.7	21.1±26.6	
Attractiveness	19.3±28.9	18.2±27.9	20.2±27.9	21.3±29.1	22.9±28.4	23.5±28.8	22.1±27.2	20.3±24.4	17.7±26.3	13.8±23.4	21.9±29.3	
Less female due to disease	16.2±27.1	16.7±27.5	16.2±27.1	18.0±28.9	19.5±28.5	20.2±28.7	18.5±26.0	17.7±24.8	13.4±21.0	14.9±22.7	17.5±27.7	
Discontented	21.2±27.1	19.1±27.4	21.2±29.6	24.2±31.3	24.9±29.6	25.9±30.0	26.9±28.9	25.9±28.9	24.0±26.9	24.0±28.0	23.7±28.9	
Sexual/ vaginal symptoms	12.5±15.6#	6.0±8.3	9.1±14.2	13.0±21.3	2.8±4.3	13.3±17.3	26.4±26.0	27.0±26.7	23.8±21.8	26.3±24.8	37.4±28.0#	*33.6±0.9*
Vaginal dryness	17.5±32.1#	9.5±15.6	12.1±22.5	30.0±33.1	5.6±13.6	20.0±29.8	16.7±27.9	30.4±30.0	16.7±20.2#	26.7±25.5#	33.3±33.3#	*1.3±0.0*
Short vagina	7.0±17.8	2.8±9.6	3.0±10.1	4.2±11.8	0.0±0.0	6.7±14.9	27.8±32.8	30.0±37.3	28.3±31.1	22.7±30.0	45.1±31.0	
Tight vagina	6.7±13.7	2.8±9.6	12.1±16.8	12.5±24.8	0.0±0.0	6.7±14.9	27.8±32.8	25.0±30.3	21.7±22.4	25.3±30.9	29.2±31.9	
Pain during intercourse	16.7±20.2#	9.5±15.6	9.1±15.6	16.7±32.4	5.6±13.6	20.0±18.3	33.3±29.8	25.4±25.6	28.3±31.1#	33.3±24.6#	42.2±29.5#	*1.2±0.0*

Table 3. Mean scores and standard deviations of the QLQ-CX24 for each time point. For each scale, the separate questions are displayed in italic. When available the age-matched norm population value is displayed as well. (continued)

	EORTC CX-24											
	Time Points											
	Week								Month			Norm
	Baseline	1	2	3	4	5	1 after	4 after	3	6	12	
	Single items											
Lymph-edema	5.9±15.4	4.8±13.3	3.7±11.4	5.7±14.7	6.6±17.7	5.8±17.4	9.8±23.1	4.0±12.0	6.4±15.5	5.6±15.2	9.6±18.8	
Tingling/ numbness	7.8±16.6	7.1±15.0	8.0±16.8	12.5±23.1	12.4±23.1	15.7±26.0	17.3±27.0	17.1±25.6	18.4±26.8	21.7±26.6	25.2±30.8	
Menopausal symptoms	11.9±20.6	17.6±24.9	17.5±25.7	17.0±23.9	20.1±28.8	22.1±31.3	22.2±30.2	24.5±29.0	20.1±27.7	20.3±29.7	25.4±29.4	
Sexual worry	19.1±32.4	11.4±27.3	9.4±22.1	12.7±26.6	16.2±29.1	17.2±30.0	21.3±33.5	23.0±29.5	22.7±29.7	24.0±30.3	39.5±29.3	
Sexual activity	8.3±16.6	6.2±14.8	3.9±10.8	4.8±11.8	3.3±11.4	2.1±8.2	3.7±10.6	13.5±20.3	16.4±23.2[#]	26.2±27.7	25.0±25.1	*31.1±0.9*
Sexual enjoyment	60.0±27.8	69.0±24.3	60.6±25.0	46.7±23.3	66.7±21.1	53.3±18.3	44.4±34.4	59.1±32.4	54.4±31.8	41.3±27.7[#]	53.3±27.6	*70.5*±1.2

Clinical impact of changes over time following the method of Osoba et al.

[#] Clinical and significant relevant compared to the norm population ($p<0.01$)

small detoriation (5-10) — small improvement

medium detoriation (10-20) — medium improvment

large detoriation (>20)

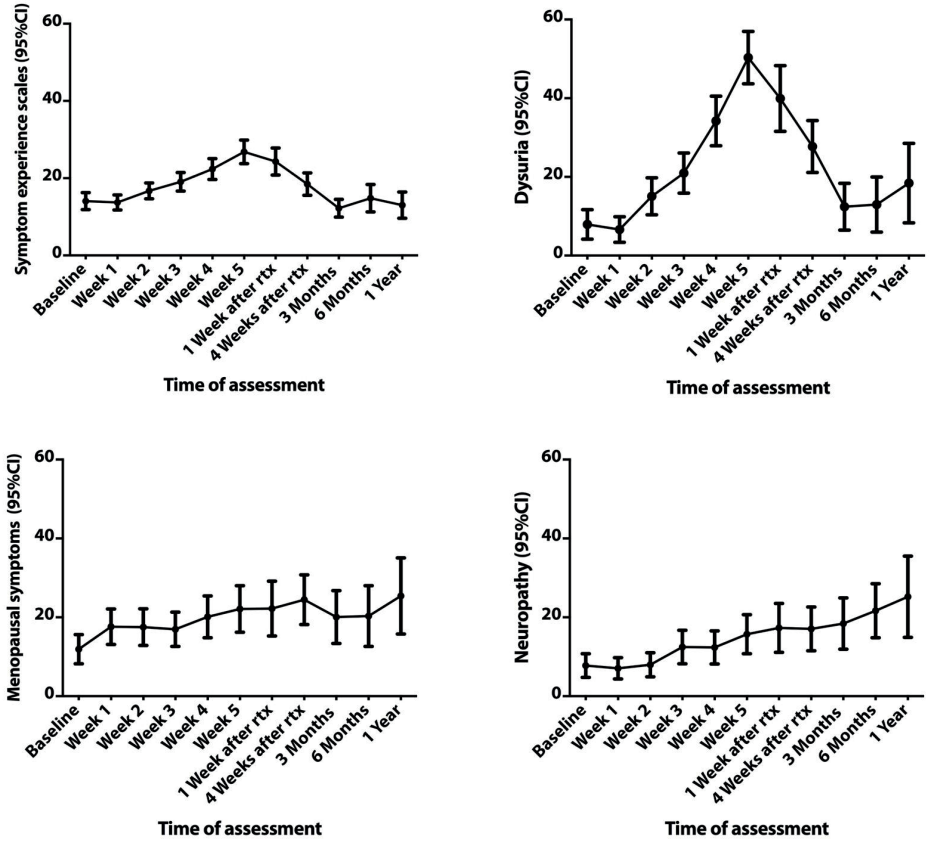

Figure 2a. Symptom scales and single-item symptoms (0 – 100) from the EORTC CX-24. Mean ± 95% confidence intervals between 0 and 60 are shown.

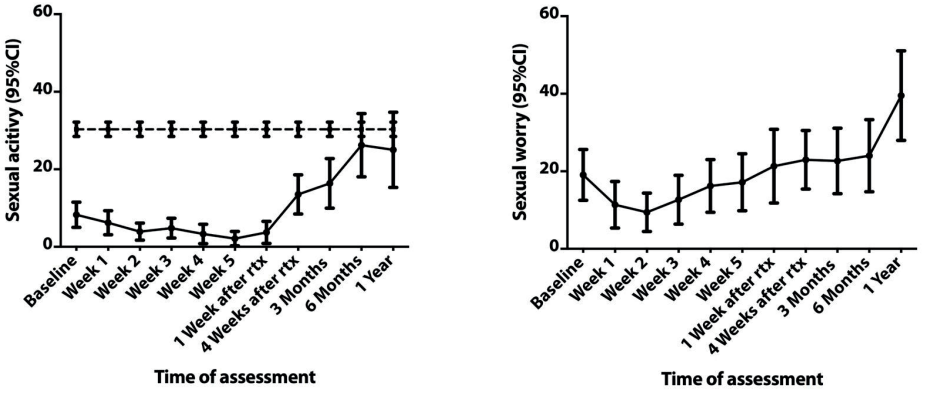

Figure 2b. EORTC CX-24 Sexual functioning and symptoms (0 – 100). Mean ± 95% confidence intervals between 0 and 60 are shown.

health status. This was followed by a rapid recovery to baseline values 3 months after treatment. However, several symptoms remained increased during further follow-up, up to one year after treatment.

The frequent assessments during and shortly after treatment revealed differences in onset and severity of symptoms over time. During the first five weeks of treatment, a large increase was observed for bowel cramps, dysuria, irritated/sore vagina, and fatigue; a medium increase for diarrhea, nausea/vomiting, appetite loss, fecal leakage, difficulties voiding, menopausal symptoms and pain; and a small increase for urinary frequency, appetite loss, tingling/numbness, dyspnea and insomnia. While most symptoms gradually increased during each consecutive week to reach a maximum at 5 weeks or 1 week after treatment, diarrhea and bowel cramps already reached a maximum within the first 3 weeks. The high cell turn-over rate of the gastro-intestinal tract explains this early response to irradiation, and most of these symptoms are a result of acute cell death and damage to the mucosa or epithelial layer (64-66). Most of the mucosal damage is repaired during the first four to six weeks after treatment, and this effect is clearly seen back in these patients reported symptoms.

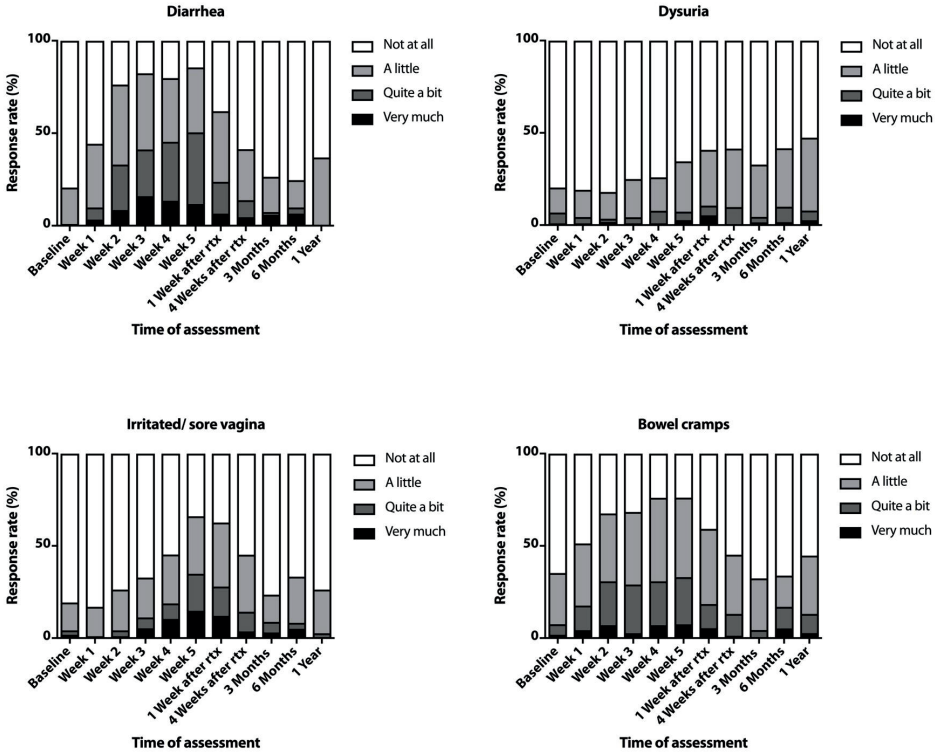

Figure 3. Most frequent reported symptoms on single item level. The response rates are shown in percentages with the answer categories: not at all, a little, quite bit, very much.

Of the symptoms that were increased during treatment, diarrhea, bowel cramps, fecal leakage, dysuria, pain, insomnia, menopausal symptoms and tingling/numbness remained lightly or moderate elevated up to one year after treatment compared to baseline values. In addition, the increase in urinary leakage, and the sexual/vaginal symptoms scale (and its items: vaginal dryness, short/ tight vagina and pain during intercourse) became clinically relevant 1 to 4 weeks after treatment and remained at a moderately increased level throughout the first year after treatment. This indicates that most long-term treatment related symptoms are already present during or shortly after treatment, linking early to long-term treatment related symptoms. However, the etiology of long-term symptoms is different, and is explained by accumulation of fibrosis and damage to the microvasculature, leading to atrophic changes and eventually tissue or organ dysfunction (67).

Patient functioning returned to baseline values 3 months after treatment and remained at this level (lower than the norm-population) until one year after treatment. Exceptions were emotional functioning that remained at baseline level throughout the observation period and cognitive functioning which showed a medium decrease 3 months after treatment. One year after treatment, sexual activity showed a medium increase, while sexual worry was medium increased and sexual enjoyment medium decreased. Although sexual activity increased from 6 months after treatment, it remained lower than the age-matched norm population.

As stated in the Introduction section, other studies have been done to report on QoL after treatment for cervical cancer. Most studies are cross sectional and heterogeneous, including both early stage patients treated with radical surgery and advanced stages treated with definitive radiotherapy, but few report on symptoms and functioning during radiotherapy treatment (50-52,54,55). Further, there is no data available of comparable studies using adaptive EBRT. Long-term side effects of radiotherapy may appear anywhere from months to years after exposure of radiation. It remains difficult to quantify whether treatment-related morbidities have short and/ or long term implications for QoL. Caution in interpretation of all studies remains needed (68,69). Furthermore, interpreting results from other QoL studies remains a challenge because of diverse patient populations, treatments (mainly 3DCRT) and cultural boundaries. Few studies put these results in perspective; Kirchheiner et al. (52) reported on a prospective cohort of 50 patients treated with definitive (chemo)radiotherapy and image guided adaptive brachytherapy using EORTC QLQ-C30 and CX24 before, during (after external beam radiotherapy, comparable to week 5), 1 week and 3 months after treatment. In this study, the brachytherapy was started after EBRT. Comparable increase of symptoms and decrease of functioning is observed during treatment in this study. In a recent analysis from the EMBRACE study (53), QoL was analyzed longitudinally among 744 patients treated with definitive (chemo)radiotherapy (74% 3D conformal, 26% IMRT) and image

guided brachytherapy. QoL was measured with the EORTC QLQ-C30 and CX24 at baseline, and at regular intervals from 3 months after treatment until 5 years. Comparing our data, functioning scales returned to baseline values after treatment as well. A similar increased level of diarrhea, menopausal symptoms and sexual items (vaginal dryness, sexual functioning, sexual activity) from 3 months onwards was found. However, in our group one year after treatment global health remained stable while role functioning decreased, fatigue, body image and sexual worry was one year after treatment increased. Park et al. (55) compared the QoL of cervical cancer survivors with a sample of the general Korean female population 5 years after radiotherapy. Cervical cancer survivors who received radiotherapy reported more impaired social functioning, more constipation, diarrhea, urinary symptoms, lymphedema and sexual dysfunction. Furthermore, other studies investigating QoL after radiotherapy reported similar persisting symptoms after treatment (50,51,54,70).

