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Plan-of-the-day strategy in external beam radiotherapy treatment for patients with locally advanced cervical cancer

A quantitative study

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This thesis is worth 30 study points.

Abstract

Background: External radiotherapy treatment (EBRT) of cervical cancer encounters challenges due to varying organ motion in pelvic anatomy. Standard EBRT utilizes a single treatment plan with population-based margins ensuring target coverage, but this approach can lead to unnecessary irradiation to healthy tissue. Adaptive radiotherapy (ART) with Plan-of-the-Day (PotD) utilizes planning images with full and empty bladder to produce a plan library with multiple treatment plans using smaller patient-specific margins. "The POD study" is a randomized controlled trial on PotD for patients with large organ motions, initiated at Oslo University Hospital (OUH). This master's thesis project aims to assess whether PotD leads to a dosimetric reduction in the total irradiated volume compared to Standard treatment.

Material and method: The project includes clinical data from 10 locally advanced cervical cancer (LACC) patients treated in the POD study. In the POD study, six patients were treated with PotD, while four were treated with a Standard plan. Cone Beam CTs (CBCTs) were obtained before each treatment. New PotD plans were created retrospectively for patients treated with a Standard plan, i.e. all 10 patients had a plan library with Standard, Full and Empty plan. Both PotD and Standard treatment was simulated. Analysis focused on differences in planning target volume (PTV), PotD plan selection frequencies, and differences in total irradiated volume.

Results: The average PTV volume was significantly reduced by 162 cm^3 and 157 cm^3 in the Full and Empty plan, respectively, compared to Standard plan (p <0.005). Plan selection analysis showed an increasing selection of Empty plan, reaching 54% in the third treatment week. Significant reductions in total irradiated volume were observed for PotD across various dose levels (p <0.005).

Conclusion: Implementing a PotD strategy in radiotherapy of LACC patients significantly reduces the average PTV volume and total irradiated volume compared to Standard treatment.

Key Words: *radiotherapy, cervical cancer, Plan-of-the-Day, normal tissue sparing.*

Sammendrag

Bakgrunn: Ekstern strålehandling (EBRT) av livmorhalskreft er utfordrende grunnet stadig og varierende organbevegelse i bekkenet. Standard EBRT består av én behandlingsplan med populasjonsbaserte marginer for å sikre dekning av målvolumet, men tilnærmingen kan føre til unødvendig stråledoser til friskt vev. Adaptiv strålebehandling (ART) med Plan-of-the-Day (PotD) benytter bildeserier med full og tom blære for å lage et planbibliotek bestående av flere behandlingsplaner med mindre pasientspesifikke marginer. «POD-studien» er en randomisert kontrollert studie om PotD behandling for pasienter med store organbevegelser, som er startet ved Oslo Universitetssykehus. Denne masteroppgaven har som mål å undersøke om PotD fører til en dosimetrisk reduksjon av totalt bestrålt volum sammenlignet med standardbehandling.

Materiale og metode: Prosjektet omfatter kliniske data fra 10 pasienter med lokal avansert livmorhalskreft (LACC) behandlet i POD-studien. I POD-studien ble seks pasienter behandlet med PotD, mens fire ble behandlet med en enkelt standardplan. Cone-Beam CTer (CBCTer) ble tatt daglig før hver behandling. Nye PotD-planer ble laget retrospektivt for pasientene behandlet med én standardplan. Alle 10 pasienter hadde da et planbibliotek med Standard-, Full- og Tom-plan. Behandling med både PotD og Standard plan ble simulert. Analysen fokuserte på forskjeller i planleggingsvolum (PTV), hyppigheten av planvalg ved PotD, samt forskjeller i totalt bestrålt volum.

Resultater: Gjennomsnittlig PTV volum ble signifikant redusert med henholdsvis 162 cm^3 og 157 cm^3 med Full- og Tom-plan, sammenlignet med standardplan (p <0.005). Analyse av PotD-planvalg viste en økende preferanse av Tom-plan, som i den tredje behandlingsuken nådde 54%. Signifikant reduksjon i totalt bestrålt volum ble observert med PotD ved flere ulike dosenivåer (p <0.005).

Konklusjon: Implementeringen av en PotD strategi i strålebehandlingen av LACC-pasienter reduserer signifikant gjennomsnittlig PTV-volum og totalt bestrålt volum sammenlignet med standardbehandling.

Nøkkelord: *stråleterapi, livmorhalskreft, Plan-of-the Day, sparing av normalvev.*

Author`s Preface

This master's thesis is part of the master's program in Clinical Health Work, Radiation in Diagnostics and Treatment, at the University of South-Eastern Norway, and constitute the final work for my master's degree. The thesis is based on a prospective randomized controlled trial on Plan-of-the-Day radiotherapy for patients with locally advanced cervical cancer (the POD study), at Oslo University Hospital. The thesis is primarily tailored for radiation therapists and other professions with relevant knowledge in radiation therapy. Selection of topic was driven by a desire to enhance the knowledge of the Plan-of-the-Day approach in radiotherapy, and its potential efficacy. All descriptions of protocols, procedures, and guidelines are reflective of the standards in place at the time the thesis was written.

I want to thank my supervisors, Assoc. Prof. Anita Nordsteien at USN, and Assoc. Prof. Taran Paulsen Hellebust at UiO, head of section for Research and Education at the department of Medical Physics at OUH. Thank you for your input and guidance throughout this master's thesis, and for valuable feedback during the finalization.

Thank you to my manager, Hildegunn Aase, at the unit for radiotherapy planning at OUH, Radium Hospital, for supporting my pursuit of a master's education and for facilitating the combination of this with my daily job. Combining a demanding education with a full-time job has been challenging, but also rewarding, and today I have a feeling of pride and accomplishment.

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At last, but not least, thank you to Harald for being patient with me, and loving me through the emotional rollercoaster this master's program has been. Thank you for always believing in me, even at times when I did not, and for giving me time alone to finish the thesis in peace.

Oslo, 14.01.2024
Trine Martens

List of abbreviations

ART	Adaptive radiotherapy
Anterior	Forward direction in the patient
CBCT	Cone beam computed tomography
CT	Computed tomography
CTV	Clinical target volume
EBRT	External beam radiation therapy
FDG	2-deoxy-2[^{18}F]fluor-D-glucose
GTV	Gross tumor volume
Gy	Gray
HPV	Human papilloma virus
IGRT	Image guided radiation therapy
IMRT	Intensity modulated radiation therapy
Inferior	Downward direction in the patient
Intrafraction	Changes or movement occurring during a radiotherapy treatment (fraction)
ITV	Internal target volume
LACC	Locally advanced cervical cancer
Large mover	Movement of the tip of uterus ≥ 2,5 cm
Lateral	Right and left side in the patient
Linac	Linear accelerator
LN	Lymph node
MR	Magnetic resonance imaging
OAR	Organ at risk
OUH	Oslo University Hospital
PET-CT	Positron emission tomography – computed tomography
Posterior	Backwards direction in the patient
PotD	Plan of the day
PTV	Planning target volume
SIB	Simultaneously integrated boost
Superior	Upward direction in the patient
TPS	Treatment planning system
VMAT	Volumetric modulated arc therapy

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1 Introduction

Cervical cancer ranks as the fourth most prevalent cancer among women worldwide and is also the fourth leading cause of cancer-related mortality (Sung et al., 2021). In 2020, there were over 600,000 estimated new cases of cervical cancer globally. In Norway, approximately 300 new cases of cervical cancer is reported each year, and is the third most common cancer type among women aged 25 – 49 (Cancer Registry of Norway, 2022, pp. 20-33, 91). In 2022, the median age at diagnosis was 51 years, with a 5-year overall survival of 82,7% for all stages (National Quality Registry for Gynecological Cancer, 2023, pp. 47, 60).

The primary curative treatments for cervical cancer include surgery, radiotherapy, and chemotherapy (Norwegian Directorate of Health, 2016). For patients with locally advanced cervical cancer (LACC), the standard curative treatment involves radiotherapy combined with chemotherapy. In 2022, 51.2% of cervical cancer patients (153 individuals) received radiotherapy treatment (National Quality Registry for Gynecological Cancer, 2023, p. 44). Radiotherapy employs high doses of ionizing radiation to eliminate cancer cells, while minimizing exposure to healthy tissue and organs at risk (Cramb, 2008, p. 172). Radiotherapy treatment for LACC combines external beam radiotherapy (EBRT) with internal radiation through brachytherapy (Norwegian Directorate of Health, 2016, p. 6.15).

EBRT aims to deliver the prescribed radiation dose to a clinical target volume (CTV). In cervical cancer, the CTV encompasses the cervix, upper part of the vagina, parametria (bilateral), the entire uterus and elective lymph node regions (Norwegian Directorate of Health, 2016, p. 6.15). Treating a pelvic target volume with EBRT poses challenges due to variations in the shape and filling of adjacent organs, such as the bladder and rectum, affecting the position and anatomy of the target volume (Ahmad et al., 2008; Chan et al., 2008; Jadon et al., 2014). To account for uncertainties and ensure the entire target volume receives the prescribed dose, safety margins are applied during treatment planning (Levernes, 2012). These margins are often asymmetric and based on recommendations from studies examining internal organ movement in the pelvis (Jadon et al., 2014; Taylor & Powell, 2008).

Advanced EBRT techniques like Intensity Modulated Radiation Therapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT) allow for more conformal dose adaptation to the target volume,

with a steep dose gradient outside to reduce dose to organs at risk (OAR) (Portelance et al., 2001; Roeske et al., 2000; van de Bunt et al., 2006). Image guided radiotherapy (IGRT) with cone beam computed tomography (CBCT) helps minimize uncertainties related to patient positioning on the treatment unit. CBCT provides volumetric images of the patient in treatment position before and during treatment (Wu et al., 2011). The CBCT offers good visualization of soft tissue and facilitate monitoring of the target volume and organ movement (Jensen et al., 2019). Standard EBRT involves a single treatment plan with sufficiently large safety margins to ensure coverage of the target volume through potential variations in organ motion during treatment. An alternative approach with aim of reducing dose to OARs, is to create a plan library with multiple treatment plans covering the target volume in different anatomical positions (Flinton, 2019, p. 188). Each treatment, the most suitable plan from the plan library is selected based on pre-treatment CBCT, a method known as Plan-of-the-Day (PotD).

At Oslo University Hospital (OUH), the current guideline for standard EBRT treatment is a single treatment plan with individually adapted safety margins to account for organ movement (Appendix 3). OUH is investigating an alternative treatment method with PotD through the "POD study protocol" (Appendix 1). The POD study is a prospective randomized control trial for LACC radiotherapy that started inclusion in 2022. The treatment plan library in the POD study includes two treatment plans featuring smaller internal target volume (ITV) adapted to different CTV positions, and one robust treatment plan equivalent to a Standard treatment plan (Oslo University Hospital, 2023a). Based on daily CBCT, the best fitting plan from the plan library is selected for treatment.

This master's thesis project aim is to retrospectively compare PotD treatment with Standard treatment at OUH to investigate whether PotD can lead to a dosimetric reduction of total irradiated volume (normal tissue), compared to the Standard treatment. Irradiated volume refers to the volume of tissue within the patient receiving radiation doses significant in terms of tolerance and risk of side effects (Berthelsen et al., 2007, p. 110).

Research question

To which extent can an adaptive Plan-of-the-Day strategy compared to a Standard strategy reduce total irradiated volume in patients with locally advanced cervical cancer receiving curative external radiotherapy?

2 Theory

2.1 Cervical cancer

The female reproductive system comprises of two ovaries and fallopian tubes, a uterus, cervix, and vaginal canal (Figure 1). The cervix, situated at the lowest section of the uterus, acts as a connection between the uterus and vaginal canal.