The comparison with age matched norm population data offers an additional perspective to these results. Baseline scores were lower for all functioning scales and higher for fatigue, nausea/ vomiting, constipation, appetite loss and financial difficulties in our patient group. In contrast, at one year, compared to baseline a small decrease of symptoms related to cervical cancer was found for nausea/vomiting, constipation, appetite loss, urinary frequency, vaginal discharge and blood loss.

By prospectively collecting questionnaires frequently during and shortly after treatment up to one year, a comprehensive overview of the dynamics of QoL during treatment could be given, providing useful results for patients and healthcare providers on what to expect during and shortly after treatment. Especially direct frequencies of response categories (Appendix 5B) provide easily interpretable data that may be useful during counseling. The comparison with the age-matched norm population data, using validated questionnaires, contributes to this. Though, the heterogeneity in use of chemo- and hyperthermia in this study introduced a certain limitation. Therefore, in an exploratory analysis of the impact of different patient and treatment characteristics on the most significant single-items; diarrhea and dysuria (Appendix 5C) did not reveal any prognostic factor. The lack of difference between movers and non-movers could be interpreted as a benefit of the PotD approach. However, in our opinion the subgroups were too small and heterogeneous, with corresponding broad confidence intervals, to clearly state if any of these characteristics had a significant impact on the outcome of QoL.

In this study, we reported our QoL results after six months and one year follow up in order to make it easier for the reader to position our results of the acute phase with the QoL results reported of the late phase. A limitation of that data is the response rate that dropped to 30%. The main cause was withdrawal from participation. Currently, we are implementing measures to increase the response rate for long-term follow up.

The results of long-term follow up will be reported in a future publication. To that end, prospective QoL collection is continued up to five years after treatment.
Continued development of technology can be expected in the future enabling further dose reductions to organs at risk. In this study a modern radiotherapy technique was used using small margins. Examples include improvements in the PotD strategies, in-room MRI-guidance, improvements in treatment plan generation and the use of proton therapy. Further progress in brachytherapy and systematic therapy may also be expected. The data provided in this study, especially during and shortly after treatment, could be used as reference to establish the efficacy of the new approaches in terms of patient-reported QoL. For EBRT, baseline and end of EBRT (week 5) are most sensitive to measure the impact of short treatment related toxicity and to compare improved or reduced symptom burden and QoL.

In conclusion, treatment has a profound impact on QoL, temporarily affecting functioning, but some symptoms persist and impact during further follow-up. End of external beam treatment is the most sensitive time point to measure future improvements in IGART.

5.5 ACKNOWLEDGEMENT

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Chapter 6

What is the optimal number of library plans in ART for locally advanced cervical cancer?

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ABSTRACT

Background & purpose

Library-of-plans ART is used to manage daily anatomy changes in locally advanced cervical cancer. In our institute, the library contains 2 VMAT plans for patients with large cervix-uterus motion. Increasing this number could be beneficial for tissue sparing, but is burdensome while the dosimetric gain is yet unclear. This study's aim is to determine the optimal number of plans at an individual patient level.

Material and Methods

Data of 14 treated patients were analyzed. Plan libraries were created containing 1-4 VMAT plans. Pre-treatment extent of uterus motion was defined by the Hausdorff distance (HD). For dosimetric evaluations, OARs were contoured in daily CBCT scans, plan selection was simulated, and the V_{45Gy} and V_{40Gy} parameters were recorded.

Results

Moderate to strong correlations were found between HD and the volume of spared OARs. All patients benefitted from adding a 2nd plan, as is the clinical practice. For patients with a HD between 30 and 50 mm, a 3-plan library reduced the composite V_{40Gy} with 11 ml to 21 ml compared to a 2-plan library.

Conclusion

Patients with large uterus motion (HD > 30 mm) would benefit from an extension of the plan library to 3. HD is an easy-to-implement criteria to select those patients pre-treatment.

INTRODUCTION

Cervical cancer is one of the most common female malignancies worldwide. Radiotherapy is the major treatment modality for locally advanced disease, combined with either chemotherapy or hyperthermia. Although radiotherapy have been improved with the introduction of Intensity Modulated Radiotherapy (IMRT) or Volumetric Arc Therapy (VMAT), the combined treatment is still associated with toxicity (44,55,56).

Since 2011, more than 200 locally advanced cervical cancer patients have been treated with an online adaptive Plan-of-the-Day (PotD) protocol in our institute. In this protocol, each patient has an individualized plan library containing either one or two treatment plans. The library is supplemented with a backup plan in case the observed anatomy does not fit the plans in the library or the protocol cannot be executed. A daily acquired Cone Beam CT (CBCT) scan is used to select the plan that best fits the anatomy of the day (25).

To generate the treatment plan library, each patient receives an empty and full bladder CT scan. These are used to generate model-predicted Internal Target Volumes (ITVs) that are used as input for the library of treatment plans. For patients with a tip-of-uterus displacement larger than 2.5 cm (measured in the full and empty bladder CT scan), the library contains two VMAT plans, for ITVs related to an empty-to-half-full bladder, and a half-full-to-full bladder, respectively (25). For patients with smaller motion, the library contains one VMAT plan.

Main goal of the protocol is to reduce the dose to healthy surrounding tissues. A recent prospective analysis of the patient reported Quality of Life (QoL) performed in our institute showed that bowel and bladder side effects gradually increase during the first weeks of treatment reaching the highest level in the 5^{th} week (71). These results motivate to further improve the current PotD procedure. The hypothesis is that with an increasing number of plans healthy tissues are better spared thereby potentially reducing treatment-related side effects. However, the number of library plans for a patient has to be carefully considered, because of the increased workload associated with creating multiple treatment plans per patient. Moreover, more plans and consequently smaller ITVs may also impact target coverage, as there is less room in the ITVs to accommodate deviations from the pre-treatment established motion model. In this study, we evaluated target coverage and OAR dose for plan libraries containing 1-4 VMAT plans. We also developed an easy-to-use metric to determine the optimal number of plans at an individual patient level.

MATERIALS AND METHODS

Fourteen locally advanced cervical cancer patients that were treated in our center with the PotD protocol were analyzed. Patients included in this study had large tip-of-uterus displacement (>2.5 cm) as observed between the empty and full bladder CT scan. The displacement was manually measured after fusing the empty and full bladder CT scan using the bony anatomy. Approximately 30% of all cervical cancer patients had a motion of more than 2.5 cm.

Table 1a. Patient overview and characteristics.

Patient	Age	FIGO stage	Position	Further treatment
1	37	IIB	Prone	Chemoradiation
2	34	IVA	Prone	Neoadjuvant chemotherapy followed by radiotherapy and hyperthermia
3	30	IIB	Prone	Neoadjuvant chemotherapy followed by radiotherapy and hyperthermia
4	51	IIB	Prone	Neoadjuvant chemotherapy followed by radiotherapy and hyperthermia
5	40	IB2	Prone	Chemoradiation
6	43	IIB	Prone	Neoadjuvant chemotherapy followed by radiotherapy and hyperthermia
7	43	IB2	Prone	Chemoradiation
8	50	IB1	Prone	Chemoradiation
9	41	IIB	Prone	Chemoradiation
10	32	IB2	Prone	Chemoradiation
11	44	IIB	Prone	Chemoradiation
12	43	IB2	Prone	Chemoradiation
13	41	IIB	Prone	Chemoradiation
14	44	IIB	Prone	Neoadjuvant chemotherapy followed by radiotherapy and hyperthermia

Table 1b. Overview of plan libraries created for all patients.

Plan library	Set of plans
1-plan library	1. empty-to-full-bladder plan
2-plan library	1. empty-1/2 bladder plan
	2. 1/2-full bladder plan
3-plan library	1. empty-1/3 bladder plan
	2. 1/3-2/3 bladder plan
	3. 2/3-full bladder plan
4-plan library	1. empty-1/4 bladder plan
	2. 1/4-1/2 bladder plan
	3. 1/2-3/4 bladder plan
	4. 3/4-full bladder plan

Patient characteristics and treatment variables can be found in Table 1a. To model each patient's bladder filling and impact on cervix-uterus motion, a full and empty bladder CT scan was acquired pre-treatment with the patient in treatment position. A drinking protocol was used to obtain a sufficiently filled bladder for the full bladder CT scan and for each treatment fraction (25). In the drinking protocol patients were asked to drink 300 ml of water two hours prior to scanning or treatment and to empty the bladder and drink an additional 300 ml of water one hour later. Patients were treated in prone position. Implanted fiducial markers are used to daily verify the position of the target (72).

Plan Library Generation

For each patient, the delineated cervix-uterus surface in the full-bladder planning CT scan was non-rigidly registered to the cervix-uterus in the empty-bladder CT scan (5,31). Patient specific motion-models were created by fitting the coordinates of registered points on cervix-uterus surfaces with linear functions of bladder volume (15). These motion-models were used to generate model-based ITVs, which account for the cervix-uterus motion due to bladder volume variations.

For this study, four plan libraries were created per patient. The libraries contained 1, 2, 3, or 4 treatment plans, based on ITVs covering the full cervix-uterus motion sub-ranges. Figure 1 shows these ITVs for one of the patients. Each of these ITVs was extended with a 10 mm PTV margin, which is also used in current clinical practice. To establish full PTVs, the cervix-uterus PTVs were combined with the nodal CTV, extended with a 7 mm PTV margin. Table 1b provides an overview of the generated plan libraries. Two cases in our study, where mostly full, or empty plans were selected are patients 7 and 14 (Fig. 2). Introducing a 2nd plan to the library for the patient with mostly full plans (P7) reduced significantly V_{40Gy} of the bladder (17 ml), compared to the limited reduction of the bowel cavity V_{40Gy} (2.3 ml). For the patient with mostly empty plans selected (P14), reduction of V_{40Gy} for the bladder was relatively small (7 ml), but high for the bowel cavity (33 ml).

Treatment Planning

For all PTVs, VMAT plans were created to deliver 95% or more of the prescribed dose to a minimum of 99.5% of the PTV, while no more than 0.2% of the PTV should receive more than 110% of the prescribed dose. The prescribed dose was 46 Gy delivered in 23 fractions of 2 Gy per fraction [4]. Treatment plans were generated using our in-house developed optimizer for fully automated multi-criterial optimization (Erasmus-iCycle) (20). The optimizer was used for fluence profile optimization using a fixed beam arrangement of 20 equi-angular beams mimicking VMAT (29). Plan optimization was based on an a-priori defined "wish-list" with hard constraints, and prioritized objectives. Sparing of small bowel had a higher priority than reducing delivered dose to the rectum and bladder. The cervical cancer wish-list as used in this study has been reported in (29,73).

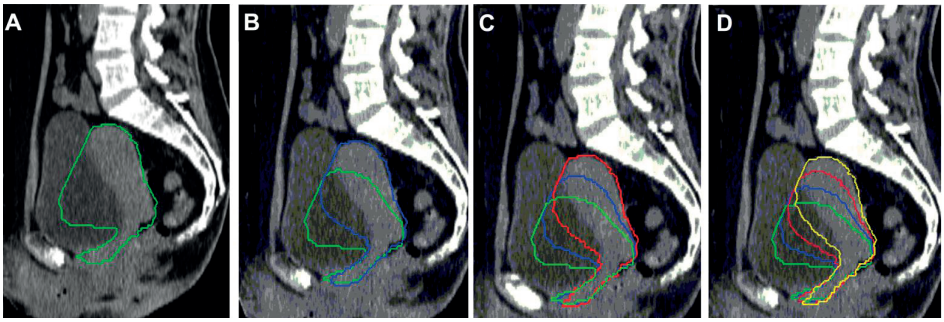

Figure 1. ITVs constructed for a single patient from the full and empty bladder pre-treatment CT scans. ITV ranges: A: an empty-full bladder (green). B: an empty-1/2 bladder (green), 1/2-full bladder (blue). C: an empty-1/3 bladder (green), 1/3-2/3 bladder (blue), 2/3-full bladder (red). D: an empty-1/4 bladder (green), 1/4-1/2 bladder (blue), 1/2-3/4 bladder (red), 3/4-full bladder (yellow).

Treatment Simulation and Dosimetric Evaluation

For the dosimetric simulations, the cervix-uterus and the bladder, rectum and bowel cavity were delineated in each daily CBCT scan by a single investigator according to the RTOG guidelines (39,40). Contours were reviewed by an experienced radiation oncologist. The *bladder* and rectum *were* contoured as *solid organs*. The bowel cavity was defined as all loops of small bowel, colon, including peritoneal space between the loops. Each CBCT scan was registered to the planning CT scan using a rigid bone match (as performed during actual treatment). Similar to clinical practice, plans were selected based on the bladder volumes in the daily CBCT scans, (13). Coverage was assessed by calculating the daily V_{95} (%), i.e. the volume receiving at least 95% of the prescribed daily dose.

For each plan library, the V_{45Gy} (ml) and V_{40Gy} (ml) for the bowel cavity, V_{40Gy} (ml) for the rectum, and V_{40Gy} (ml) for the bladder were calculated from the daily dose volume histogram (DVH). DVH parameters were analyzed for each fraction separately, as dose warping based on deformable image registration can still lead to incorrect dose distributions in the pelvic region (74). In particular, the bowel cavity is a large structure, which exhibits sometimes large and local deformations. To summarize the findings, median DVH parameters over all fractions were calculated for each patient.