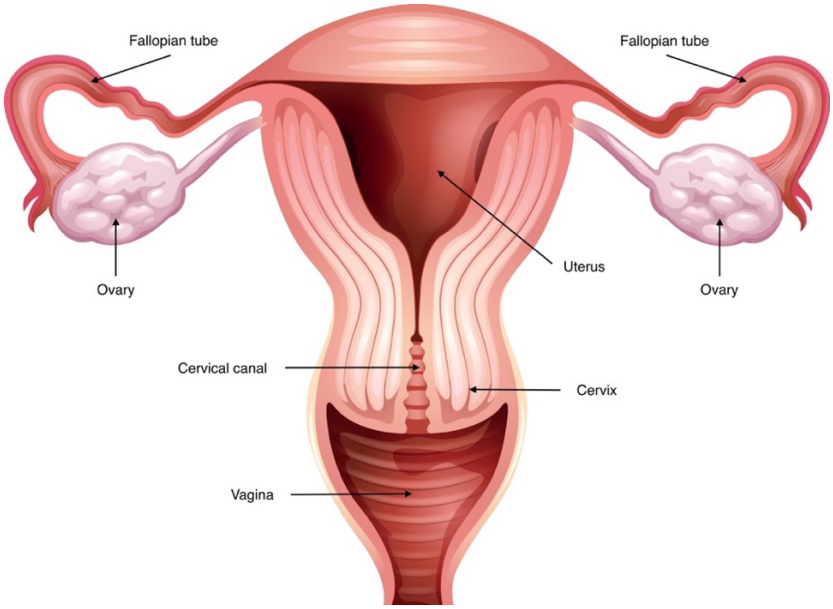


Figure 1: Anatomy of the female reproductive system: the vagina, cervix, uterus, fallopian tubes, and ovaries (adapted vector from Colourbox).

The cervix consists of two main parts (Figure 2): The exterior part (portio vaginalis) is in contact with the vaginal canal and is referred to as the ectocervix (Bhatla et al., 2021; Kristensen, 2018). The surface of the vaginal canal is composed of squamous epithelium that also cover most of the ectocervix. The supra vaginal part is known as the endocervix, forming the inner layer of the cervical canal. Both the uterus and endocervix consists of columnar epithelium. The junction where the ectocervix and endocervix, along with their distinct epithelium, meet is termed the transformation zone. The epithelium in this transformation zone is primary composed of thin metaplastic epithelium, and cervical cancer predominantly originates from this zone. According to the Norwegian Directorate of Health (2016, p. 6.2), cervical cancer is defined as cancer originating in the ecto- and/or endocervix epithelium.

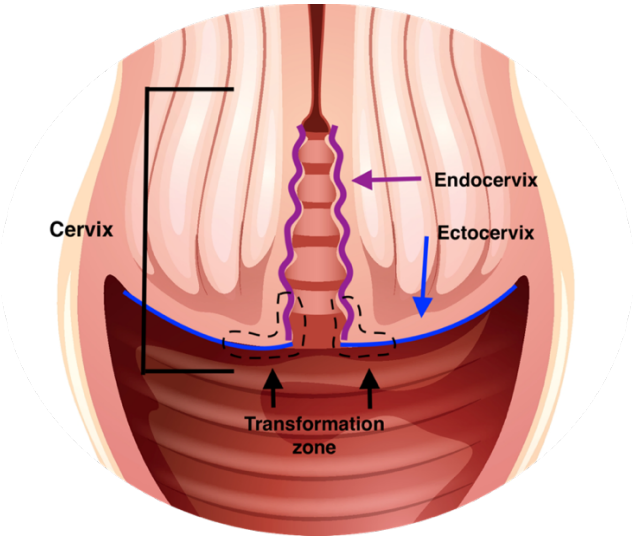


Figure 2: Overview of the cervix with endocervix (columnar epithelium), ectocervix (squamous epithelium) and the transformation zone (adapted vector from Colourbox).

In 2022, 299 new cases of cervical cancer were reported in Norway, with the highest incidence in patients aged 35 - 54 years (National Quality Registry for Gynecological Cancer, 2023, pp. 44-47). Approximately 80 - 90% of cervical cancer cases are squamous cell carcinoma, and 10 - 20% are adenocarcinoma (Norwegian Directorate of Health, 2016, p. 6.5). Human Papilloma Virus (HPV) infections, particularly HPV types 16 and 18, are considered the main cause of cervical cancer and are present in 95% of diagnosed cases (National Quality Registry for Gynecological Cancer, 2023, p. 47; Symonds, 2012, p. 468). Cervical cancer primarily spreads by directly invading structures near the cervix, such as the vagina, uterus and parametrium, and can extend into neighbouring organs, typically the rectum and/or bladder (Bhatla et al., 2021).

2.1.1 Lymph node metastases

Cervical cancer may also spread along the lymphatic system to regional lymph nodes, resulting in lymph node metastases (Bhatla et al., 2021; Symonds, 2012, p. 469). The reginal lymph nodes include the external and internal iliac (Figure 3). It can further spread to the common iliac and para-aortic nodes. Prognostic factors are more severe for patients with the presence of lymph nodes metastases at diagnosis (Kidd & Grigsby, 2011, pp. 42-43; Kristensen, 2018).

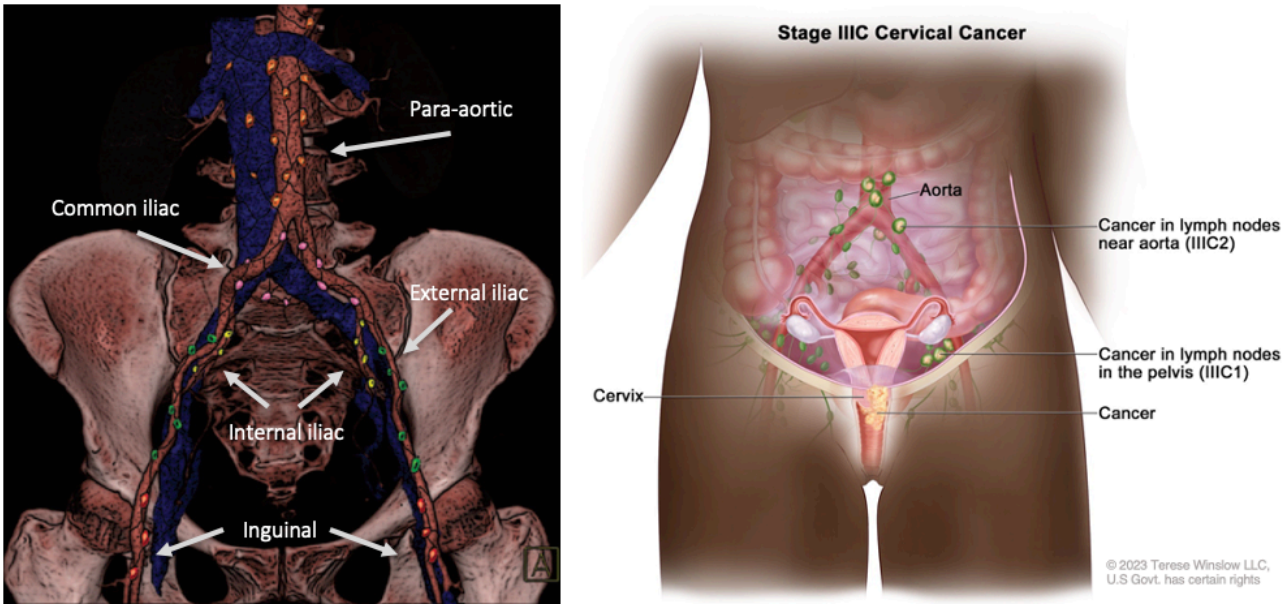


Figure 3:Illustration to the left shows the main lymph node groups involved in gynecologic cancers: para-aortic (orange), common iliac (purple), internal iliac (yellow), external iliac (green), and inguinal (red) (Reprinted from (Paño et al., 2015), RadioGraphics. With permission from Radiographic Society of North America (RSNA). Illustration to the right shows the common routes of lymphatic spread from cervical cancer, and difference in staging related to the group of lymph node(s) with the metastatic spread (Reprinted from https://www.cancer.gov/types/cervical, with permission from illustrator).

2.1.2 Cervical cancer staging

Diagnosing and staging cervical cancer is based on a gynecological examination, histological samples, together with diagnostic imaging from CT and/or MRI and PET (National Quality Registry for Gynecological Cancer, 2023, p. 48). To determine the correct stage and decide on the appropriate treatment strategy, certain elements need clarification: the tumour's size, the degree of tumour invasion in the cervix and parametria, spread to adjacent organs (uterus, vagina, bladder, rectum), involvement of the urinary tract (hydronephrosis) and metastases to lymph nodes inside and outside the pelvis (Norwegian Directorate of Health, 2016, p. 6.11). Presence of any distant metastases to other organs must also be explored prior to treatment. The national guideline for cervical cancer by the Norwegian Directorate of Health (2016) follows the international staging system (Table 1) from the International Federation of Gynecology and Obstetrics (FIGO) (Bhatla et al., 2019).

Table 1: Staging description for cervical cancer with subgroups according to FIGO 2018 (Bhatla et al., 2019). Clinical findings, radiological and/or pathological findings are allowed for correct staging.

Stage	Description
I	The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)
IA	Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion ≤5 mm
IA1	Measured stromal invasion ≤3 mm in depth
IA2	Measured stromal invasion >3 and ≤5 mm in depth
IB	Invasive carcinoma with measured deepest invasion >5 mm; lesion limited to the cervix uteri with size measured by maximum tumor diameter
IB1	Invasive carcinoma >5 mm depth of stromal invasion and ≤2 cm in greatest dimension
IB2	Invasive carcinoma >2 and ≤4 cm in greatest dimension
IB3	Invasive carcinoma >4 cm in greatest dimension
II	The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
IIA	Involvement limited to the upper two-thirds of the vagina without parametrial involvement
IIA1	Invasive carcinoma ≤4 cm in greatest dimension
IIA2	Invasive carcinoma >4 cm in greatest dimension
IIB	With parametrial involvement but not up to the pelvic wall
III	The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney and/or involves pelvic and/or para-aortic lymph nodes
IIIA	The carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (unless known to be due to another cause)
IIIC	Involvement of pelvic and/or para-aortic lymph nodes
IIIC1	Pelvic lymph node metastasis only
IIIC2	Para-aortic lymph node metastasis
IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum.
IVA	Spread of the growth to adjacent pelvic organs
IVB	Spread to distant organs

2.1.3 Cervical cancer treatment

FIGO stages IB2-IVA are defined as LACC (Norwegian Directorate of Health, 2016, pp. 6.14-15). While surgery is the primary treatment for early stages of cervical cancer, the standard treatment for LACC patients is radiotherapy with concurrent chemotherapy. The radiotherapy treatment

comprises of 25 EBRT treatments followed by four treatments with brachytherapy. Brachytherapy is internal radiotherapy and uses radioactive sources that are placed in or near the tumor, inside the patient (Cramb, 2008, p. 172). EBRT uses a linear accelerator (linac) to generate high energy ionizing radiation administered from outside the patient.

2.2 External beam radiotherapy

The name “linear accelerator” originates from the process in which electrons are accelerated in a straight line though a waveguide to create high megavolt energy (MeV) (Cramb, 2008, pp. 173-175). As illustrated in Figure 4, the main components of the linac include a source of radiofrequency electromagnetic waves (klystron or magnetron), an electron source (electron gun), and an accelerating waveguide (Mills et al., 2012, pp. 125-130). Electrons and microwaves are accelerated in a tube consisting of several cavities (the waveguide) and energy is transmitted from the microwaves to the electrons (Cramb, 2008, pp. 173-175). The energy of the electrons is increasing with each cavity the microwaves travel through. The greater number of cavities in the waveguide, the higher energy is produced. When the electrons leave the accelerating tube, they enter the head of the gantry where a bending magnet redirects the electron beam 270° towards the patient, positioned on a treatment couch. After passing through the bending magnet, the electron beam impacts a target (made of tungsten) to crate photons (X-rays). The created photons have a spectrum of energies, meaning that electrons of 6 MeV will produce a photon beam with energy ranging from 0 to 6 MeV (with 6 MeV being the maximum energy). Such beam is referred to as a 6 MV photon beam, using MV instead of MeV to reflect that this is a spectrum of energies. Although a high-energy linac can produce up to 25 MV, the most commonly energies in radiotherapy treatment are 6, 10 and 15 MV.

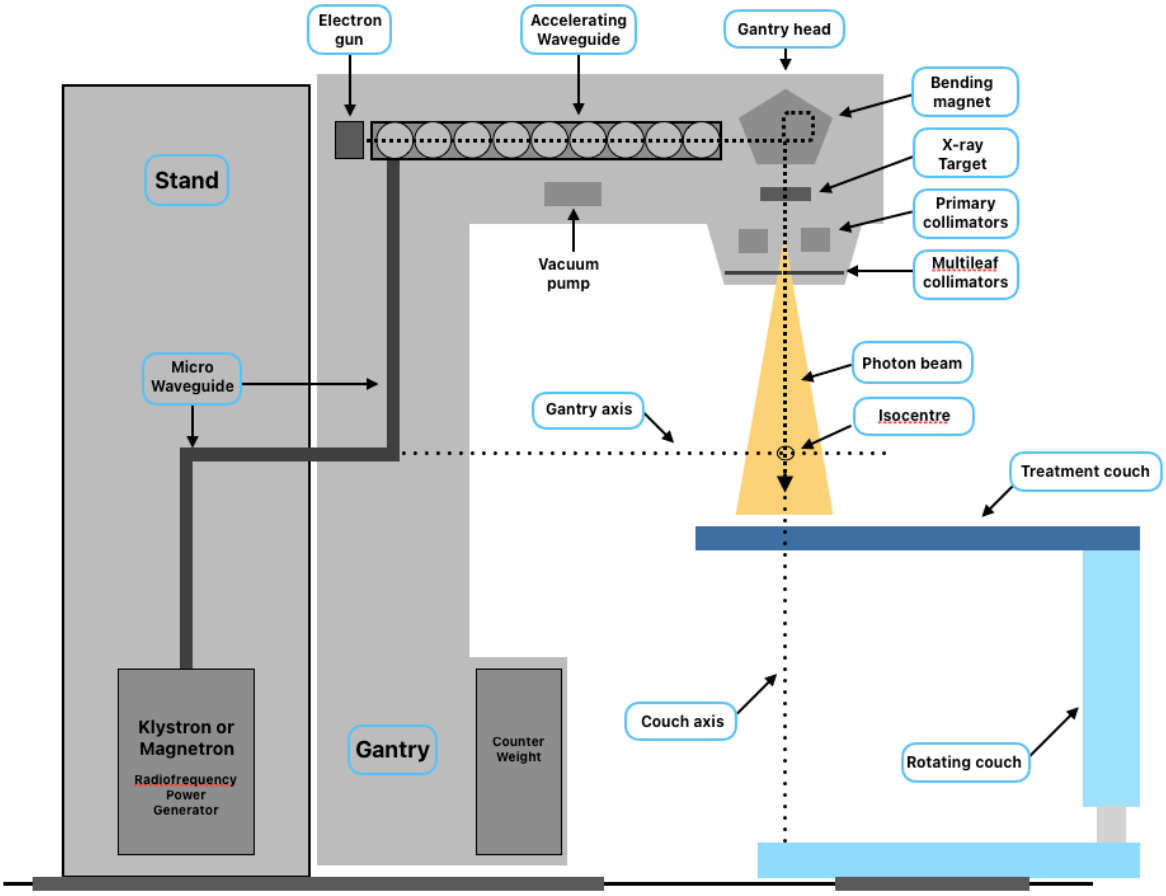


Figure 4: Illustration of the main components of a linear accelerator (inspiration from Cramb, 2008, p174).

A modern linac also includes a rotating gantry. The gantry can rotate 360° around its axis (isocenter), making it possible to treat the patient with radiation beams from various angles (Figure 5). The gantry head include components for shaping the radiation beam and one of these components is a multileaf collimator system (MLC) (Mills et al., 2012, pp. 125-130). The MLCs consists of a number of tungsten leaves, where each leaf is either 2.5, 5 or 10 mm in width (depending on manufacturer) that can move independently to shape the beam (Flinton, 2019, p. 164).

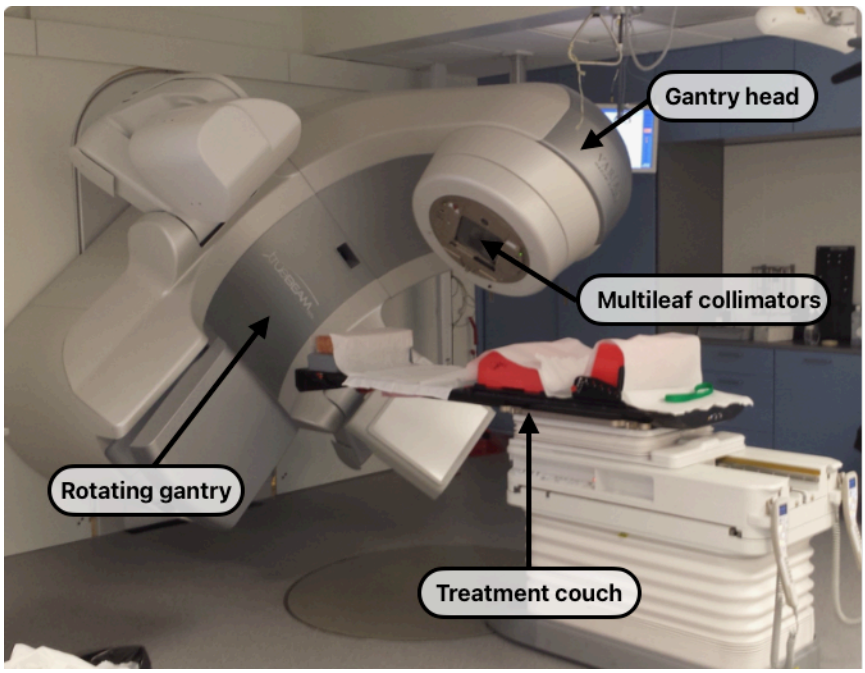


Figure 5: Image of a Varian TrueBeam® linear accelerator at the Radium Hospital, Oslo University Hospital.

2.3 Image modalities in radiotherapy of cervical cancer

Medical imaging plays an important role in radiotherapy, offering information on tumor and healthy tissue localization, being the basis for treatment planning, image guidance during patient treatment, and monitoring tumor responses. This section provides an overview of various imaging modalities used in cervical cancer radiotherapy.

2.3.1 Computed tomography

The standard imaging modality in radiotherapy treatment planning is computed tomography (CT) (Dimopoulos & Fidarova, 2011, p. 20). The CT scan provides information on the electron density in various tissue. The deposited dose in radiotherapy is dependent on the electron density and is therefore required by the treatment planning system (TPS) to calculate the dose distribution in the patient. In patients with cervical cancer, a CT scan (maximum 3 mm slice thickness) with intravenous contrast is used for the treatment planning (Norwegian Directorate of Health, 2016, p. 6.15). It is advised that patients' follow a drinking protocol prior to the CT scan, resulting in them having a comfortably filled bladder. For both the treatment planning and for every treatment

fraction, the goal is to have equal bladder filling, thereby, to reduce the radiation dose to the bladder and/or bowel (Buchali et al., 1999). The rectum and sigmoid should be as empty as possible.

2.3.2 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has an improved visualization of soft tissue compared to CT, and has an accuracy of 90% for determining tumor location, size, stromal, vaginal and parametrial extension, compared with surgical staging (Dimopoulos & Fidarova, 2011, pp. 20-21; Trovo et al., 2010, pp. 173-175). Due to spatial image distortion and missing electron density, the MRI is not suited for treatment planning. An alternate option is co-registration of CT and MRI that give high quality anatomical information as well as the electron density needed for precise dose calculation. The Norwegian Directorate of Health (2016, p. 6.15) recommend using an axial 3D corrected T2-weighted MRI scan acquired with the patient in treatment position, preferably on a flat table with radiotherapy compatible fixation, to achieve optimal co-registration with the planning CT. In the absence of a flat MRI table and/or radiotherapy compatible fixation, using a co-registration on soft tissue for guiding the delineation of the tumor and cervix, and another co-registration on bone for delineating the lymph nodes, can be an alternative. At OUH a 3D T2-weighted MRI sequence on a flat table with radiotherapy compatible fixation is standard for cervical cancer patients (Appendix 5). The MRI is imported into the TPS and used for target volume delineation together with the planning CT.

2.3.3 Positron Emission Tomography – Computed Tomography

For the assessment of gynecologic cancers a combination of FDG positron emission tomography (PET) and CT is becoming more common (Olpin & Tempany, 2011, pp. 8-9). The localization of FDG uptake is highly accurate with PET-CT, compared to PET or CT alone. PET-CT is more accurate in diagnosing nodal metastases than MRI or CT and improves the detection of both pelvic and para-aortic lymph nodes (Dimopoulos & Fidarova, 2011, p. 23; Trovo et al., 2010, pp. 173-175). For the detection of metastatic lymph nodes larger than 5 mm, a sensitivity and specificity of 100% and 99.7%, respectively, have been observed for FDG PET-CT (Sironi et al., 2006). Lymph node status is important for both prognosis and treatment planning (Kidd & Grigsby, 2011, pp. 42-43). Information supplied by FDG PET-CT in the treatment planning phase can result in adjusting the radiation treatment field size so that the affected lymph nodes are included and treated with an

acceptable margin. National guidelines recommend acquiring PET-CT if there is suspicion of metastases and the patient might be treated with radiotherapy (Norwegian Directorate of Health, 2016, p. 6.10). At OUH imaging with PET-CT is standard for LACC patients treated with radiotherapy (Appendix 6), with some exceptions due to limited allocated time at the PET-CT machine. The PET-CT is performed on a flat table with radiotherapy specific fixation, and the CT image is acquired using a diagnostic quality sequence with intravenous contrast that is suitable for treatment planning. An additional appointment for a planning CT is therefore not necessary.

2.3.4 Cone Beam Computed Tomography

Cone-beam computed tomography (CBCT) with kilovoltage energy (kV) is a relatively recent technological advancement that uses the linac gantry to acquire three-dimensional (3D) volumetric images of patients in their treatment position *(Murphy & Li, 2010, p. 9).* To incorporate kV CBCT imaging into the radiotherapy treatment process, an additional kilovolt (kV) source, such as an X-ray tube, and a digital flat panel detector is installed onto the gantry (Figure 6) (Holborn & Perry, 2019, pp. 224-227; Oelfke & Nill, 2011, pp. 147-148). The X-ray source creates multiple planar 2D images through either a 180° or 360° gantry rotation and reconstructs the images into a 3D volume (CT). The CBCT is registered to the planning CT with rigid image registration to reveal patient setup and rotation errors (Xing et al., 2011, p. 20), see chapter 2.4.