The following analyses were performed based on the simulated PotD treatments:

1. We assessed target coverage of the cervix-uterus and OAR sparing by comparing the recorded DVH parameters of the 1-plan library to the 2-plan, 3-plan, and 4-plan library.
2. We developed an easy-to-use metric to determine the optimal number of plans for each patient based on the pre-treatment CT scans. To that end, we evaluated the Pearson correlation between the DVH parameters of the different plan libraries and

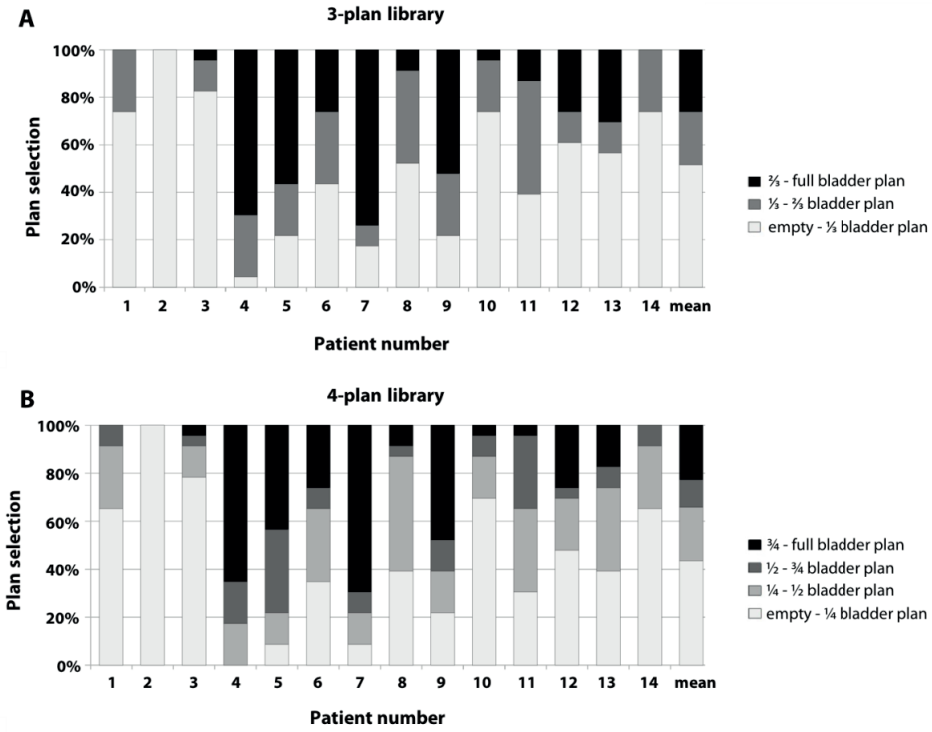

Figure 2. Bar chart of the selected plans for each patient for the 3-plan library and 4-plan library approach. Data are expressed as percentages.

the extent of cervix-uterus motion observed between the *full and empty bladder CT scan*. The extent was quantified as the Hausdorff distance (HD). To calculate the HD, we determined the minimal distances between all corresponding surface points of the cervix-uterus in the full and empty bladder CT scan. The HD is defined as the largest minimal distance of all surface points. To eliminate the effect of delineation outliers, we took the 99-percentile HD, which we denote as HD in this manuscript.

3. To assess the global benefit of plan-library expansion for all surrounding healthy tissues, we calculated a composite DVH parameter (the composite V_{40Gy}) for each patient by summing up the DVH parameters of the bowel cavity, bladder, and rectum.

A Wilcoxon signed-rank test was used to assess statistical differences among strategies. Statistical analyses were performed using SPSS Statistics version 21 (IBM, Armonk, NY, USA) and *p*-values < 0.05 were considered statistically significant.

RESULTS

Plan Selection and Target Coverage

Consistent with earlier findings, bladder volume decreased during treatment, with median bladder volumes of 208 ± 44 ml, 183 ± 23 ml, 154 ± 25 ml, and 153 ± 4 ml during the 1st, 2nd, 3rd, and 4th treatment quarter, respectively. This is reflected in the plan selection. During the second half of the treatment, empty bladder plans were selected 20% more often and full plans 11% less often compared to the first half of the treatment. Intermediate plans were selected 10% more often during the first half of the treatment. Figure 2 shows the distribution of selected plans for each patient for a 3-plan and 4-plan library.

Two patients (P1, P4) were identified as outliers. Patient (P1) had 39% of the fractions an emptier bladder than on the empty-bladder CT scan taken prior to treatment. Patient (P4) had 65% of the fractions a fuller bladder than on the full planning CT scan. In these cases, model-predicted ITVs derived from the empty and full bladder planning CT scans were not correct for those fractions and the data do not follow the pattern of the observations for other patients. Data of these two patients were therefore excluded from further analysis. In clinical practice, such cases would receive new treatment planning CT scans with full and empty bladder and a new library would be created.

The V_{95} of the cervix-uterus was ≥ 99.5% for 318 (99%), 316 (98%), 314 (97.5%) and 313 (97%) of the fractions for the 1-plan, 2-plan, 3-plan and 4-plan library, respectively (Fig. 3). The V_{95} was below 99.5% for 2 patients in 3 fractions for the 1-plan and 2-plan library, and in 4 fractions for the 3-plan and 4-plan library. The V_{95} for each patient and each plan library was plotted in Appendix 6A.

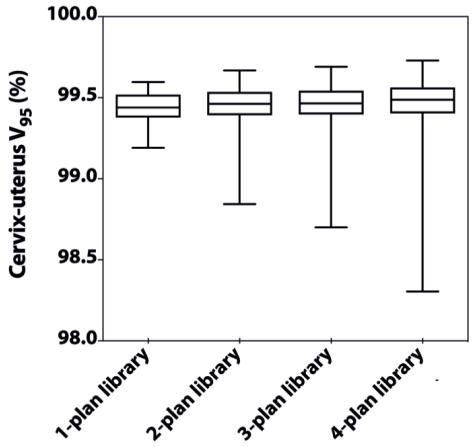

Figure 3. Box plot of the cervix-uterus V_{95} for all patients and individual approaches. The boxes are the first and third quartiles, with median as the horizontal line inside the box. Upper and lower limits are the 95 and 5 percentiles.

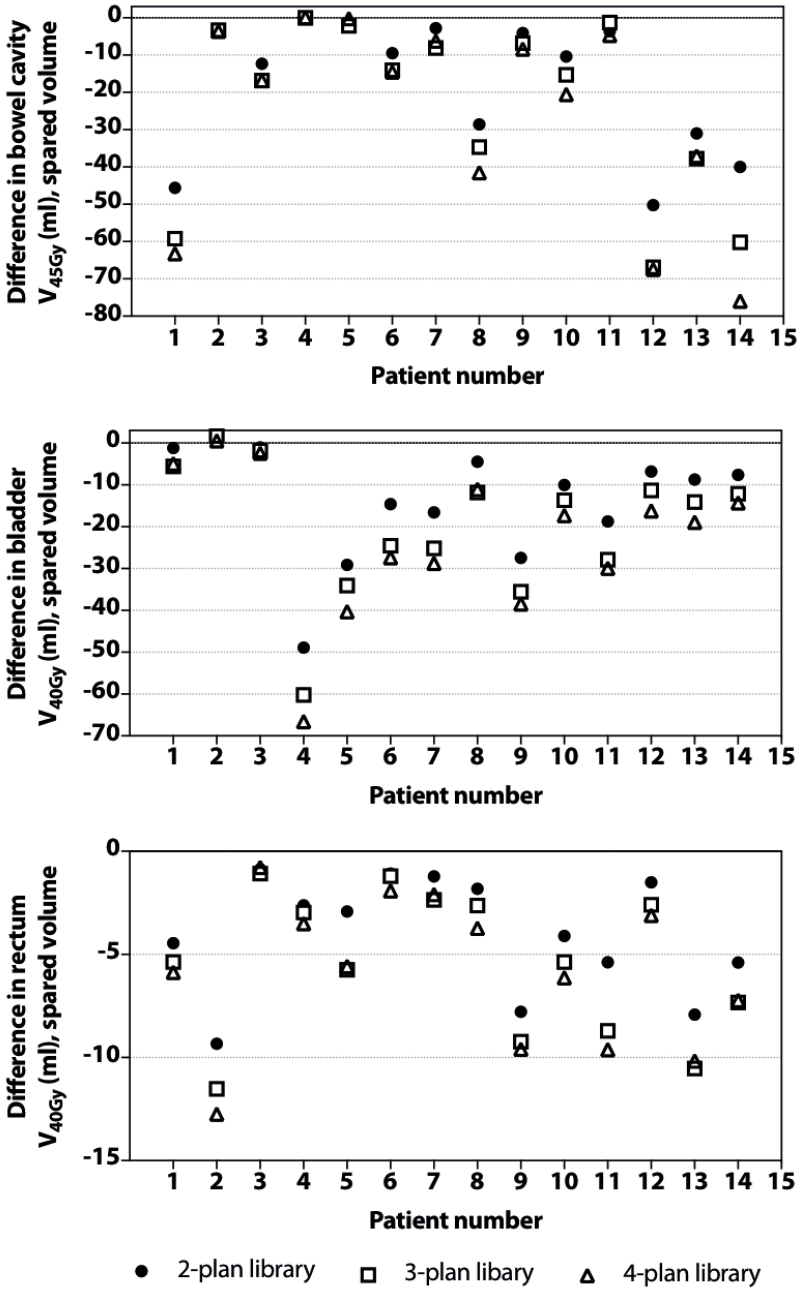

Figure 4. Differences in the average DVH parameters for bowel cavity, bladder and rectum for different plan library approaches, for each patient. The data is presented relative to the 1-plan library. The patients are sorted in increasing order of HD.

OAR sparing

The dosimetric effect on the OARs of increasing the number of library plans is shown in Fig. 4 for each patient. The median bowel cavity volume V_{45Gy} averaged over all patients was reduced by 17.3 ml (range 50 to 0.1 ml), 23.6 ml (range 67 to 0 ml), and 26 ml (range 73 to 0.1 ml) comparing 2, 3, and 4-plan libraries to a 1-plan library, respectively. All differences were statistically significant with p=0.001.

The median bladder volume V_{40Gy} averaged over all patients was reduced by 14 ml (range 49.0 to 1.3 ml), 20.0 ml (range 60 to 1.7 ml), and 23 ml (range 67 to 0.5 ml) comparing 2, 3, and 4-plan libraries to a 1-plan library, respectively. All differences were statistically significant with p=0.001.

The median rectum volume V_{40Gy} averaged over all patients was reduced by 4.0 ml (range 9 to 0.8 ml), 5.5 ml (range 12 to 1 ml), and 6 ml (range 13 to 0.8) ml) comparing 2, 3 and 4-plan libraries to a 1-plan library, receptively. All differences were statistically significant with p=0.001.

A moderate correlation was found between patient pre-treatment extent of uterus motion (HD) and a reduction in V_{45Gy} of the bowel cavity (R=0.71, 0.73, and 0.77 for 2, 3, and 4-plan libraries compared to an 1-plan library, respectively). There was not a significant correlation found between pre-treatment extent of uterus motion (HD) and reductions in bladder V_{40Gy} or rectum V_{40Gy}.

In order to evaluate the global benefit of library expansion for each patient, we also calculated a composite volume by summing up the DVH parameters for the bowel cav-

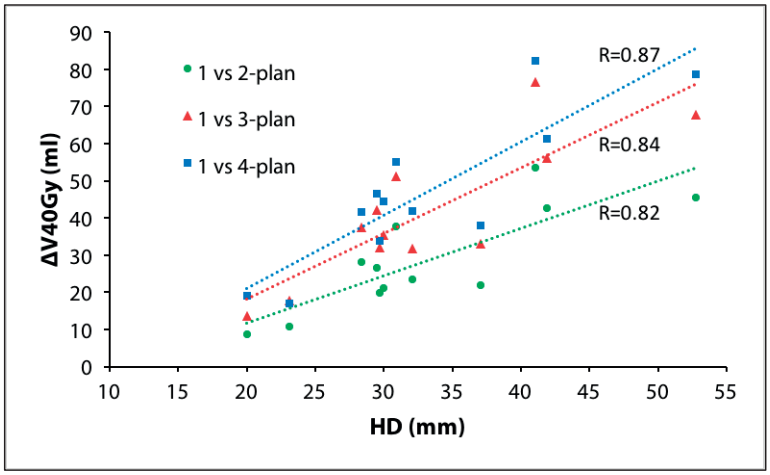

Figure 5. Linear regression analysis plots. Overall gain of V_{40Gy} for bowel, bladder and rectum by adding 2nd (blue), 3rd (red) or 4th plan (green) to the plan library compared with a 1-plan library. The data is correlated with the HD of the cervix-uterus. R = Pearson correlation coefficient. Observations of two patients were identified as outliers and were excluded from this analysis. More detailed explanation of the cause of the outliers can be found in the text.

ity, bladder, and rectum for each patient. This composite parameter was also related to the pre-treatment extent of uterus motion (HD).

Figure 5 shows the reduction in V_{40Gy} comparing a 2, 3, or 4-plan library to a 1-plan library. Considering that a reduction in the composite V_{40Gy} of more than 10 ml justifies the addition of a plan to the library, the linear fit to the 2-plan vs. 1-plan data shows that patients with a HD>20 mm benefit from adding a 2nd plan to library. This resembles current clinical practice. The linear fits to the data also show that for patients with a HD between 30 and 50 mm a 3-plan library could be recommended reducing the composite V_{40Gy} with 11 ml to 21 ml compared to a 2-plan library and with 36 ml to 71 ml compared to a 1-plan library. For patients with a HD>50 mm a 4-plan library could be considered reducing the V_{40Gy} with at least 9, 30, and 80 ml compared to a 3, 2, and 1-plan library, respectively.

DISCUSSION

In this study we performed a dosimetric analysis to investigate the benefits of increasing the number of library plans in Plan-of-the-Day adaptive radiotherapy in locally advanced cervical cancer. A strong correlation was found between the pre-treatment extent of uterus motion (HD) and the reduction in composite V_{40Gy} of the 2, 3, and 4-plan libraries compared to a 1-plan library. Therefore, this metric can be used to determine, pre-treatment, the number of library plans at an individual patient level.

Our results show that patients with a HD>20 mm benefitted from the 2-plan library compared to a 1-plan library, resembling current practice. Patients with large uterus motion (HD>30 mm) would have benefitted from adding a 3rd plan to the library. Here, we considered that a reduction in the composite V_{40Gy} of more than 10 ml justifies the addition of a plan to the library. Patients with extremely large motion (HD>50 mm) could benefit from adding a 4th plan to the plan library, though the reduction in V_{40Gy} is modest by adding a 4th plan to the 3-plan library. All strategies resulted in acceptable target coverage.

We found that an extension of the plan library for patients with large cervix-uterus motion is most beneficial for the bowel cavity. The gain in bladder sparing was moderate and the gain in rectum small. Most complications after radiotherapy for cervical cancer originate from the dose to the bowel cavity (44,48,56) and we consider this as the most important OAR. Therefore, we hypothesize that the use of more plans in the library leads to a reduction in bowel toxicity rates and improved patient symptoms and QoL. Future research has to confirm this hypothesis.

The gain in bowel and bladder sparing depended on the volume of the bladder in the daily treatment fractions. The bladder volume affected the dose received by the bowel

cavity. This can be explained by the fact that a full bladder pushes the bowel upward thus out of the irradiated volume (75,76). We also observed that in this case the V_{40Gy} of the bladder increased. This exchange in sparing between bowel cavity and bladder was the reason to calculate a composite metric to assess the global benefit of expanding the plan library. The composite metric, however, is difficult to relate to a specific symptom.

In our population, we observed large bladder filling variations and a gradual reduction in bladder volume despite the use of a drinking protocol aiming for a full bladder. This finding is consistent with published data (10,77,78). The decrease of the bladder volume with time can be explained by increasing radiation cystitis as well as inadequate hydration secondary to diarrhea and nausea (77).

A recent study of van de Schoot et al. (78) quantified the potential dosimetric benefits of a daily adaptive plan selection strategy compared with a non-adaptive treatment approach in cervical cancer. They found significant improvements in target coverage when applying adaptive radiotherapy in line with Heijkoop et al. (25). A significant reduction in dose to bowel and rectum was observed as well. The study, however, did not address the optimal number of plans in a plan library. A study of Seppenwoolde et al. (79) confirmed better dosimetric results for a 2-plan library approach compared to a margin concept for cervical cancer patients. However, the main conclusion was that the ITVs based on the planning CT scan could change during the course of treatment and that therefore adapted ITV margins based on a repetitive motion evaluation in the first week of treatment could provide improvements over the static margin concept. In our study, we introduced an objective metric to individualize the number of plans in the library. With this metric, the consideration between OAR sparing and workload can be made prior to treatment planning (80-83).

Future improvements could be achieved by reducing the CTV-to-PTV margin around the nodal CTV and the model-predicted ITVs. However, careful monitoring of the position of the target volumes will be mandatory in order to avoid any geometrical misses. This should be combined with efficient updates of the plan library in case the plan library is not representative anymore for the current anatomy of the patient.

There are limitations in this simulation study. DVH parameters were analyzed for each fraction separately, as dose warping based on deformable image registration can still lead to incorrect dose distributions in the pelvic region (74). In particular, the bowel cavity is a large structure, which exhibits sometimes large and local deformations. The bladder and rectum were contoured as solid organs, which is not fully representative for their actual shape (84). However, contouring the walls in the CBCT scans would be very challenging and prone to observer variation.

In conclusion, our dosimetric simulation study demonstrated that patients with large bladder-induced motion of the cervix-uterus benefit from expanding the plan library from 2 to 3 or 4 treatment plans. Furthermore, we introduced and tested an objective

metric that can be used to choose, pre-treatment, the number of plans on an individual patient level. This metric is the 99-percentile of the Hausdorff distance between the cervix-uterus surface points in a full and empty bladder CT scan (HD). For patients with moderate to large uterus motion (20 mm ≥ HD > 30 mm) we recommend a 2-plan library, for patients with large cervix-uterus motion (HD > 30 mm) we recommend a 3-plan library, and for patients with extremely large motion (HD > 50 mm) a 4-plan library could be considered.

Chapter 7

Discussion

7.1 INTRODUCTION

This thesis focuses on an online adaptive approach for EBRT in locally advanced cervical cancer patients, based on patient-specific plan libraries that are used in a so-called Plan-of-the-Day (PotD) strategy. The aim was to evaluate and optimize this adaptive approach, and to investigate important factors having an impact on daily clinical practice.

7.2 IMPROVEMENT OF PATIENT TREATMENT

After the preliminary research by Ahmad et al. and Bondar et al. (9,15), the PotD adaptive approach for cervical cancer patients was introduced in our clinic in June 2011 (Chapter 2). Until February 2017 more than 200 patients were treated with the PotD protocol. Since the implementation, various steps have been taken to optimize the protocol, which will be discussed in this section.

Quality of the plan library

For the first patients, the library plans were sometimes not optimally suitable for treatment. One of the causes was that the CT-scans acquired during planning did not include a scan with a really empty or a really full bladder. In current clinical practice, the acquired scans are immediately checked for this by visual inspection. It was furthermore observed that for some patients, the rectum filling in the planning CT scans differed substantially from the filling in the daily CBCT scans. To improve this, in May 2014 we started to use rectum laxatives for all patients, prior to acquisition of the planning CT scan, to have a more representative rectum filling for EBRT.

Daily plan selection

Initially, the patient's PTV structure was displayed on the matched CBCT scan for daily plan selection. In September 2014, it was decided to replace the PTV by the 95% isodose line, as it will result in sufficient coverage with less necessity for selection of the backup plan.

In the second phase of implementation, the group of patients with large cervix-uterus motion ('movers') initially received a post-treatment CBCT to ensure that the correct treatment plan was selected, given potential bladder filling during treatment and thereby intra-fraction motion. Based on the findings in Chapter 3 and the transition to VMAT, the post CBCT scan has been discarded from the protocol since April 2015.

Vaginal catheter

Initially, a vaginal catheter was used for verification of the cervix position in the planning CT scan. However, Langerak et al. (72) showed that the vaginal catheter resulted in a mean displacement of the markers implanted in the vaginal fornices of 1.3 mm in the caudal direction, as compared to the first CBCT scan where no catheter was used. Currently, the use of a vaginal catheter is no longer needed because planning CT-scans are matched with an MRI scan. In june 2016, the use of vaginal catheters was stopped. It will be evaluated wheter less backup plans will be selected.

Quality of Life questionnaires

Since December 2011, Quality of Life (QoL) questionnaires have been collected to investigate the dynamics of patient reported symptoms and QoL during the acute phase of treatment until one year (Chapter 5). However, we observed high response rates at the beginning of treatment with a drop after some months. The response rate after one year of treatment was only 39%. Some patients didn't reach this follow-up point, but most patients stopped responding despite intensive contact by email, phone and the outpatient clinic. In the last few years, the response rate has improved due to sending automatically generated emails to patients including the questionnaires next to using paper forms. The younger patient cohort showed an increased response rate due to the digitalization, but for the older patients an improvement was not seen. To further improve response rates, especially for older patients, a new digital application will be created for the outpatient clinic. Patients will be asked by their own radiation oncologist to fill out the digital questionnaire on site, just prior to the regular follow-up visits. The outcome of the questionnaire will then be discussed immediately during the follow-up visit (fig 1).

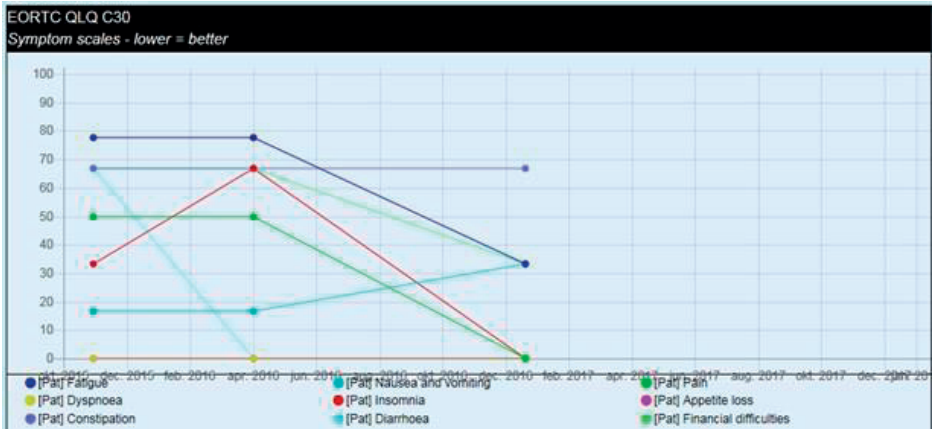

Figure 1. Example of patient reported symptoms using the EORTC QLQ-C30 questionnaire. Lower scores point at better QoL. Measurements at different time points are shown. [Pat] refers to patient.

Plan-of-the-Day functionality in the Linear Accelerator (linac) Record & Verify system

Initially, our record and verify system, Mosaiq (version 2.3, Elekta AB, Stockholm), did not support online adaptive PotD strategies (Chapter 2). All library plans were enabled at each treatment day, from which only one was selected and executed. To reduce the risk of double or triple exposure, the one or two "other" plans had to be manually removed immediately after treatment delivery. Accumulated dose was not recorded for the PotD approach, so delivery of the correct number of fractions was not guaranteed by the system. Although in that time the protocol contained some minor errors, delivery errors did never occur. However, to enhance safety, Erasmus MC and Elekta collaborated on the development of a dedicated feature in Mosaiq for safe and efficient application of PotD protocols (85), which was implemented in Mosaiq version 2.5 (fig 2). A straightforward plan selection dialog is presented to the RTTs, which immediately disables the unchosen plans, thereby eliminating the risk of excessive dose delivery. Moreover, the total dose is now correctly registered to avoid delivery of an erroneous number of treatment fractions. The feature was implemented in our clinic in October 2014.

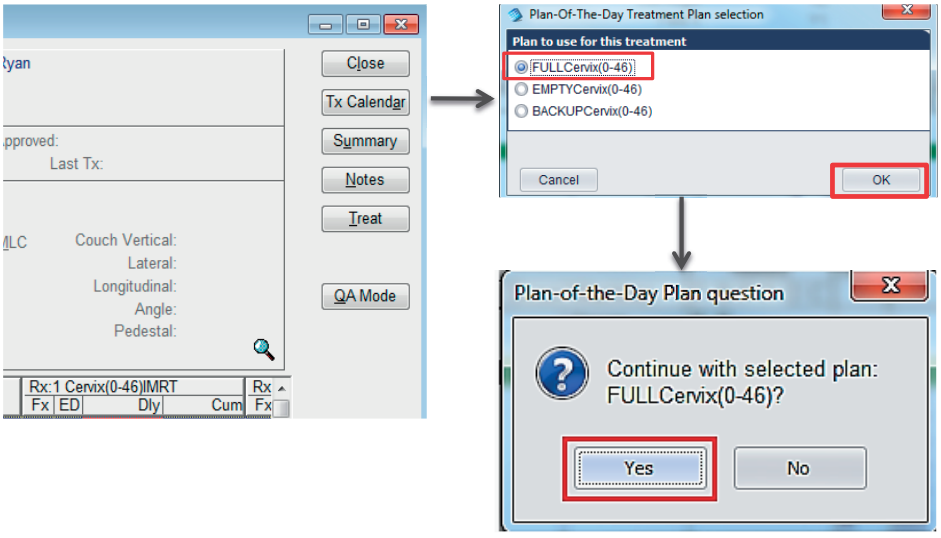

Figure 2. Example of a treatment dialog for a mover (3 plans available in the plan library).

VMAT only – no 3DCRT, no IMRT

In October 2014, the applied IMRT technique was replaced by VMAT. The use of VMAT led to a major reduction in treatment time from 12 minutes to 4.8 minutes. The applied VMAT plans are fully automatically generated (29,73). The quality of these plans is superior to manually generated plans (29). Since March 2015, the motion robust backup plan is also delivered with VMAT, instead of the previously used 3DCRT. This VMAT plan

has generous margins (2 cm around the Internal Target Volume (ITV) and 1 cm around the lymph nodes). As all plans are now VMAT, the treatment time in all fractions is approximately the same, which has logistic advantages.

Prone instead of supine treatment

In Chapters 2 and 3, all results were obtained for patients treated in the prone position using a bellyboard. The choice for the prone treatment position was based on an in-house study from Olofsen-van Acht et al. for 3DCRT treatment (9). However, a disadvantage of using a bellyboard is reduced CBCT image quality, on top of occurrence of rotations (42) and discomfort for the patients. Because of these disadvantages and the need to match the planning CT scan with MRI, the question emerged whether the historical advantage for the prone position was also valid for complex IMRT/ VMAT techniques and adaptive approaches. As a result of the study reported in Chapter 4, since June 2016, all patients are treated in supine setup. Having a more stable position in supine, the nodal margin could also be reduced from 10 mm to 7 mm.

7.3 TOWARDS FUTURE CLINICAL IMPLEMENTATIONS AND STUDIES

In Chapter 6, the patient-specific optimal number of library plans was investigated for patients with large cervix-uterus motion ('movers'). In case of a tip of uterus motion >30 mm, adding a 3rd tight-margin VMAT plan to the library showed reduced OAR dose, and for motion >50 mm, a 4th plan could be considered for further reduction. Due to the automated plan generation (above), extra plans can be generated with no extra planning workload. However, it must be considered that the workload for the RTTs at the linac may rise drastically. In the current version of the XVI software (version 5.0, Elekta AB) all structures are displayed in a drop-down menu, when the CBCT scan is matched to the planning CT scan. For the current approach with 2 tight-margin plans in the library for all movers, the drop-down menu list already shows many options to choose from. Adding more plans to the library automatically leads to an enhanced number of options. This will lead to an increased workload because the RTTs need to consider which treatment plan best fits the observed anatomy for that day. Also, having more options could lead to an increased fault percentage. Input from specialized RTTs learned that currently a total of 4 plans in the library is the maximum feasible, considering daily workload with the current software, which should be adapted before clinical introduction of libraries with > 4 plans. Fortunately, the majority of patients treated is non-mover with only one tight-margin VMAT plan in the library. For this group, the workload is low. Extremely large motion, requiring 4 tight margin library plans, is expected to occur in our clinic at a maximum 3 times a year. Therefore, this will not affect the overall workload significantly.

Development of daily automatic plan selection could potentially solve both problems of the workload and plan selection errors. As a result of this study, for some patients with very large motion, plan libraries will be expanded in the near future.