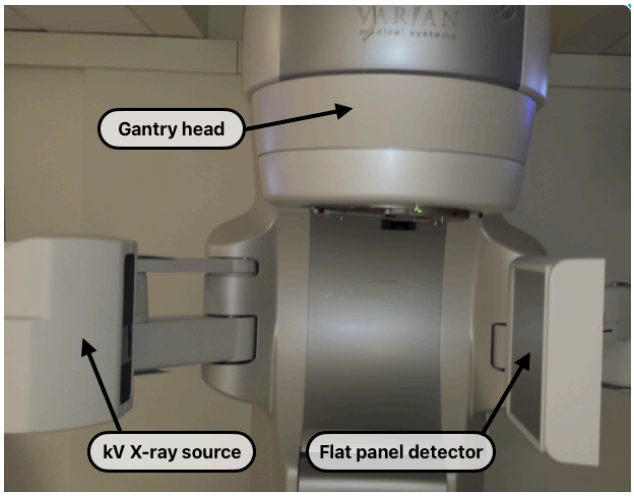


Figure 6: Image of kV CBCT equipment (kV X-ray source and a digital flat panel detector) on a Varian TrueBeam® linear accelerator gantry at the Radium Hospital, Oslo University Hospital.

2.4 Image registration in radiotherapy

Image registration in radiotherapy becomes necessary when various imaging modalities, such as CT, PET, MRI, and CBCT are to be used together for treatment planning and patient treatment (Brock et al., 2017; Wright et al., 2019, p. 104). Image registration is the procedure of overlaying images with one another to identify the geometric transformation that connects correlating anatomic points in two image series. This can be performed both in the TPS and on the linac. Consequently, image registration may occur either between two images from the same modality or between images of different modalities. Image registration can be performed rigidly or by deformation.

2.4.1 Rigid image registration

Rigid registration is used when it is assumed that the patient's anatomy in the images has a rigid connection (Murphy & Li, 2010, p. 4; Wright et al., 2019, pp. 105-106). This means that the two image sets can be aligned through three translational (x: left-right, y: anterior-posterior, z: superior-inferior) and three rotational (pitch, rotation, yaw) adjustments, additional to scaling. Thus, change in the shape of an organ will for example not be accounted for. Rigid image registration is commonly applied to treatment planning images (CT, MRI, and PET) to assist with delineations. Additionally, it is utilized in radiotherapy treatment during patient setup, where CBCT images are rigidly registered to the planning CT to assess differences in patient positioning.

2.4.2 Deformed image registration

Deformable registration (DIR) becomes necessary when there are changes in the relative position of patient anatomy, such as patient position or target volume/organ movements, where rigid registration alone cannot accurately align all parts of the image (Murphy & Li, 2010, p. 4; Wright et al., 2019, p. 106). DIR involves determining the geometric transformation between two images, allowing them to be aligned in a shared coordinate system (Bastien Rigaud et al., 2019). This process enables the spatial relationship to be deformed to align all areas of the volumetric images. Unlike rigid registration, which includes only translation or rotation, DIR is a non-linear process that incorporates deformations like stretching and shrinking by creating a unique displacement vector for each voxel in the image sets (Brock et al., 2017). In treatment planning, DIR can be used to map structures from one image set to another, facilitation faster delineation (Bastien Rigaud et al., 2019). DIR can also be used to accumulate dose by mapping fraction dose distribution from daily CBCT to planning CT with utilizing the deformable vector fields generated by DIR. The accumulated

doses from these deformed fractions can be summed, a valuable method for reporting the actual delivered dose, or for comparison with the planned dose. Information from the dose accumulation can be used to initiate adaptive replanning. In context of cervical cancer, a surface-based DIR can be used to estimate intermediate positions of the uterus between anatomies with a full- and empty bladder, facilitating the creation of multiple plans for a treatment plan library.

2.5 Radiotherapy treatment planning

The process of radiotherapy treatment planning takes place within a treatment planning system (TPS). Planning images such as CT, PET-CT, and MRI are imported into the TPS to facilitate delineation of volumes and for creating and calculating the treatment plan(s) (Appendix 3). Target volumes are delineated by an oncologist, while delineation of organs at risk (OARs) involves collaboration between radiation therapist and oncologist. Once delineation is complete, the treatment planning proceeds, encompassing the setup of treatment beams, selection of energy, dose calculation and evaluation. Evaluation of the treatment plan is conducted through the examination of the visual dose distribution on CT images (isodose lines), accompanied by dose statistics and dose volume histogram (DVH) analysis.

2.5.1 Volumes in radiotherapy planning

Volumes in radiotherapy planning are usually defined as targets and OAR. The target volume is the volume that will receive the prescribed dose, and OAR are volumes that ideally should receive as little dose as possible. The main target volumes in radiotherapy planning, illustrated in Figure 7, are the Gross Tumor Volume (GTV), Clinical Target Volume (CTV), Internal Target Volume (ITV) and Planning Target Volume (PTV). The GTV is the extension of malignant disease visual on diagnostic images (International Commission on Radiation Units and Measurements, 1993). In the presence of more than one GTV, for example a primary tumor and a pathological lymph node metastasis, they will be defined as separate volumes: GTVp (primary) and GTVn (lymph node) (Levernes, 2012, pp. 16-21). The CTV includes the GTV with margin for subclinical (microscopic) malignant disease and is the anatomic volume in the patient to be treated with the prescribed dose. In the example of a GTVp and GTVn a margin will be added to each volume to create two separate CTVs: CTVp and CTVn. To ensure that the prescribed dose is delivered to the CTV, an ITV can be created by adding an internal margin (IM) accounting for anatomical changes such as bladder filling, and/or potential

physiological movement such as breathing. To ensure dose coverage to the CTV/ITV a PTV with setup margin (SM) is created to account for uncertainties with daily patient positioning on the linac, as well as patient movement during treatment.

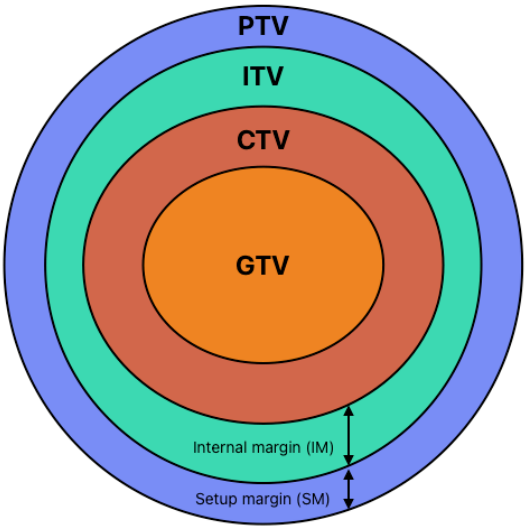


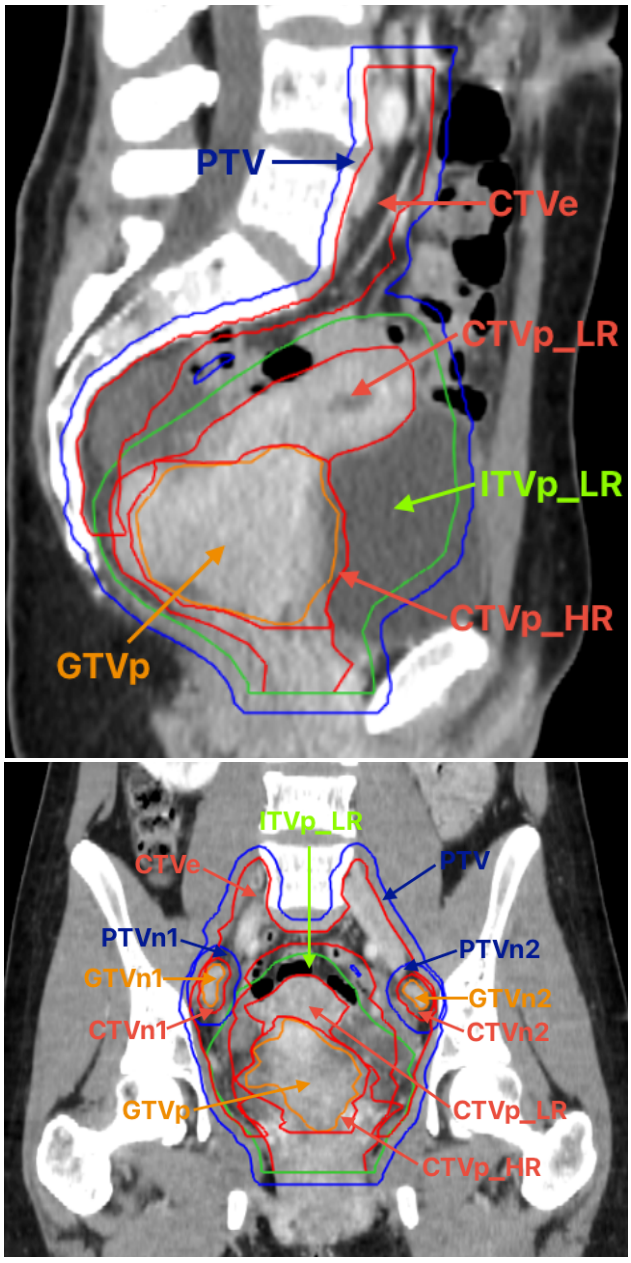
Figure 7: Target volumes in radiotherapy with the gross tumor volume (GTV), clinical target volume (CTV), internal target volume (ITV) with an internal margin (IM) and planning target volume (PTV) with a setup margin (SM).

OARs are defined as organs or healthy tissue that will impact the treatment planning and/or dose prescription as the radiation can cause acute and late toxicities (Levernes, 2012, p. 20). These OARs are often placed close to the target volume. OARs are delineated on planning images, and margins IM and SM can also be added to account for uncertainties if necessary. The different functional structures of OARs and their sensitivity to radiation, results in different dose tolerances.

2.5.2 Target volumes and organs at risk for cervical cancer

Delineation of the target volume and OAR follow local guideline and nomenclature for treatment planning and radiotherapy of cervical cancer at OUH (Appendix 3). The OUH guideline is based on the EMBRACE II study protocol (Tanderup et al., 2015), and corresponds to national guidelines by the Norwegian Directorate of Health (2016). Volumes are delineated on a planning CT with intravenous contrast using co-registered CT scans, T2-weighted MRI and PET-CT scan, and results from clinical gynecological examination, as aid for delineation. Figure 8 describes the guidelines for target volume delineating with illustration from axial, sagittal and coronal CT images.

In cervical cancer the target volumes associated with primary tumor has index “p”, target volume associated with lymph nodes has index “n”, and index “e” as an indication of target volume where no tumor has been detected, i.e., areas to have elective irradiation (Norwegian Directorate of Health, 2016, p. 6.15) (OUH guideline - Appendix 3).

Target volumes	CT images (sagittal, coronal, axial)
GTVp: is the primary tumor defined on the MRI, with support from clinical examination. **CTVp_HR:** includes the GTVp and the whole cervix, that is not infiltrated with tumor, on the MRI. The term HR indicates a high-risk of tumor infiltration in clinical target volume. **CTVp_LR:** is a low-risk clinical target volume and includes the CTVp_HR, bilateral parametria, uterus and 2 cm of the vaginal canal (measured from the caudal part of CTVp_HR). **ITVp_LR:** includes the CTVp_LR with an internal margin with individual adaptations that account for target/organ movement visual on multiple planning images. **GTVn:** is the pathological lymph node. If there is more than one lymph node, the lymph nodes are delineated as separate volumes and indexed with numbers and preferably the prescribed dose, i.e. GTVn1_55 and GTVn2_57.5. **CTVn:** includes the GTVn with a 3mm margin for subclinical disease (extracapsular growth) and should include the whole lymph node on the planning CT and MRI. **CTVe:** is an elective volume covering the lymph node regions. Which nodal regions to include depends on the risk of lymphatic	

tumor spread. If there are pathological lymph nodes, the CTVn is included in the CTVe volume.
PTV: includes ITVp_LR and CTVe with an added 5 mm margin to account for daily patient setup and positioning on the linac.
PTVn: includes the CTVn, with a 5mm setup margin.