Our department will participate in the EMBRACE II study. Compared to the current PotD protocol, treatment planning will have to be adapted as different constraints are set on PTV coverage (86). With the introduction of this protocol, our margins will also be adapted, for the cervix-uterus ITV-to-PTV from 10 mm to 5 mm, and for the nodal CTV-to-PTV from 7 mm to 5 mm (86). Further, underdose of the tip of the uterus is allowed. The applied margin reductions could result in more frequent selection of motion backup plans, which could possibly counteract advantages of the margin reductions. On the other hand, the allowed underdose in the tip of the uterus could lead to reduced selection of backup plans. The margin reductions could potentially negatively impact the loco-regional control rate, which needs to be monitored closely.

7.4 CLINICAL EVIDENCE FOR THE PLAN-OF-THE-DAY APPROACH

PotD involves treatment with tailored, patient-specific PTV margins. For movers, the daily used IMRT/ VMAT plan depends on the actual position and shape of the target. Using a personalized approach, OAR dose delivery is kept minimal for every patient. For movers with very large cervix-uterus motion, PotD may also limit underdose compared to conventional treatment with one IMRT/VMAT plan with population-based margins.

So far, no clinical evidence has been gathered proving superiority of the PotD approach compared to conventional treatment. Such evidence is desired as PotD has higher executional costs than conventional treatment. Conducting a randomized clinical trial may be challenging because of the problematic weighting of a likely reduction in toxicity with some increase in cost. In the Netherlands, randomized clinical trials comparing proton therapy with photon therapy are largely avoided in case of expected toxicity reduction. Instead, the so-called model-based approach is followed (87). In principle, this could also be done for PotD. However, the highly patient-specific variations in bladder filling with resulting mobility of the target, and the lack of toxicity prediction models make this approach challenging. In the international, prospective EMBRACE II study, participating centers are allowed to use different strategies for the EBRT part of the treatment. Centers with basic IGRT (standard population based margins), intermediate IGRT (individualized margins), and advanced IGRT (PotD with individualized patient libraries) can all participate. QoL and toxicity will be scored in a consistent way at several time points. This data could be used to compare conventional EBRT with PotD approaches to assess to presumed clinical advantage of the latter.

7.5 YOUNG PATIENTS - OVARIAN FUNCTION & RADIATION THERAPY

For the patients analyzed in Chapter 5, the median age at diagnosis was 52 years (range 27 – 86). For young women who have not yet reproduced at the time of treatment, sparing of the ovaries may be of major importance (88). In order to preserve the ovaries in these young patients, cryopreservation of ovarian tissue or transposition of the ovaries prior to radiation therapy are options (89,90).

In 2015, we observed for 4 patients that despite ovarian transposition, the total function of the ovaria was lost 6 months after treatment. For two patients, the D_{mean} was set to < 8Gy and for the other two patients the D_{mean} was < 4Gy. The loss in ovaria function may have been caused by the applied radiation dose. Ovarian tissue is highly sensitive to radiation (13) and doses ≥4 Gy result in infertility for almost all women over 40 years of age, and for one third of the young women (10). Several studies have estimated that doses lower than 2 Gy will destroy half of immature oocytes (91,92). On the other hand, the applied chemotherapy (cisplatin) also contributes to reduced ovarian function (93), although the exact role of chemotherapy on ovarian function has not been defined yet. For locally advanced cervical cancer patients, no studies have been performed on the interaction and relative importance of the extra role of chemotherapy combined with radiotherapy in relation to functioning of the ovaries. Also, a role of the daily imaging dose of the CBCT cannot be excluded.

Possibly, better sparing of the ovaries is possible with a modified approach for ovary transposition. This needs further research. Another option could possibly be treatment with partial arc VMAT, excluding beams passing through the ovaries. Further, in our current protocol, the entire uterus is included in the Clinical Target Volume (CTV), because uterus and cervix are embryological one unit with interconnected lymphatics and no clear separating fascial plane. There is however only little clinical evidence to support this approach (41). Recurrence is not expected in the fundus part (94). Because of anatomical proximity of the fundus and the ovaries, excluding the fundus from the target volume could possibly allow reduced dose delivery to the ovaries. By decreasing ovary doses close to 0 Gy, the role of chemotherapy could be further explored.

Another solution to maintain ovarian function and fertility is ovarian tissue cryopreservation and re-transplantation. It must however be emphasized that for cervical cancer patients a gestational carrier is needed. In the Netherlands, cryopreservation is still considered to be in an experimental phase. For cervical cancer patients, re-transplantation of preserved ovarian tissue has not yet been performed.

7.6 FUTURE OUTLOOK

The main goal of the PotD approach for locally advanced cervical cancer has always been reduction of dose to OARs and thereby reduction of acute and late toxicity. Chapter 5 shows that for bowel and bladder related problems there is still a lot to gain in terms of reducing toxicity. Many measures have been taken to improve the current PotD approach (above). However, the question rises if the current technique using X-ray beams and CBCT based image guidance should still be used for this patient group with introduction of new techniques such as in-room MR guidance and proton therapy.

Possibly, a big step forward in the treatment of cervical cancer patients could be the use of daily online adaptive replanning. With high quality in-room imaging, uncertainty margins could probably be effectively reduced with this approach, which might result in lower OAR dose delivery. This needs proper investigation, as even with a zero margin, healthy tissues will always be irradiated due to the ballistic properties of the photons or particles used. Limited quality of CBCT images is already an important challenge for current daily plan selection, and fast and accurate daily contouring by a physician or automatic segmentation, as needed for on-line replanning, might even be a bigger challenge. Possibly, quality of in-room CT-images may improve with better hard- or software. However, most probably, the quality of those images and especially the soft tissue contrast will remain inferior to MR-images, especially those provided by future integrated MR-linac systems with high magnetic field. (95).

Another question is whether cervical cancer patients could benefit from proton therapy with the upcoming availability of proton therapy in the Netherlands (HollandPTC). Intensity Modulated Proton Therapy (IMPT) could result in a decrease of OAR doses, enabling dose escalation to the tumor and lymph nodes (96). Especially in terms of small bowel and bone marrow sparing, IMPT has a potential for significant dose reductions (97,98). As proton therapy is expensive and its capacity low, pre-treatment selection of patients with large expected clinical benefit is important. In a recent dosimetric comparison using robust proton therapy planning, it was shown that IMPT resulted in dose reductions in bowel, bladder, sigmoid, and rectum, without compromising target coverage, especially for locally advanced cervical cancer patients with lymph nodes in the para-aortic region (99). Another recent study demonstrated that image guided proton therapy using a plan library based PotD approach results in a target coverage like in photon therapy with significant dose reductions in bladder, bowel and rectum (100). In contrast to X-ray treatment units, currently there are no proton therapy systems with in-room MR-guidance. The most modern proton systems (like in HollandPTC) will be equipped with an in-room diagnostic CT-scanner. Especially the soft-tissue contrast of these devices is inferior to that of high magnetic field MR-scanners. Further research is needed to investigate the future roles of CBCT guidance at a linac, in-room low [Mrid-

ian] or high field MR-guidance at a linac, and CT-guidance at a proton facility. For all techniques, we need to be aware of the impact of treatment time. An enhanced treatment time requires an enhanced margin to compensate for the increase in intra-fraction motion, especially for large movers (Chapter 3).

7.7 CONCLUSION

In this thesis we have described the implementation, evaluation, and optimization of an online adaptive Plan-of-the-Day approach in radiotherapy for locally advanced cervical cancer. We have demonstrated enhanced OAR sparing with this approach. However, clinical evidence for superiority compared to conventional treatment is not yet available. In the near future, new opportunities (e.g. in-room MR guidance, proton therapy) will become available to possibly further reduce OAR doses, potentially improving the QoL for this patient group.

Appendices

2A

Plan-of-the-Day in the Record and Verify System

At present most commercially available record and verify systems do not support online adaptive plan of the day strategies. This means that it is not supported to have multiple treatment plans enabled, from which only one is selected and executed. In the implementation of the plan-of-the-day approach reported in this study MOSAIQ version 2.3 (Elekta AB, Stockholm) was used as record and verify system. In the workflow all available library plans are imported in advance and scheduled in the treatment calendar. At each treatment fraction the operator executes the selected plan. To mitigate the risk of double or triple exposure, our protocol prescribes the immediate removal of the one or two obsolete plans from the treatment calendar after the delivery of the treatment fraction. The protocol further requires that this procedure is verified by a second operator. In the MOSAIQ software the so-called "treatment site" records the executed plan and the so-called "secondary dose site" is used to record the total dose delivered.

To reduce workload and enhance safety, the plan selection and administration workflow was automated, using the IQ Scripting Engine in MOSAIQ version 2.5 in collaboration with Elekta. The scripting allows MOSAIQ users to add new functionality, e.g. scripts that define a workflow of configurable activities and that can be executed by a user-defined trigger point. The script, exclusively designed for daily plan selection, presents to the operator a straightforward plan selection dialog, it immediately disables the unchosen plans, and correctly administers the plans and total dose delivered. This script will be used for future plan-of-the-day treatments (1).

REFERENCES

1. Schillemans W, Seppenwoolde Y, Akhiat H, Heijmen B, Hoogeman M. IQ scripting in MOSAIQ facilitates safe plan-of-the-day selection for adaptive cervix irradiation. IPEM Conference on Adaptive Radiotherapy. Leeds: IPEM; 2013.

2B

Dosimetric Evaluation of the Impact of the Plan-of-the-Day Strategy

The potential dosimetric impact of the plan-of-the-day strategy was estimated by evaluating Dose Volume Histogram (DVH) parameters for the relevant organs at risk, i.e. the V90% (%) for bladder and rectum, and the V99% (cc) for the bowel cavity (as surrogate for small bowel). This evaluation was performed for all 11 patients with two IMRT plans (second phase only) and for one representative case with small cervix-uterus motion

(one IMRT plan). The dose was evaluated on the full and empty bladder CT-scans as during the treatment course both anatomical situations occur. To that end, the rectum, bladder, and bowel cavity were contoured in the full and empty bladder CT-scans by a single investigator (SH) and carefully checked by an experienced radiation oncologist (JM). The empty bladder CT-scans were rigidly aligned to the full bladder CT-scans (the planning CT-scan) using the bony anatomy in order to project the dose distributions onto the empty bladder CT-scan. Subsequently, DVHs of the 3DCRT backup plan were calculated for the full and empty bladder CT-scans. The DVHs of the half-full-to-full IMRT plans were calculated for the full bladder CT-scans and the DVHs of the empty-to-half-full IMRT plans were calculated for the empty bladder CT-scans. For the representative case with one IMRT plan the DVHs were calculated for both the full and empty bladder CT-scans.

Figures 1(a) to 1(f) illustrate the potential benefit for patients that were treated with two IMRT plans. The figure demonstrates a consistent improved sparing of the OARs in favour of the IMRT plans. A pronounced benefit was observed for the bowel cavity when the bladder was empty. For the full bladder CT-scan the benefit for bowel cavity was less pronounced as a full bladder pushes the bowel partly outside the treated volume resulting in overall less bowel being irradiated.

Figure 2 illustrates the potential benefit for a patient with small cervix-uterus motion. IMRT yielded a considerable sparing of the OARs compared with the 3DCRT plan. The sparing was most pronounced for the bowel cavity in the empty bladder CT-scan. In the full bladder CT-scan the advantage for the bowel cavity was less evident as the full bladder pushed the small bowel partly outside of the treated volume.

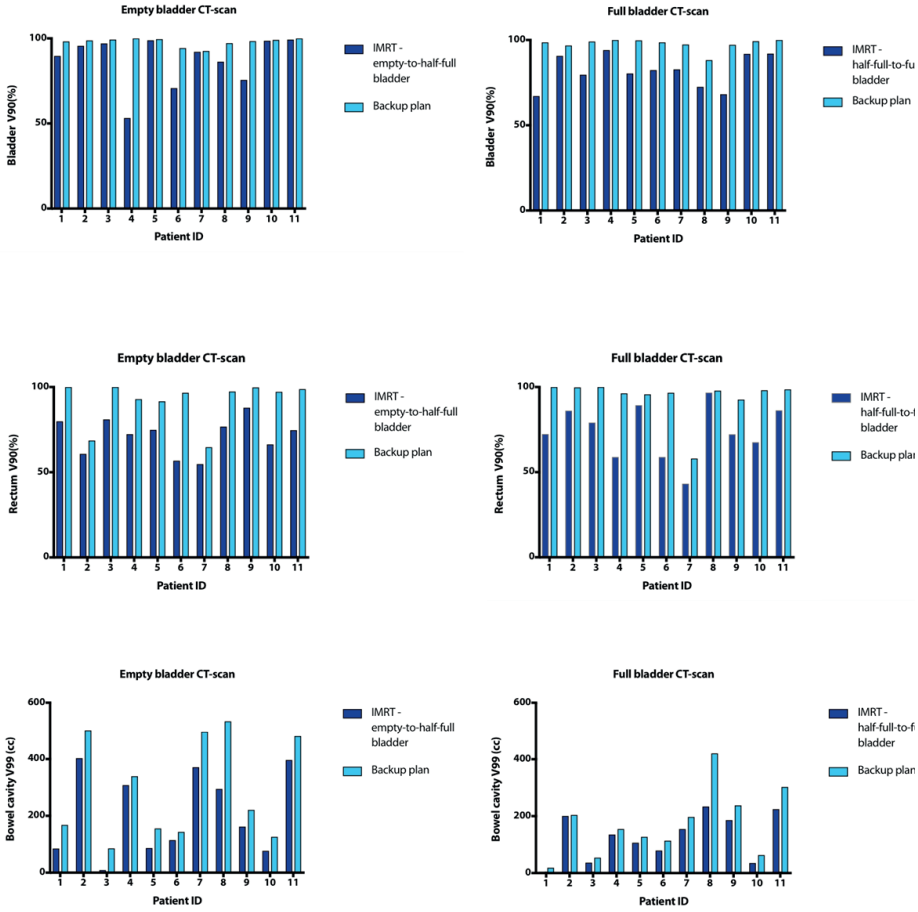

Figure 1. DVH parameters for the IMRT plans and the 3DCRT backup plan. The left column shows the DVH parameters for the empty bladder CT-scan and the right column shows the DVH parameters for the full bladder CT-scan.

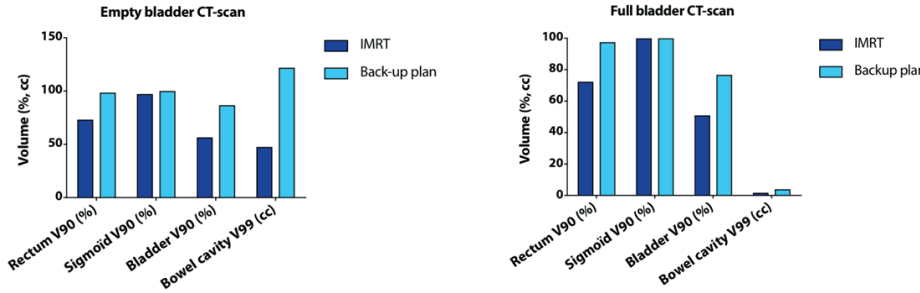

Figure 2. DVH parameters for a representative case with small cervix-uterus motion. The left graph shows the DVH parameters of the IMRT and 3DCRT plan calculated on the empty bladder CT-scan. The right graph shows the DVH parameters for the full bladder CT-scan.

3A

Table 3a. Intra-fraction changes in setup for each patient individually with the mean and the SD in the three directions.

Patient motion	LR (mm)	CC (mm)	AP (mm)
# 1 Mean±SD	0.4±0.9	0.6±0.6	0.1±1.4
# 2 Mean±SD	-0.2±0.7	0.6±0.9	1.1±1.4
# 3 Mean±SD	-0.1±0.5	0.5±0.6	1.4±0.5
# 4 Mean±SD	2.4±2.3	0.7±1.6	0.2±2.6
# 5 Mean±SD	-1.1±1.7	0.7±0.6	1.6±0.9
# 6 Mean±SD	-0.9±0.6	0.1±0.3	1.3±0.4
# 7 Mean±SD	0.4±0.8	1.0±0.4	1.6±0.6
# 8 Mean±SD	2.6±1.2	0.2±0.7	0.9±0.9
# 9 Mean±SD	-0.7±0.8	0.3±0.6	0.4±0.5
# 10 Mean±SD	-1.8±2.1	-0.1±2.2	1.1±1.6
# 11 Mean±SD	0.3±1.8	-0.1±0.6	1.2±0.4
# 12 Mean±SD	-0.0±1.1	0.7±0.8	1.6±0.7
# 13 Mean±SD	-2.9±2.3	-0.2±1.5	1.1±0.9
# 14 Mean±SD	0.2±1.1	0.6±0.9	0.8±0.3
# 15 Mean±SD	-0.4±1.3	0.8±0.8	1.6±1.3
# 16 Mean±SD	-0.1±0.5	0.7±1.1	1.2±0.6

4A

Table 4a. For both patient groups, the dosimetric differences for the bowel cavity between prone and supine position for matching primary/nodal margin combination.

	Bowel cavity D_{mean} (Gy)	Bowel cavity V_{15Gy} (cm^3)
	All patients	*All patients*
5/5mm		
Mean±SD	0.7±4.4	376.2±301.7
P-value	0.2	<0.001
5/7mm		
Mean±SD	0.7±4.4	407.7±328.2
P-value	0.4	<0.001
10/5mm		
Mean±SD	0.7±4.6	385.0±311.9
P-value	0.4	<0.001
10/7mm		
Mean±SD	0.8±4.5	406.3±324.4
P-value	0.2	<0.001
10/10mm		
Mean±SD	0.8±4.6	447.6±344.5
P-value	0.3	<0.001
10/15mm		
Mean±SD	0.8±4.7	493.0±370.4
P-value	0.2	<0.001
20/7mm		
Mean±SD	1.2±4.8	418.3±333.4
P-value	0.1	<0.001
20/10mm		
Mean±SD	0.9±4.7	452.4±345.2
P-value	0.3	<0.001
20/15mm		
Mean±SD	0.8±4.8	491.1±374.8
P-value	0.2	<0.001

4B

Table 4b. For both patient groups, the dosimetric differences (OARs) between prone and supine position for matching primary/ nodal margin combination. Positive values indicate that the prone position is in favor.

	Bladder V_{40Gy}(%)	**Rectum V_{40Gy}(%)**
	All patients	*All patients*
5/5mm		
Mean±SD	-7.0±11.0	10.5±13.2
P-value	0.003*	<0.001
5/7mm		
Mean±SD	-4.5±9.9	8.7±14.1
P-value	0.013*	0.004
10/5mm		
Mean±SD	-7.3±10.8	12.9±15.7
P-value	0.001*	0.001
10/7mm		
Mean±SD	-4.1±12.5	12.4±15.9
P-value	0.03*	0.001
10/10mm		
Mean±SD	-7.3±10.4	12.3±16.3
P-value	0.001*	0.001
10/15mm		
Mean±SD	-8.2±10.7	11.2±17.1
P-value	0.001*	0.001
20/7mm		
Mean±SD	-10.8±13.5	13.4±16.9
P-value	<0.001*	0.002
20/10mm		
Mean±SD	-10.4±12.8	14.7±16.0
P-value	<0.001*	<0.001
20/15mm		
Mean±SD	-10.5±12.0	13.2±14.6
P-value	<0.001*	<0.001

*Supine position in favor

5A

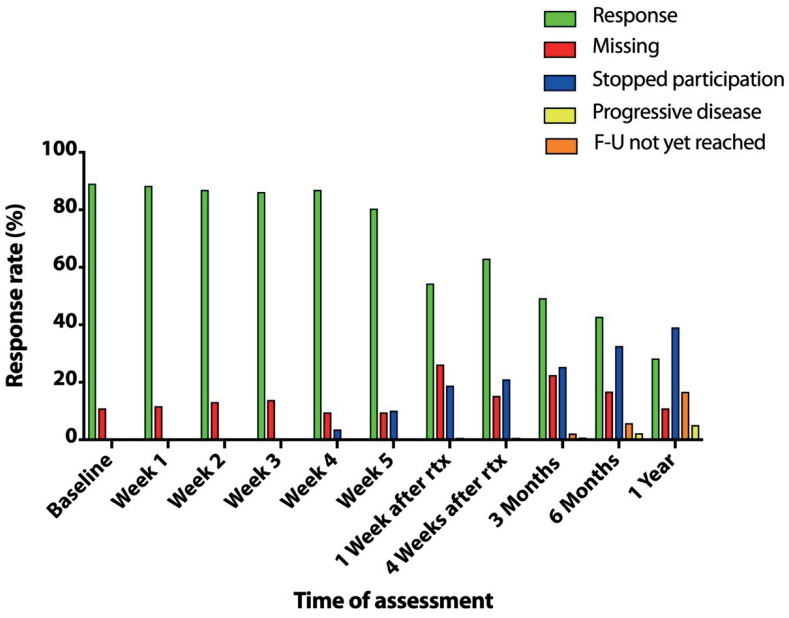

Figure 5a. Response rate by week. Patients either missed the assessment, stopped participating, had progressive disease or the follow-up at the time of evaluation was not yet reached.

5B

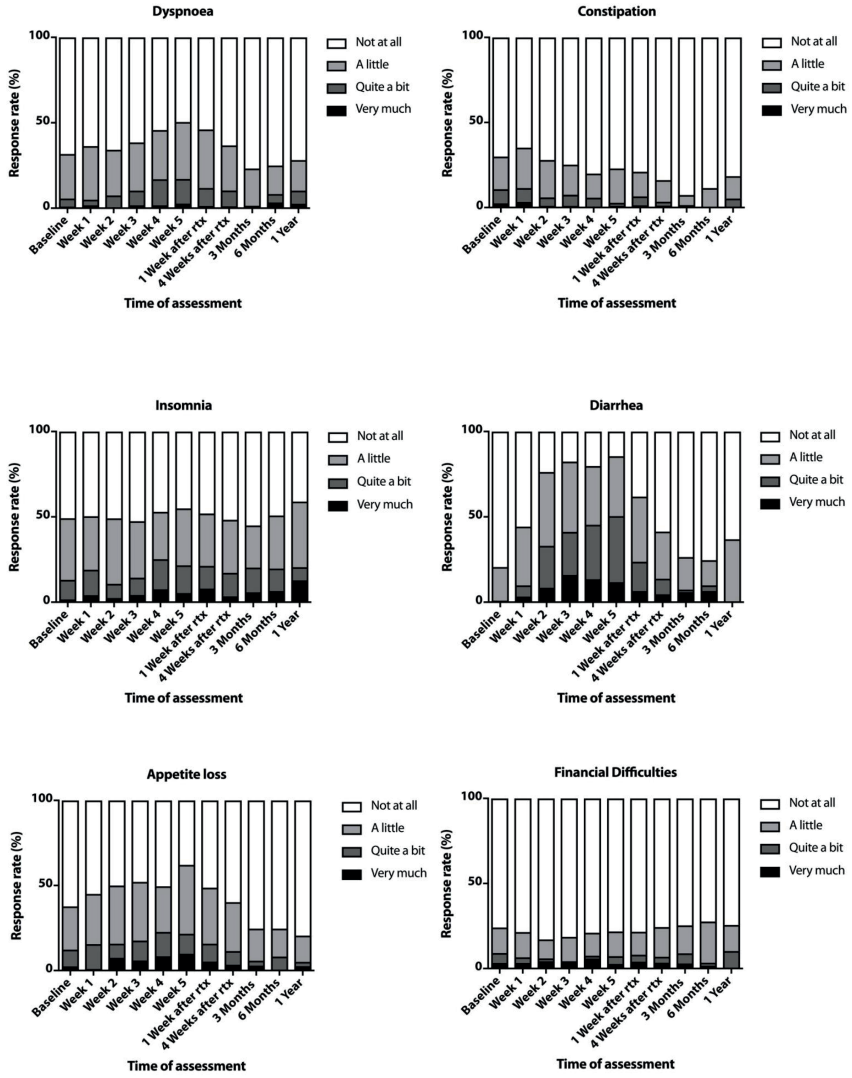

Figure 5b. This figure represents for each single-item symptom the distribution of the response rates in percentages. (continued)

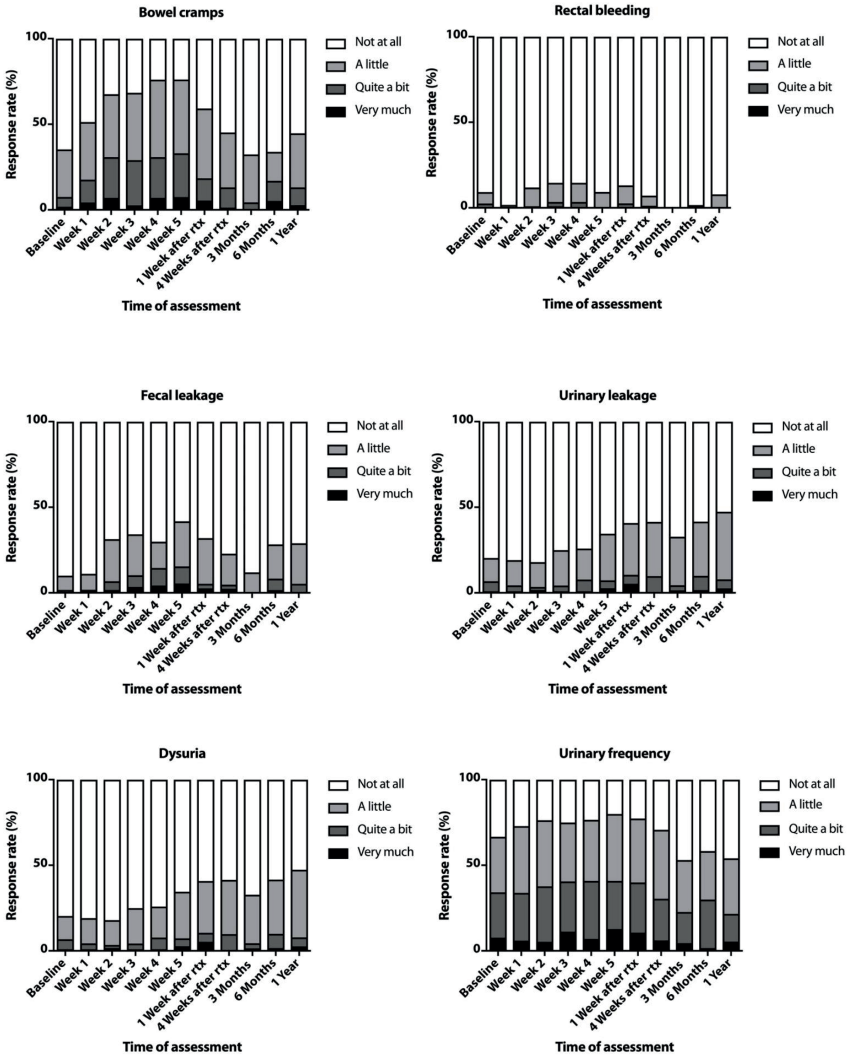

Figure 5b. This figure represents for each single-item symptom the distribution of the response rates in percentages. (continued)