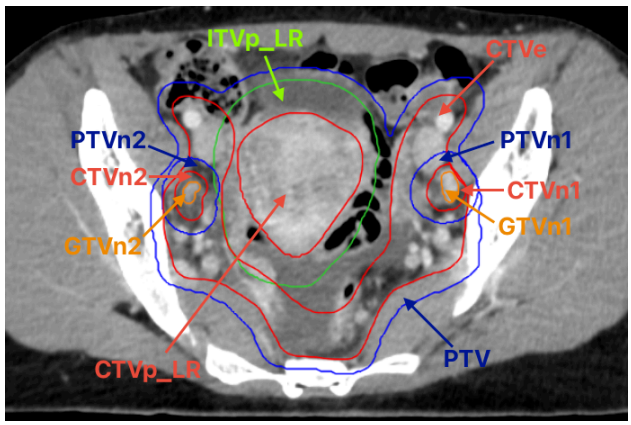


Figure 8: Target volumes for cervical cancer, illustrated with delineations on CT images (sagittal, coronal and axial view); GTVp and GTVn (orange), CTVp_HR, CTVp_LR, CTVe and CTVn (red), ITVp_LR (green), PTV and PTVn (blue) (Norwegian Directorate of Health, 2016) and (OUH guideline - Appendix 3). CT images from RayStation® TPS, with permission from patient.

OARs for cervical cancer patients are positioned close to the target volume as shown in the sagittal CT image in Figure 9. The figure also demonstrates how the ITV (green) and PTV (blue) overlap with some of the OARs. The purpose of margins used to create ITV and PTV, is that they should be large and robust enough to ensure coverage of the CTV through the course of radiotherapy treatment. The consequence is that sometimes large parts of OARs will receive high radiation dose, with risk of leading to both acute and late side effects (Norwegian Directorate of Health, 2016).

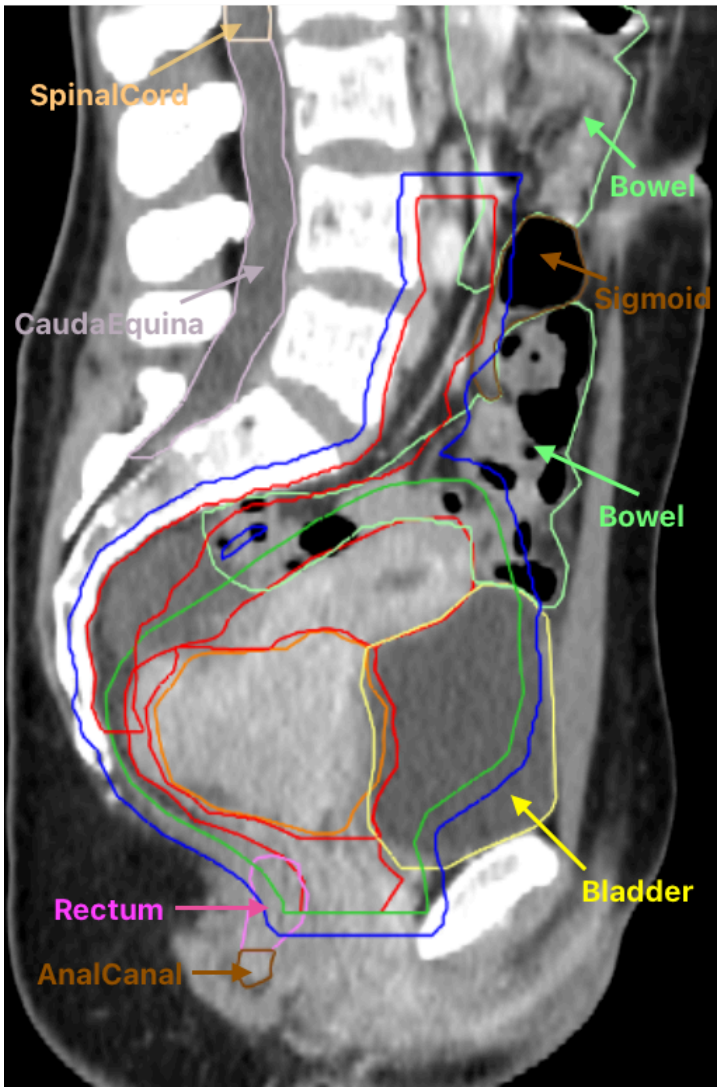
Organs at risk volumes	Delineation on CT image (sagittal)
Bladder: the whole bladder volume is delineated, including the bladder wall. **Rectum:** includes the entire rectum including rectum wall, from ani-rectal sphincter to recto-sigmoid junction. **Sigmoid:** includes the segment of large bowel from the recto-sigmoid junction to left iliac fossa. **Bowel:** is delineated as the outer contour of bowel loops, including the mesenterium (not including large blood vessels or muscles). Cranial limit is L4 for pelvic irradiation and L1 for para-aortic irradiation. **Femoral heads:** both femoral heads. **Kidneys:** the outer contour of both kidneys is delineated for para-aortic irradiation (excluding the renal pelvis) **Spinal Cord:** delineated for para-aortic irradiation and includes the outer contour from Cauda Equina junction (L2-L3) to the cranial part of the kidneys. **Cauda Equina:** outer contour is delineated from Spinal Cord junction (L2-L3) to S1-S2.	

Figure 9: Organs at risk for cervical cancer, illustrated with delineations on a CT in sagittal plane, showing the bowel (green), sigmoid (brown), bladder (yellow), rectum (pink) anal canal (brown) and cauda equina (light pink) (Appendix 3). CT images from RayStation® TPS, with permission from patient.

2.5.3 Cervical cancer and organ motion

Treating a target volume in the pelvic area with EBRT is challenging, due to variations in the shape and filling of adjacent organs, such as the bladder and rectum. Such variation can impact the position and shape of the target volume. This variation can especially affect the vagina, cervix, and

uterus. Daily variation in bladder volume during radiotherapy treatment can result in the tip of the uterus moving up to several centimeters, mainly in the anterior-posterior and superior-inferior direction (Chan et al., 2008; Jadon et al., 2014). Studies have shown a systematic reduction in bladder volume throughout radiotherapy treatment, influencing the position of the uterus and cervix (Ahmad et al., 2008). For the rectum, no systematic change in volume and/or filling has been shown throughout the radiotherapy treatment, but daily variation could impact the position of the lower part of the uterus, cervix and upper vagina (Jadon et al., 2014; Taylor & Powell, 2008).

One approach to reduce movement of the uterus and cervix is to use a bladder filling protocol (Taylor & Powell, 2008). Striving for consistent bladder filling during both planning image acquisition and at each treatment fraction allows for smaller margins for ITV and/or PTV. Having a filled bladder during treatment can also offer a protecting effect on small bowel (Wang et al., 2017). A bladder volume exceeding 200 ml can significantly reduce radiation dose to the small bowel and bladder compared to a smaller bladder volume. At OUH, the standard procedure involves the patients emptying their bladder and then consuming two glasses of water, approximately 300 ml, an hour before the planning CT/PET-CT and before each treatment (Appendix 3). However, there is still doubt about the effectiveness of the method for reducing margins, as variations in both shape and filling of the bladder still occur (van de Bunt et al., 2008). In some patients the bladder volume on the planning CT will rarely or never be representative of the patient' bladder volume during treatment (Bondar et al., 2012).

Both bladder filling and uterus movement are highly individual, and using population based margins for ITV and PTV for all patients may lead to significant radiation of OAR and healthy tissue for some patients (Ahmad et al., 2011). An alternative approach is to use individually adapted ITV margins that consider changes in anatomy due to varying bladder filling for each patient. This is done by acquiring planning images (CT/MRI) with both a full and empty bladder, then co-register these image series (Lim & Bedi, 2019, pp. 27-30). These images provide information on patient-specific movement of the target volume, enabling individually adapted ITV to be generated. In a study by Bondar et al. (2012), the use of individual margins, compared to standard margins, resulted in the mean volume from CTV to PTV being reduced by 48%. The volume of rectum and bladder overlapping with the PTV was also significantly reduced. At OUH, an individual adaptive ITV strategy

based on imaging with different bladder filling is standard for radiotherapy of LACC patients (Appendix 3).

2.6 Radiotherapy treatment planning for cervical cancer

With the introduction of MLC came the ability to shape the radiation beam and make it conform around the PTV (Flinton, 2019, pp. 186-187). The conventional treatment for cervical cancer was a 4-field technique where the gantry was rotated to 0°, 90°, 180° and 270° angle, delivering a conformed radiation beam from each angle (Figure 10). Planning such treatment is called forward planning since the planner is repeatedly changing the field parameter to achieve an optimal plan. While the 4-field technique ensured coverage of the target volumes, it had limited effectiveness in sparing normal tissue. Technological advancements in EBRT have given rise to more sophisticated treatment techniques, including Intensity Modulated Radiation Therapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT). IMRT uses several treatment fields (often between 5-9 fields) distributed at different angles around the patient, and the radiation intensity from each angle varies over the radiation field (fluence) (Purdy, 2011). Each individual radiation field is composed of numerous small segments of different sizes, each providing a small dose contribution. With VMAT, the linac rotates around the patient in an arc, delivering radiation continuously with varying intensity, while the radiation field constantly changes shape (Flinton, 2019, p. 187). Such techniques cannot be performed with forward planning due to too many degrees of freedom. Instead, so called inverse planning is used, where the desired outcome for target coverage and OAR sparing is defined as objectives in the TPS and an advanced iterative algorithm calculate the optimal beam shape and fluence (Muzumder & Sebastian, 2020). Both IMRT and VMAT offer the advantage of delivering beams from any angle (360°) around the patient. For EBRT of LACC patients, these techniques allow adapting the dose more conformally to the PTV, and simultaneously provide a steep dose gradient outside that helps reduce the dose to the OAR (Figure 10) (Portelance et al., 2001; Roeske et al., 2000; van de Bunt et al., 2006). In a study by Mundt et al. (2003) IMRT resulted in less gastrointestinal toxicity compared to previous standard 4-field technique treatment, and Forrest et al. (2012) found a significant reduction in dose to the bladder, rectum, bowel and sigmoid when using IMRT. Although no significant difference in dose to OAR has been found between the IMRT and VMAT techniques, VMAT may be advantageous due to shorter treatment time and reduced incidences of intrafraction movement (Bai et al., 2018; Flinton, 2019, p. 187). At OUH, VMAT is the

standard technique for all EBRT of cervical cancer (Appendix 3) and (Oslo University Hospital, 2023a).

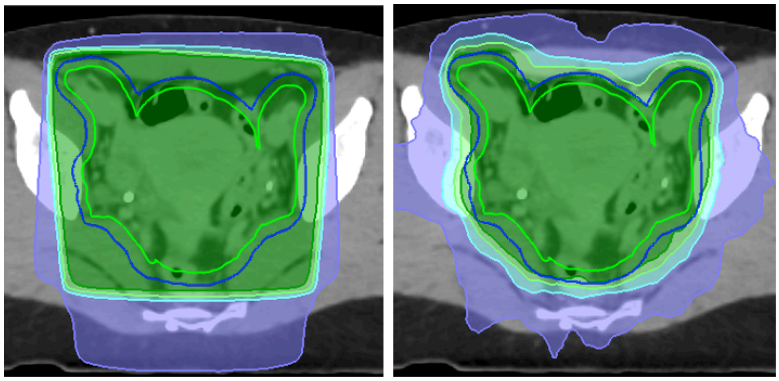


Figure 10: Axial CT images illustrating the difference in dose distribution between 4-field technique (left image) and VMAT (right image) visualized with isodose lines. The green isodose line represent the desired dose level to cover the PTV (42.75 Gy). The light green (40.5 Gy), light blue (36 Gy) and purple line (27 Gy) illustrate lower dose levels. Gy = unit for absorbed dose. CT images from RayStation® TPS, with permission from patient.