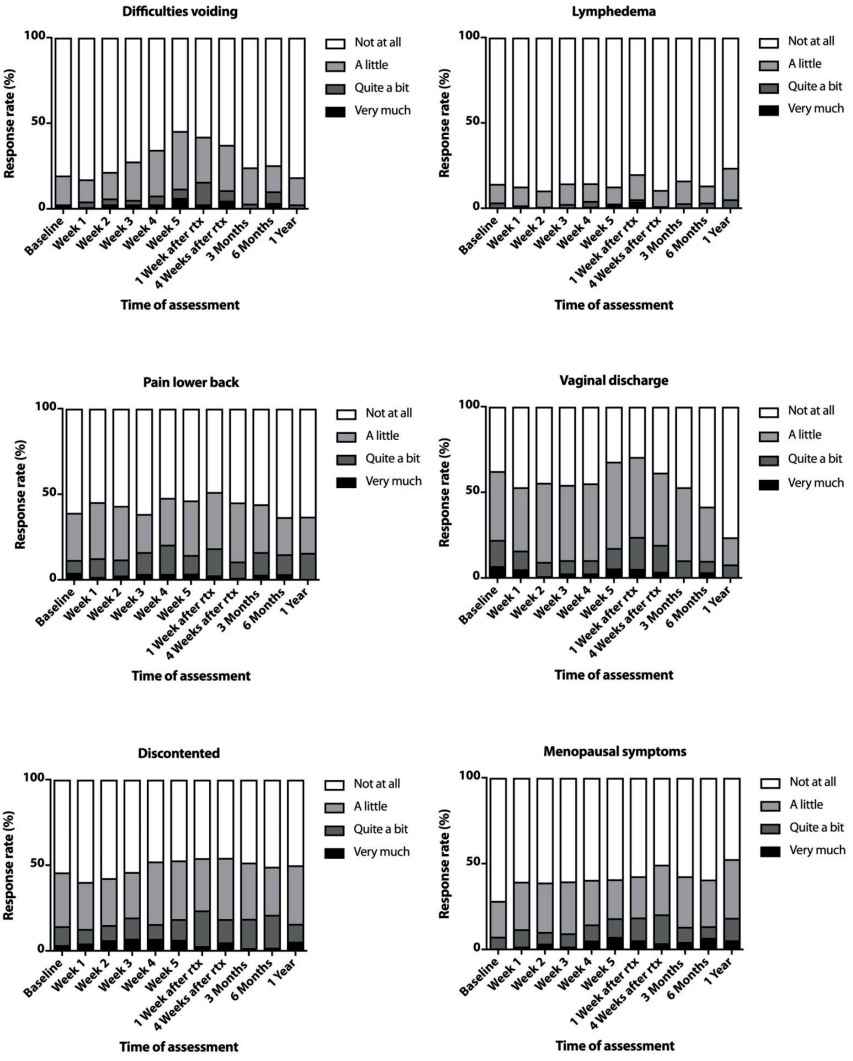

Figure 5b. This figure represents for each single-item symptom the distribution of the response rates in percentages. (continued)

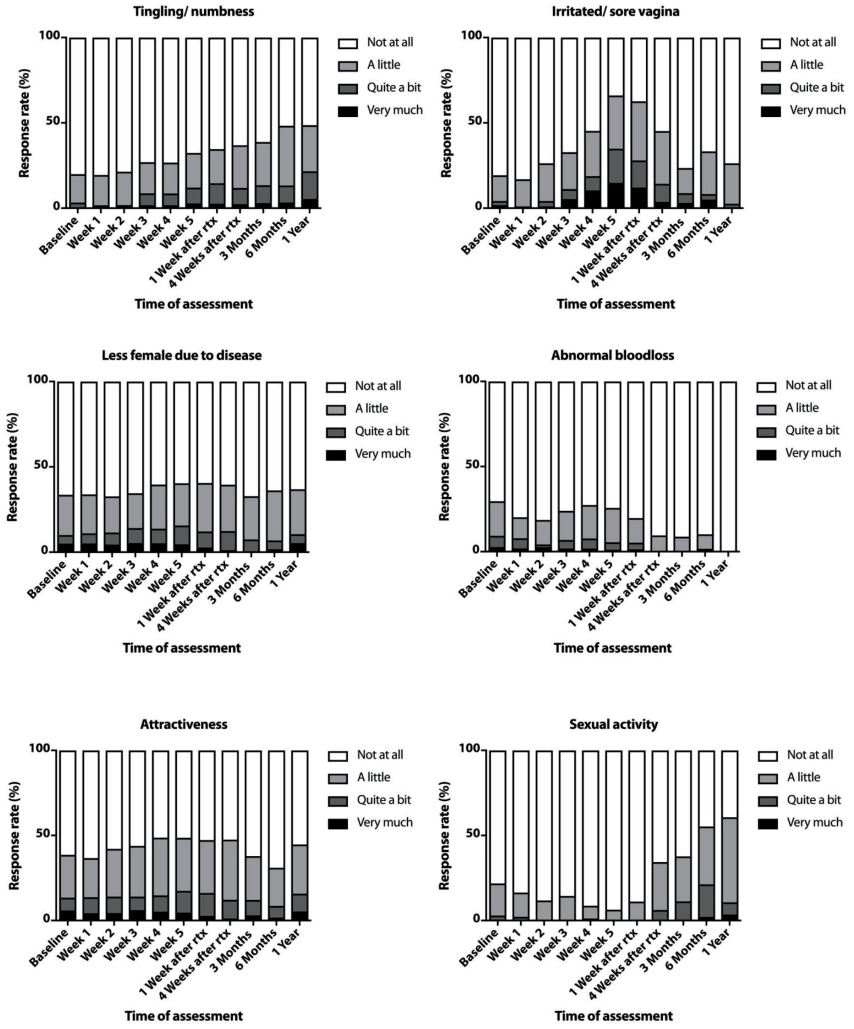

Figure 5b. This figure represents for each single-item symptom the distribution of the response rates in percentages. (continued)

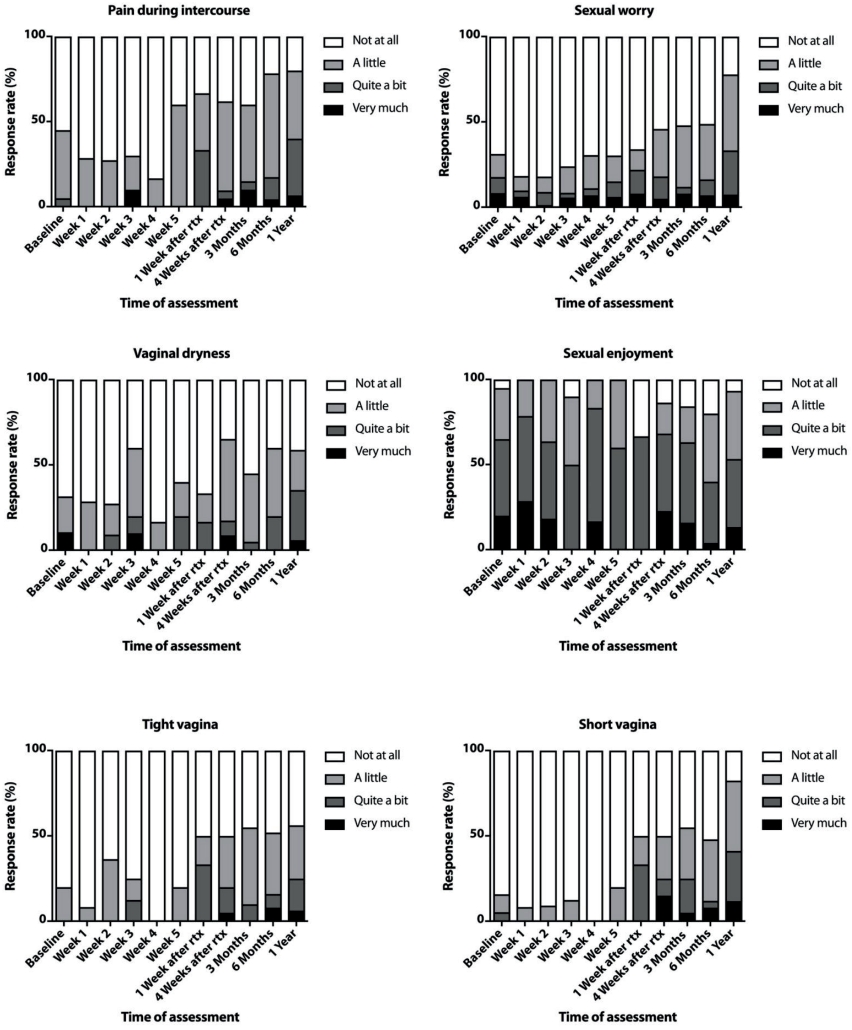

Figure 5b. This figure represents for each single-item symptom the distribution of the response rates in percentages. (continued)

5C

Table 5c. Influence of different patient and treatment characteristics on the outcome of the most reported single item symptoms diarrhea and dysuria.

	Diarrhea (5th week)*	Dysuria (5th week)#
	P-value	**P-value**
Nodal boost		
Yes/no	0.74	0.53
Motion		
Mover vs non-mover	0.27	0.75
Treatment		
CT+RT, NACT+RT+HT		
RT+HT	0.12	0.14
RT		
LN		
PAO	0.10	0.38
Treatment position		
Prone vs supine	0.28	0.16
Selection backup plan		
(>5)	0.17	0.64
Volume		
PTV	0.79 (R=0.16)	0.57 (R=0.24)

*Mean 49.2±29.4 (n=111)
#Mean 50.3±35.2 (n=110)

6A

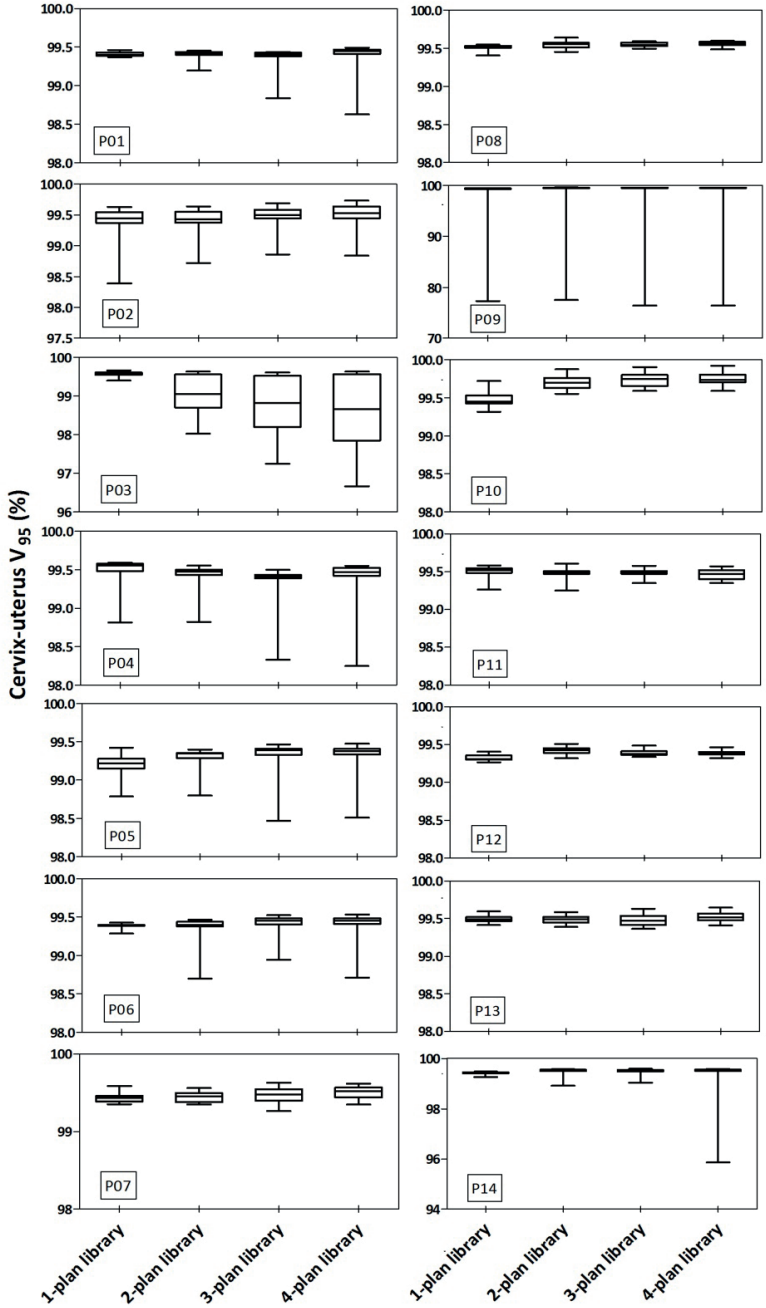

Figure 6a. Box plot of the cervix-uterus V_{95} for each patient. The boxes are the first and third quartiles, with median as the horizontal line inside the box. Upper and lower limits are the 95 and 5 percentiles.

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LIST OF PUBLICATIONS

This thesis

Chapter 2

Clinical implementation of an online adaptive Plan-of-the-Day protocol for nonrigid motion management in locally advanced cervical cancer IMRT
Heijkoop ST, Langerak TR, Quint S, Bondar L, Mens JW, Heijmen BJ, Hoogeman MS.
Int J Radiat Oncol Biol Phys. 2014 Nov 1;90(3):673-9.

Chapter 3

Quantification of intra-fraction changes during radiotherapy of cervical cancer assessed with pre- and post-fraction Cone Beam CT scans
Heijkoop ST, Langerak TR, Quint S, Mens JW, Zolnay AG, Heijmen BJ, Hoogeman MS.
Radiother Oncol. 2015, Dec;117(3):536-41.

Chapter 4

Optimal patient positioning (prone versus supine) for VMAT in gynecologic cancer: a dosimetric study on the effect of different margins
Heijkoop ST, Westerveld H, Bijker N, Feije R, Sharfo AW, van Wieringen N, Mens JW, Stalpers LJ, Hoogeman MS.
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Chapter 5

Dynamics of patient reported quality of life and symptoms after image-guided online adaptive external beam radiation therapy for locally advanced cervical cancer
Heijkoop ST, Nout RA, Quint S, Mens JWM, Heijmen BJM, Hoogeman MS.
Accepted for publication in Gynecologic Oncology, 2017 Aug

Chapter 6

What is the optimal number of library plans in ART for locally advanced cervical cancer
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PLoS One. 2016 Dec 29;11(12):e0169202

SUMMARY

The focus of this thesis lies on describing, evaluating and improving an online, adaptive Plan-of-the-Day approach (PotD) in EBRT for locally advanced cervical cancer patients.

Chapter 1 contains a general introduction into cervical cancer and the use of online adaptive radiotherapy in locally advanced cervical cancer treatment. It concludes with a brief overview of the research described in the thesis.

In **Chapter 2** we evaluated the clinical implementation of the online PotD protocol for treatment of locally advanced cervical cancer, to cope with patient-specific, non-rigid target motion. Based on the first 64 patients, it was concluded that the PotD approach was feasible with limited extra treatment time. Two phases of clinical implementation were investigated. In the first phase, the plan library contained one IMRT plan for each patient based on a personalized ITV, and a motion robust 3DCRT backup plan. This first phase was beneficial for patients with < 2.5 cm tip of uterus motion ('non-movers'; assessed from full and empty bladder planning CT scans). For patients with > 2.5 cm motion ('movers'), the advantage of IMRT was lost because of the large margins that were needed. In the second phase, movers had two IMRT plans in the plan library, one for relatively filled bladders, and the other for relatively empty bladders. For non-movers still had one IMRT plan. Compared to the motion robust backup plan, movers with two IMRT plans showed a reduction of 26-29% in volume of small bowel cavity receiving >99% of the prescription dose.

Chapter 3 describes the quantification of intra-fraction cervix-uterus motion, using pre- and post-fraction CBCT scans of 16 movers. A correlation was found between the bladder inflow rate and the intra-fraction motion. Considerable intra-fraction cervix-uterus motion was observed, requiring appropriate PTV margins (5 mm margin for the AP direction, covering 90% of the patients). For all patient included in the study, the applied CTV-to-PTV margins were sufficient. Since the introduction of VMAT, the treatment time has reduced from 11 minutes to 4.8 minutes. Most probably, this reduces the extent of intra-fraction motion for most patients.

Chapter 4 reports on the value of treatment in prone position compared to supine. At the time of the study, patients were routinely treated prone in a bellyboard, based on a previously observed advantage for small bowel. However, this was based on 3DCRT/IMRT and the use of large margins. The question was whether the advantages would still be true would still remain in modern adaptive radiotherapy using smaller margins. In collaboration with the Academic Medical Center, Amsterdam, a treatment planning study was performed for 26 patients. Using 9 different CTV-to-PTV margins we demonstrated that with small margins and a modern delivery technique (VMAT), the prone position has no significant advantage compared to the supine position; there was no preference for a prone or supine setup in terms of small bowel sparing for PTV margins

(<10mm). The recommendation of this study was to treat all gynecological cancer patients with image guided radiotherapy in supine position. However, when large margins are needed, the prone position still has a significant advantage over the supine position.

Chapter 5 discusses prospective assessments of Quality of Life and toxicity symptoms in the acute treatment phase until one year after treatment with a focus on the first three months. Most symptoms had the highest incidence at the end of treatment with return to baseline values at three months. Several symptoms, including diarrhea, dysuria, bowel cramps and sexual problems, became apparent during treatment and persisted thereafter. Probably, the end of external beam treatment is a suitable time point for assessment of future improvements in adaptive therapy regarding acute toxicity. Especially baseline and the fifth week of treatment could be used to compare observed symptoms with our data.

In **Chapter 6**, the patient-specific, optimal number of library plans in PotD adaptive radiotherapy for locally advanced cervical cancer was investigated. Main endpoint was OAR dose reduction. Fourteen patients with large cervix-uterus motion (movers) were evaluated. For each patient, plan libraries containing 1-4 VMAT plans with individualized tight margins were investigated. The plans were generated for ITVs resulting from different bladder filling ranges. All study patients showed reduced OAR dose with two tight margin plans in the library instead of one, in line with the current treatment protocol. Patients with tip of uterus motion >30 mm showed further reduction of bowel dose delivery with three plans in the library. Adding a fourth plan could be beneficial for patients with extremely large motion (Hausdorff distance ≥50 mm). The overall conclusion was that extending the plan library to more than three tight margin plans was only beneficial for a small subgroup of patients. At individual patient level, the Hausdorff distance could be used to select patients that would benefit most from adding extra plan(s) to the plan library.

Chapter 7 wraps up this thesis with a general discussion related to the main topics described and discussion about future research.

NEDERLANDSE SAMENVATTING

De focus van dit proefschrift ligt op het beschrijven, evalueren en verbeteren van een online adaptief 'Plan-of-the-Day' protocol bij uitwendige radiotherapie voor patiënten met een lokaal uitgebreid cervixcarcinoom (baarmoederhalskanker).

Hoofdstuk 1 bevat een algemene inleiding over cervixcarcinoom en het gebruik van een online adaptieve bestralingstechniek in de behandeling van lokaal uitgebreid cervixcarcinoom. Aan het einde volgt een kort overzicht over het onderzoek zoals dat beschreven is in dit proefschrift.

In **hoofdstuk 2** onderzochten we de klinische implementatie van het online adaptieve 'Plan-of-the-Day' protocol voor de behandeling van lokaal uitgebreid cervixcarcinoom en om te gaan met de patiënt-specifieke, niet-rigide, baarmoeder beweging. Op basis van de eerste 64 patiënten konden we concluderen dat deze online aanpak realiseerbaar was in een beperkte extra behandeltijd. Twee fases van de klinische implementatie werden onderzocht.

In de eerste fase bestond de plan bibliotheek uit één intensiteitgemoduleerde radiotherapie (IMRT) plan voor elke patiënt op basis van een gepersonaliseerd intern doelvolume (Internal Target Volume, ITV) en een 3D conformeel radiotherapie (3DCRT, 'backup plan') dat rekening houdt met onverwachte beweging van de uterus (baarmoeder) en cervix (baarmoederhals). De eerste fase was met name gunstig voor patiënten met minder dan 2.5 cm cervix-uterus beweging (zogenoemde 'non-movers'; beoordeeld naar aanleiding van een volle en lege blaas planning CT-scan). Voor patiënten met een cervix-uterus beweging van meer dan 2.5 cm ('movers'), werd het voordeel van de IMRT tenietgedaan door de grote marges die nodig waren. In de tweede fase hadden deze 'movers' twee IMRT plannen in de plan bibliotheek, één voor een (nagenoeg) volle blaas en het andere voor een (nagenoeg) lege blaas. De 'non-movers' hadden nog steeds één IMRT plan. Vergeleken met het 'backup plan' hadden 'movers' met twee IMRT plannen een volumereductie van 26 – 29% van de dunne darm dat meer dan 99% van de voorgeschreven dosis kreeg.

Hoofdstuk 3 beschrijft de kwantificering van intra-fractie baarmoeder beweging met behulp van pre- en post fractie 'cone-beam' CT (CBCT) scans van 16 'movers'. Een correlatie werd gevonden tussen de blaasvulling (ml/min) en de intra-fractie beweging van de cervix-uterus. Er werd aanzienlijke intra-fractie cervix-uterus beweging waargenomen, waarvoor geschikte planning doelvolume (Planning Target Volumes, PTV) marges nodig waren (5 mm marge voor de beweging in anterior-posterior (AP) richting, geschikt voor 90% van de patiënten). Bij alle patiënten in de studie waren de toegepaste klinisch doelvolume (Clinical Target Volume, CTV) naar PTV marges voldoende. Sinds de introductie van volumetrisch gemoduleerde rotatietherapie (VMAT) is de behandeltijd

sterk verminderd van 11 minuten naar 4,8 minuten. Zeer waarschijnlijk reduceert dit de intra-fractie beweging voor de meeste patiënten.

In **hoofdstuk 4** is de behandeling in buikligging vergeleken met die in rugligging. Op het moment van de studie werden de patiënten routinematig behandeld gebruikmakend van een zogenaamd 'bellyboard', als gevolg van een eerder waargenomen voordeel voor de dunne darm. Echter, dit was gebaseerd op 3DCRT/ IMRT en het gebruik van grote marges. De vraag was of de voordelen van het 'bellyboard' nog steeds stand zouden houden in moderne adaptieve radiotherapie technieken met kleinere marges. In samenwerking met het Academisch Medisch Centrum, Amsterdam, werd een planningsstudie uitgevoerd voor 26 patiënten. Negen verschillende CTV naar PTV marges werden onderzocht en er werd aangetoond dat wanneer er gebruik gemaakt kan worden van kleine marges en een moderne behandeltechniek (VMAT), de buikligging geen significant voordeel meer heeft ten opzichte van rugligging. Er was geen significant voordeel van buik- of rugligging ten aanzien van dunne darm sparing voor PTV marges kleiner dan 10 mm. De aanbeveling uit deze studie was om alle gynaecologische kankerpatiënten met beeld-geleide radiotherapie in rugligging te behandelen. Echter, wanneer er grote marges nodig zijn heeft de buikligging nog steeds een significant voordeel ten opzichte van de rugligging.

Hoofdstuk 5 beschrijft de prospectieve beoordeling van de kwaliteit van leven en toxiciteit symptomen in de acute behandelfase tot één jaar na behandeling met een focus op de eerste drie maanden. De meeste klachten hadden de hoogste incidentie aan het eind van de behandeling met terugkeer naar baseline waardes op 3 maanden. Sommige symptomen, met inbegrip van diarree, dysurie, darmkrampen en seksuele problemen kwamen aan het licht tijdens de behandeling. Waarschijnlijk is de eindfase van de uitwendige bestraling het meest geschikte tijdstip voor de evaluatie van toekomstige verbetering van adaptieve radiotherapie technieken wat betreft acute toxiciteit. Vooral de resultaten uit de formulieren van de baseline en de vijfde week van de behandeling kunnen worden gebruikt om de nieuwe waargenomen symptomen te vergelijken met onze gegevens.

In **hoofdstuk 6** werd het optimale aantal plannen voor de planbibliotheek in 'Plan-of-the-Day' adaptieve radiotherapie voor lokaal uitgebreid cervixcarcinoom onderzocht. Belangrijkste eindpunt van de studie was reductie van de dosis in de kritieke organen. Veertien patiënten met een grote cervix-uterus beweging ('movers') werden geëvalueerd. Voor elke patiënt werd een plan bibliotheek, 1-4 VMAT plannen bevattend, met geïndividualiseerde krappe marges onderzocht. De plannen werden gegenereerd voor ITVs van verschillende blaasvolumes. Bij alle patiënten uit de studie namen we verminderde dosis van de kritieke organen waar bij het toevoegen van twee krappe marge plannen ten opzichte van één plan met individuele marges aan de planbibliotheek, in lijn met het huidige behandelprotocol. Patiënten met een cervix-uterus beweging van

meer dan 30 mm hadden een verder gereduceerde darmdosis bij het toevoegen van drie plannen in de planbibliotheek. Het toevoegen van een vierde plan zou gunstig zijn voor patiënten met extreme cervix-uterus beweging ('Hausdorff distance' ≥50 mm). De algemene conclusie was dat de uitbreiding van de planbibliotheek met meer dan drie krappe marge plannen alleen gunstig was voor een kleine subgroep van patiënten. Op individueel patiëntniveau kan de 'Hausdorff distance' gebruikt worden om patiënten te selecteren die het meeste voordeel zouden hebben van het toevoegen van extra plan(nen) aan de planbibliotheek.

Hoofdstuk 7 sluit deze thesis af met een algemene discussie die betrekking heeft op de belangrijkste onderwerpen uit dit proefschrift en bevat tevens een discussie over toekomstige onderzoeksmogelijkheden.

CURRICULUM VITAE

Sabrina Heijkoop was born on August 27th, 1987 in Dordrecht, The Netherlands. In 2006, she started her medical education at the Erasmus University of Rotterdam. During her study, she was engaged in medical research at the department of Obstetrics and Gynecology under the guidance of Dr. H.C. van Doorn, gynecologist-oncologist. Sabrina obtained her medical degree, with cum laude distinction, in 2013. Thereafter she started her PhD at the Erasmus MC Cancer Institute in Rotterdam, researching the role of adaptive radiotherapy in the treatment of locally advanced cervical cancer. This thesis is a result of this 4 year research. As of April 2017, she has started her residency in Radiotherapy at the Erasmus MC Cancer Institute. Sabrina lives together with Kevin and their son Floris.

DANKWOORD

Vaak veruit het meest interessante en meest gelezen stuk van een thesis (ik blader in ieder geval altijd snel door); het dankwoord.
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PHD PORTOFOLIO

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Promotor:	Prof. dr. Ben J.M. Heijmen
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1. PhD training

	Year	Workload (ECTS)
General Courses		
Basic introduction to SPSS (statistics)	2013	1.0
BROK (basiscursus regelgeving klinisch onderzoek)	2013	1.5
Workshop on Microsoft Excel &	2014	2.0
Access		
Biomedical English Writing and Communication	2014	3.0
Biomedical English Writing Course	2014	2.0
Research management for PhD students	2014	0.5
Research Integrity	2015	0.3
Training feedback geven en ontvangen	2015	0.5
Specific courses		
Stralingscursus 5A/ 5B	2013	1.0
Nederlandse vereniging voor Oncologie: Basiscursus oncologie	2013	1.3
ESTRO course: Physics for modern radiotherapy	2015	1.3
Oral presentations at international conferences		
ESTRO 33, Vienna, Austria	2014	2.0
3rd ESTRO forum, Barcelona, Spain	2015	2.0
ESTRO 35, Turin, Italy	2016	2.0
ESTRO 36, Vienna, Austria (2 oral presentations)	2017	3.0
Oral presentations at national conferences		
Wetenschappelijke Kringdag Klinische Fysica Radiotherapie, Amsterdam	2014	1.0
Invited speaker Nederlandse Vereniging voor Radiotherapy en Oncologie (NVRO): wetenschappelijke vergadering gynaecologische tumoren	2017	1.0

Seminars and workshops		
PhD day, Erasmus MC	2013	0.3
R&D Physics meetings, department of Radiation Oncology	2013 - 2017	2.0
Refereeravond, department of Radiation Oncology	2013 – 2017	2.0
Research rounds, department of Radiation Oncology	2015 – 2017	1.0
Research day, department of Radiation Oncology	2015 – 2017	1.0
Journal Club, department of Radiation Oncology	2013 – 2017	2.0
Other		
NVRO platform LPRGT (oral presentation)	2014	0.5
6 peer reviewed papers in 6 journals	2014 – 2017	
In-house presentations		
Journal Club: QALY and the use in Radiotherapy	2014	1.0
Journal Club: Protons for children: indications, goals, techniques used and results	2015	1.0
Research Day: Quality of Life for locally advanced cervical cancer patients treated in a PotD protocol	2016	1.0
Research Day: Plan of the Day for locally advanced cervical cancer patients: an overview	2017	1.0
Refereeravonden	2014 – 2016	2.0
2. Teaching activities		
Lecturing		
Plan-of-the-Day protocol in de bestraling bij cervixcarcinoom/ laboranten in opleiding	2013 – 2016	2.0
Bijscholing radiotherapeutisch laboranten: update cervix protocol	2016	1.0
Education AIOS Radiation Oncology, Erasmus MC	2017	0.5
Distinctions		
Article selected as Issue Highlight of the International Journal of Radiation Oncology Biology and Physics	2014	