The current standard EBRT treatment of LACC at OUH involves a single treatment plan with an adaptive ITV margin (described in Figure 8) following local guidelines (Appendix 3). The EBRT treatment is 25 fractions in total, where the patient receives one fraction each weekday, equivalent to five fractions each week. The ITV is treated with 1.8 Gy per fraction, reaching a total radiation dose of 45 Gy. If the patient has pathological lymph node in the pelvic area, a simultaneous integrated boost (SIB) is applied with 2.2 Gy per fraction to achieve a total of 55 Gy. For lymph nodes in the common iliac- and/or paraaortic region, the SIB involves 2.3 Gy per fraction to achieve 57.5 Gy in total dose. The prescription of lower dose to pelvic lymph nodes is based on the estimation of 3-4 Gy contribution to these nodes from the brachytherapy treatment (Mohamed et al., 2015).

2.6.1 Plan evaluation with isodose lines

Plan evaluation tools in the TPS facilitate the assessment of dose distributions to determine whether the target volume and OAR tolerances have been met (Bridge, 2019, pp. 207-208). The most straightforward way to assess if a plan meets the criteria is visually evaluating the dose distribution (Figure 11). This assessment considers the coverage of the target volume by the desired

isodose lines and the sparing of OAR and healthy tissue. Additionally, visually identifying the location of the maximum dose within a slice or the entire volume can help to determine if the plan's highest dose point is within the target volume. Another approach for plan evaluation is with a dose-volume histogram.

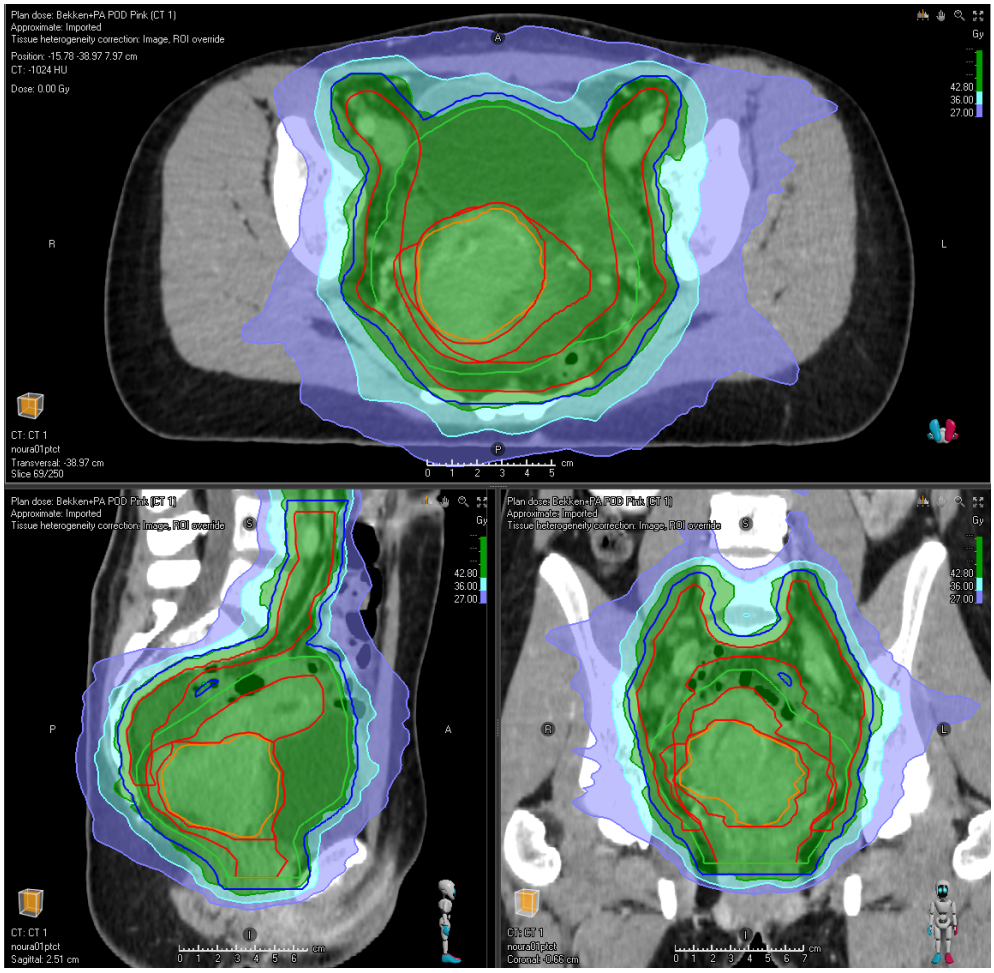


Figure 11: Illustrating the visual assessment of dose distribution with isodose lines in RayStation® TPS. Green isodose line represent the desired dose level to cover the PTV (42.75 Gy). The light blue (36 Gy) and purple line (27 Gy) illustrate lower dose levels. CT images from RayStation® TPS, with permission from patient.

2.6.2 Plan evaluation with dose-volume histogram

The data from the 3D dose distribution can be summarized into a 2D graph, called dose-volume histogram (DVH), that illustrates the dose distribution of a specific volume of interest (Figure 12) (Childs & Bidmead, 2012). In the DVH, the horizontal axis represent dose and the vertical axis

represent volume, and both can be viewed in relative or absolute scale (Pandit, 2020). DVH can be also in differential or cumulative form, where the cumulative is more commonly used for plan evaluation. A cumulative DVH shows a volume (V) that receives a dose (D). Typical DVH parameters are D_V and V_D (Levernes, 2012, pp. 22-25). The first parameter is the dose (or higher) that is delivered the volume of a structure/organ expressed in Gy or as a percentage of the prescribed dose. The latter parameter is the volume of a structure/organ receiving more than or equal to the dose expressed in cm^3 or as a percentage. One example is D_{100} that is the dose delivered to 100% of the volume, representing the minimum dose to the volume D_{min}. D_{max} is the maximum dose to a point in the volume. Improved dose distribution in the target volume is indicated by higher V_D values, ideally close to 100% (with D being the prescribed dose), and a sharp dose fall-off after the prescribed dose limit (Bridge, 2019, pp. 207-208; Pandit, 2020). For OAR, the more optimal dose distribution is lower V_D, meaning the dose to a volume should fall to 0% as fast possible. A DVH is an important tool for plan review and evaluation during treatment planning, as it can be used to establish whether the dose to the target is uniform across the target volume and how the dose distribution is to an OAR (Childs & Bidmead, 2012). They can also be used to visually compare different treatment plans. The DVH display is often supplemented by dose summaries (statistics), including maximum, minimum and mean doses within a structure, offering clarity on whether doses to target and OAR are within acceptable limits (Bridge, 2019, pp. 207-208). A limitation of DVH is the lack of spatial information, for instance, the DVH might show a specific volume receiving a dose below the lower tolerance but does not specify the location of that lower dosage within the target. Despite this, combining DVH with dose statistics and visual evaluation of dose distribution (isodose lines) enables an effective assessment of treatment plan quality.

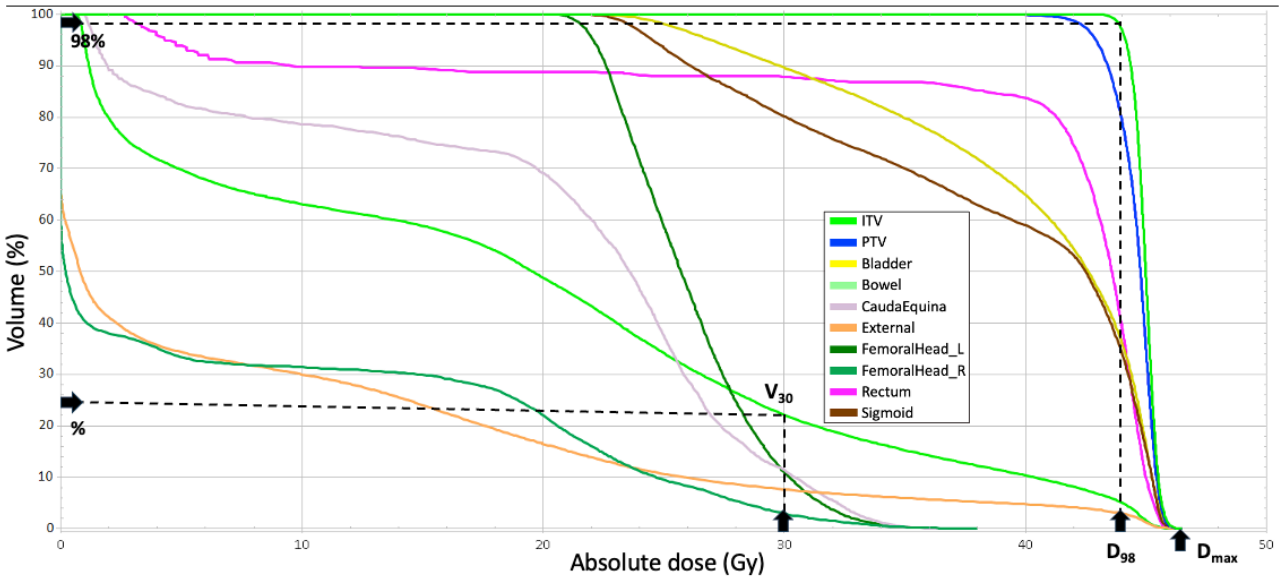


Figure 12: Illustration of a cumulative dose volume histogram (DVH) showing the percentage of a volume that receives a specific dose or higher. The vertical axis shows the volume in percent, and the horizontal axis shows the radiation dose (Gy) in absolute dose. The DVH illustrates radiation dose distribution to both target and organs at risk volumes. The highlighted DVH parameters (dashed lines) is V_{30} for Bowel (OAR): the percentage of bowel volume that receives 30 Gy or more; D_{98} to ITV (target): the dose (Gy) that 98% of the ITV receives; D_{max}: the maximum dose to the volume. Retrieved from RayStation® TPS.

2.6.3 Image-guided radiotherapy

Image guided radiotherapy (IGRT) is a description of radiotherapy where imaging is used for treatment verification (Holborn & Perry, 2019, pp. 224-227; Wu et al., 2011). The primary purpose of IGRT is to guide patient positioning reducing the uncertainties associated with daily treatment on the linac, and to ensure correct delivery of the planned treatment. An important technique in IGRT is the CBCT. A CBCT of the patient in treatment position is taken prior to the radiotherapy treatment and assessed against the planning CT with rigid registration (Figure 13). CBCT provides good visualization of skeletal anatomy and is a useful tool for checking and adjusting setup uncertainties (Laursen et al., 2012). In radiotherapy of cervical cancer, the increased accuracy when positioning the patient has made it possible to reduce the PTV margin around the CTV that includes elective lymph node regions, without compromising dose coverage. CBCT images also provides relatively good information on soft tissue anatomy, and visualizes anatomical structures such as the

uterus, cervix, vagina, bladder, and rectum. CBCT is therefore a good method for monitoring both the target volume and organ movement (Jensen et al., 2019). Daily CBCT is a valuable tool for detecting if the target volume moves more than expected and assess if the movement result in inferior dose coverage. If necessary, replanning can be performed using the image information from the CBCT to adapt the treatment plan.

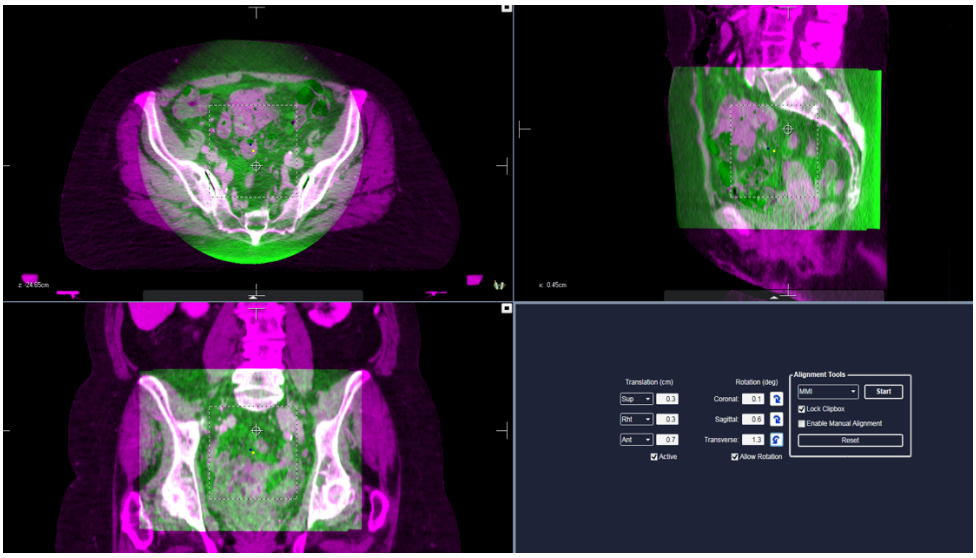


Figure 13: Illustration of an online CBCT match on a linac. CBCT image (green) is rigidly registered to the planning CT (pink) based on bony anatomy. If patient position error is detected, corrections can be made (translation and rotation) before treatment is administered.

2.6.4 Adaptive radiotherapy

Adaptive radiotherapy (ART) acknowledges that relying on a single treatment plan for a whole course of radiotherapy treatment, can often result in suboptimal treatment due to anatomical changes that may occur over time (Flinton, 2019, p. 188). These changes can stem from factors such as systematic alterations in patient position, weight loss, internal organ motion, or tumor response (shrinkage). IGRT can address some of these changes by adjusting the patient's position using couch shifts to ensure accurate treatment delivery, but the treatment is always based on the one initial treatment plan.

With ART the treatment plan is modified based on observed anatomical changes identified by imaging (Flinton, 2019, p. 188; Holborn & Perry, 2019, p. 229). ART can be planned in advance,

where multiple planning images (CT/MRI/PET-CT) showing varying organ motion/filling are used to create adapted margins for ITV/PTV. Adjustments can also be made during the treatment course with the use of image information from CBCT. Any modifications to the treatment plan can be implemented either "off-line" or "on-line." Off-line ART is used to address progressive changes, such as cumulative tumor shrinkage, triggering a replan for future treatments. However, this method relies on subjective assessments to determine the most appropriate time to replan. On-line ART, on the other hand takes place immediately after CBCT imaging and deals with random day to day changes. A current approach to on-line ART involves the use of plan libraries, known as the 'plan-of-the-day' approach. Here, multiple treatment plans are created on the planning CT to encompass various potential anatomical variations of the target volume (CTV). Each treatment fraction, the most suitable plan is selected based on the CBCT images.

2.7 Radiotherapy treatment with Plan-of-the-Day

Plan-of-the-day (PotD) is an ART strategy that uses anatomical information from two planning images with a full and an empty bladder, respectively, to generate a plan library consisting of two or more treatment plans that cover the target volume in different anatomical positions (Bondar et al., 2012). The image information in CBCTs is central to the work with PotD because of the visualization of both bony and soft tissue anatomy. During each daily treatment session, positional corrections are made first (based on bony anatomy), followed by the selection of a plan from the plan library that best aligns with the soft tissue anatomy on that day (Holborn & Perry, 2019, p. 229). This approach is based on predictable changes in shape/position of the target volume that can be pre-planned and is illustrated in Figure 14. The quality of CBCT can sometimes have lower quality that reduce the visualization of soft tissue, making it difficult to choose a plan (Heijkoop et al., 2014). It is therefore recommended to have a motion robust plan as a backup plan available in the plan library, to be chosen when needed. A study on PotD, “the POD study”, has recently been initiated at OUH (Appendix 1).

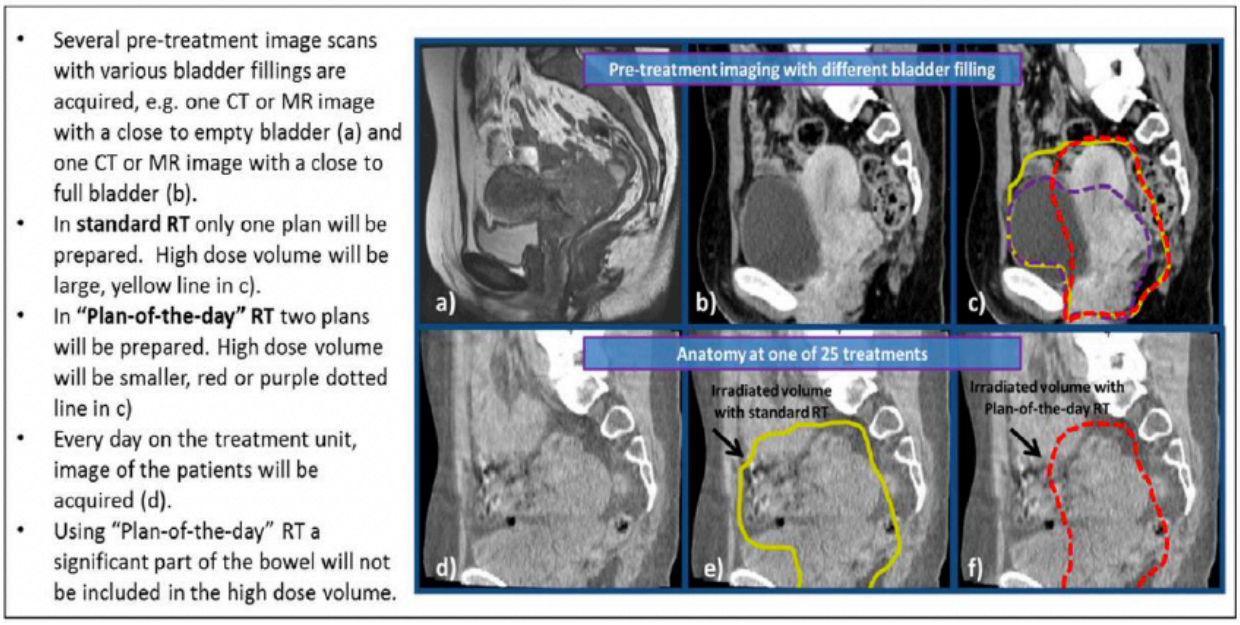


Figure 14: Illustrating the Plan-of-the-Day strategy in the POD study protocol. Plan-of-the-Day radiotherapy with two treatment plans (red and purple dashed lines). Standard radiotherapy plan (yellow solid line). RT = radiotherapy. (POD study protocol, Appendix 1).

2.8 The POD study at OUH

The POD study is a prospective single blinded randomized controlled trial for LACC patients (FIGO 1b1 – IVa) with curative intent (Appendix 1). The overall aim of the study is to investigate if PotD strategy results in less side effects both during and after radiotherapy.

Only patients categorized as large movers are included in the POD study. Categorizing a patient as a large mover is based on measuring the movement of fundus uteri (tip of uterus) on image sets with different bladder filling acquired for treatment planning. Patients with a large movement of the uterus are typically treated with large margins in standard EBRT to ensure target coverage during treatment, and might benefit the most with a PotD strategy (Bondar et al., 2012). The workflow of the POD study is illustrated in Figure 15 and will be described in more detail.

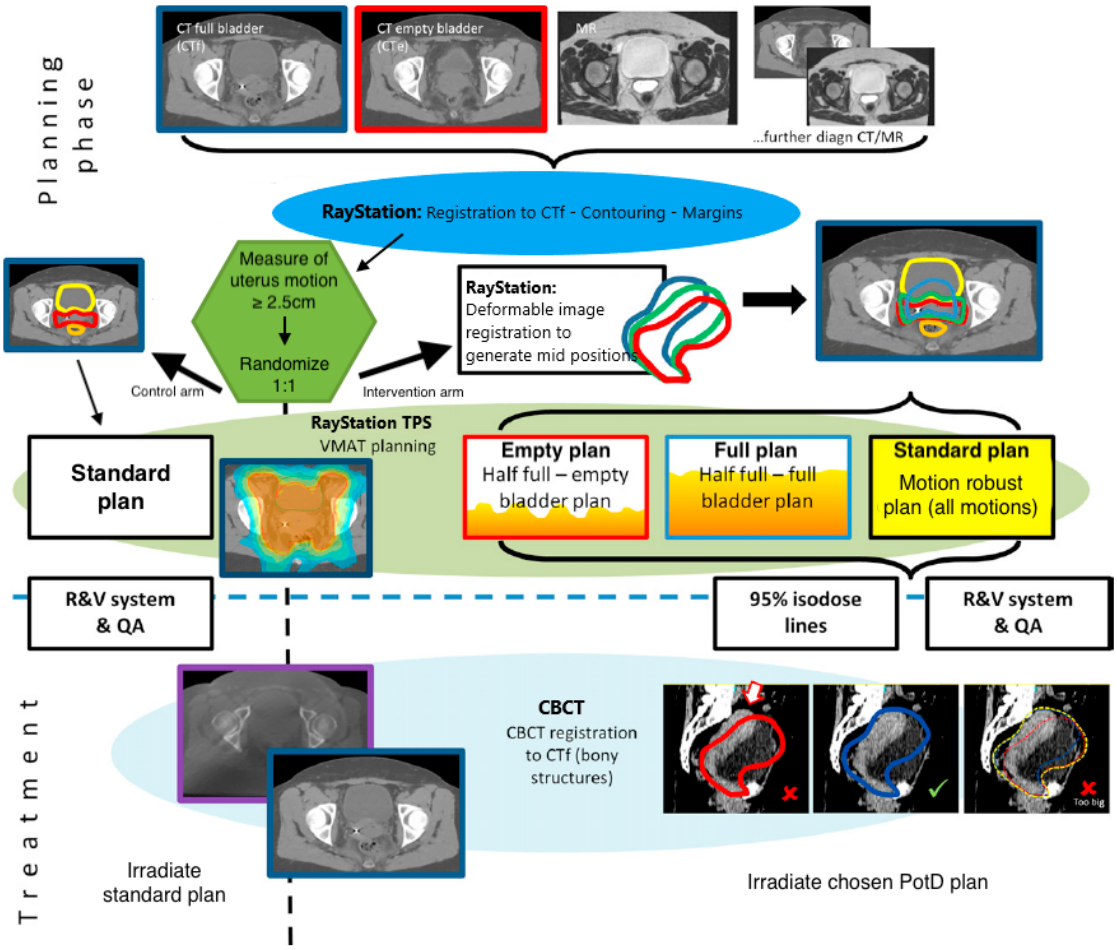


Figure 15: Sketch of the POD study workflow. TPS: treatment planning system; R&V: record and verify; CBCT: cone beam computed tomography (volume imaging). (Adapted sketch from Buschmann et al., 2018, Z Med Phys 28(3):184-195. With permission from author and Copyright Clearances Center's RightsLink®)

2.8.1 Planning phase:

Two CT scans in supine position are acquired for each patient during the PET-CT procedure (General Electric (GE) Healthcare Discovery™ MI Gen 1, 4-ring, Milwaukee, WI, USA). Prior to the procedure, the patient has a Foley bladder catheter inserted (Appendix 7). The first CT scan is performed with an open catheter and, thereby, empty bladder, with low-dose CT scan protocol to minimize unnecessary radiation. After the first CT scan the bladder is manually filled through the catheter with 250 ml of saline water and a new CT scan protocol (diagnostic quality) with intravenous contrast and full bladder is acquired. The catheter is then removed. In addition, an MRI scan

(Siemens® Magnetom Vida Fit 3T, Erlangen, Germany) is acquired approximately one week before the PET-CT scan with an empty bladder.

The two CTs-, PET- and MRI scan are imported in to RayStation® TPS (RaySearch, v 11A, RaySearch Laboratories, Stockholm, Sweden). The CT with full bladder is set as the primary image set and the empty bladder CT, and MRI is registered rigidly to aid delineation for treatment planning (Oslo University Hospital, 2023b). The PET is automatically registered to the CT as they were both acquired during the same session and share the same frame of reference (FoR). Target volumes and OARs are delineated on the full bladder CT. This CT is also used for treatment planning and dose calculation.

Based on the CT images with full and empty bladder, the tip of uterus movement is measured. Patients with a measured movement of ≥ 2,5cm are defined as large movers and can be included in the POD study. Included patients are then electronically randomized (1:1) to either the intervention arm with PotD radiotherapy, or control arm with Standard radiotherapy.

2.8.1.1 Control arm:

For the patients in the control arm, only one Standard treatment plan is crated following local guidelines for standard radiotherapy of LACC at OUH (Appendix 3). An ITV margin is created to cover the full movement of the uterus visualized on both full and empty bladder CT scan. To create the PTV, a 5mm margin is added to the ITV and CTVe (elective lymph node regions).

2.8.1.2 Intervention arm:

For patients in the intervention arm, a DIR is created in RayStation® TPS to generate a model that estimates intermediate positions of the uterus, i.e. uterus positions between the full- and empty bladder position. A user manual on the DIR procedure and treatment planning in the POD study can be viewed in Appendix 4.

Deformable image registration in the intervention arm:

The CTV_LR (cervix, parametria, upper vaginal canal and uterus) and bladder volume is delineated on the CT with full and empty bladder, respectively (Oslo University Hospital, 2023a). A DIR is performed with these structures as controlling regions of interest (ROIs), and other image information is discarded (user manual – Appendix 4). The quality of the registration is then assessed

before proceeding. With the use of an in-house developed python script in RayStation® TPS, four intermediate positions of CTV_LR, in addition to the full and empty bladder position, is created as six new CTV_LR volumes based on the DIR. The six volumes are then divided into two groups, one covering the position of CTV_LR for half full - full bladder volume and the second covering positions for half full - empty bladder volume (Figure 16). An additional 3 mm internal margin is added around each group of CTV_LR to create an ITV covering half full-full positions, and an ITV covering half full-empty positions (Oslo University Hospital, 2023a). Two PTVs is created with a 5mm margin added to the each of the ITVs and CTVe.

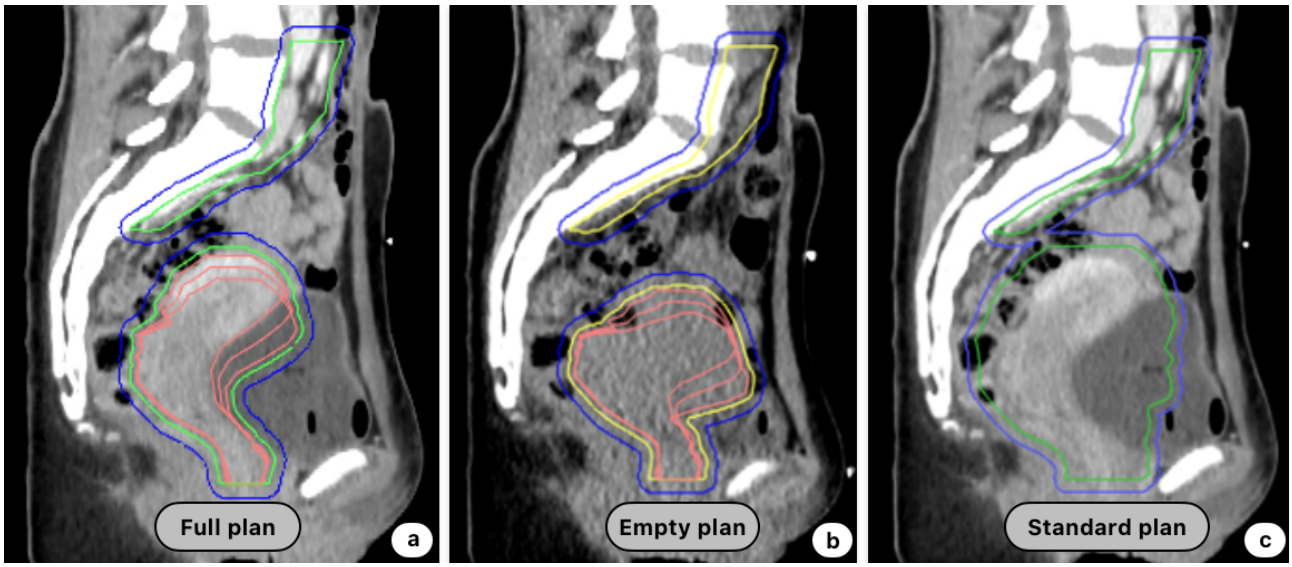


Figure 16: Illustration of the CTV, ITV and PTV according to the POD study procedure. Pink lines in image a and b represent the full, empty, and intermediate positions of the CTV, created with DIR and python script in RayStation® TPS. A 3mm margin is added to create the ITV (a: green, b: yellow), and additional 5mm to the PTV (blue). Image c represent the Standard plan that covers the full movement of the CTV with an added 10 mm margin (5 mm laterally) to create the ITV (green). A 5 mm margin is added to the ITV to create PTV (blue). CT images from RayStation® TPS, with permission from patient.

2.8.1.3 Treatment planning:

All treatment planning is performed in RayStation® TPS. For the intervention arm a plan library is prepared with three treatment plans (Figure 17). Two PotD treatment plans are created: "Full plan" take into account uterus position for half full - full bladder volume and "Empty plan" take into

account uterus position for half full - empty bladder volume. A Standard plan that covers the full uterus motion from the full- and empty bladder CT scan (motion robust plan) is also prepared. From each of the three plans, the 95% isodose line (42.75 Gy) is created as a structure volume to be overlaid and visualized on the CBCT image for daily plan selection.

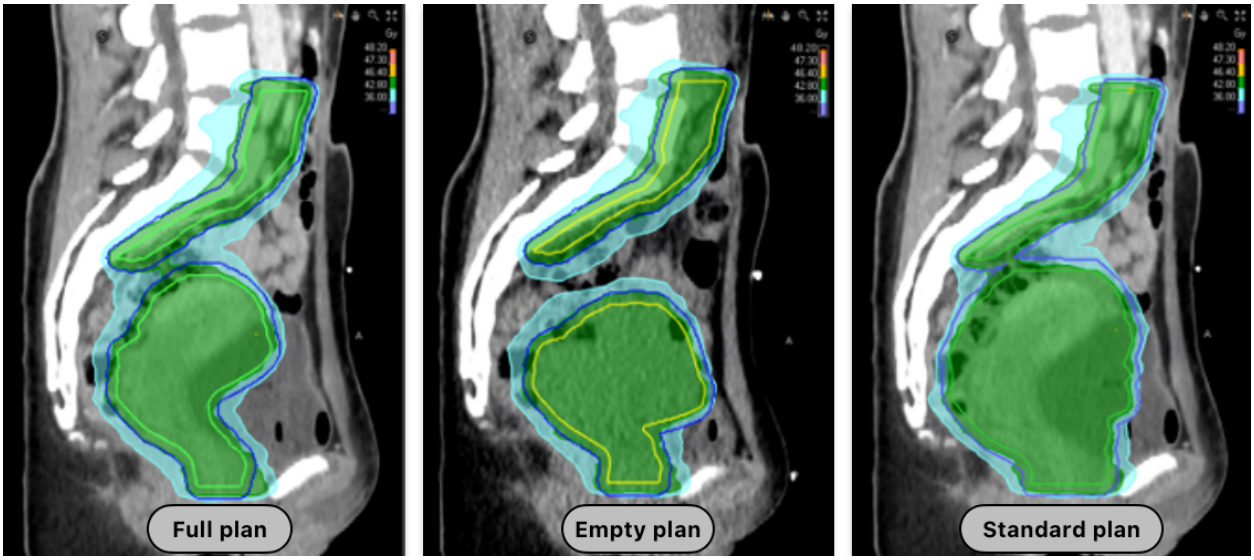


Figure 17: Illustration of the PotD plan library containing three treatment plans: Full, Empty and Standard plan. The 95% isodose line (green) from each plan is overlaid on the CBCT image for daily plan selection. CT images from RayStation® TPS, with permission from patient.

The full bladder CT with intravenous contrast is used for treatment planning. All treatment plans are generated in RayStation® TPS with dual arc VMAT technique for a Varian TrueBeam® linear accelerator, Millennium 120MLC® (Varian Medical Systems INC., Palo Alto, CA) with 6MV photon energy.

All VMAT plans follow planning aims from OUH guidelines. The control arm follow the standard guidelines for cervical cancer (Appendix 3), and the intervention arm follow the Plan-of-the-Day guidelines for cervical cancer (Oslo University Hospital, 2023a). Table 2 contain planning aims for target volumes for both the Standard and PotD plans. The planning aims that only apply for PotD are marked with an asterisk (*). Planning aims for OAR are identical for the two treatment strategies and is summarized in Table 3.

Table 2: Planning aims for target volumes. Definitions: D_{min}; minimum dose to the volume, D_{max}; maximum dose to a point in the volume, D_V; dose that a volume of a structure/organ receives or exceeds, V_D; volume of a structure/organ receiving more than or equal to dose.

Volume	Hard dose constraints	Soft dose constraints
ITV_45 ITV_45_Full* ITV_45_Empty*	D_{Min} > 95% (42.8Gy)	D_{Max} < 107% (42.8Gy) **
PTV_45 PTV_45_Full* PTV_45_Empty*	$V_{95\%}$ > (42.8Gy) D_{Max} < 107% (42.8Gy) **	$V_{95\%}$ > (42.8Gy)
CTVn	D_{98} > 100% of prescribed LN dose	D_{50} > 102% of prescribed dose
PTVn	D_{98} > 90% of prescribed LN dose D_{Max} < 107% of prescribed LN dose	
xCTVp_HR+10 (help contour)		D_{Max} < 103% (46.4Gy)
Conformity index		1.10 (V42.8Gy/Vol PTV) 1.55 (V36.0Gy/Vol PTV)

*Volumes are only used for patients in the POD intervention arm (PotD)
**If SIB to lymph node (LN), D_{max} < 107% of prescribed LN dose.

Table 3: Planning aims for organs at risk.

	Without boost to lymph nodes		With boost to lymph nodes	
Organ	**Hard dose constraints**	**Soft dose constraints**	**Hard dose constraints**	**Soft dose constraints**
Bowel	D_{Max} < 105% (47.3Gy)	V_{40Gy} < 250cm^3 * V_{30Gy} < 500cm^3 *	D_{Max} < prescribed LN dose D_{Max} < 47.3Gy (in areas 10–15 mm outside PTVn)	Pelvic irradiation: V_{40Gy} < 250cm^3 * V_{30Gy} < 500cm^3 * Para-aortic irradiation: V_{40Gy} < 300cm^3 * V_{30Gy} < 650cm^3 *
Sigmoid	D_{Max} < 105% (47.3Gy)		D_{Max} < prescribed LN dose D_{Max} < 47.3Gy (in areas 10–15 mm outside PTVn)	
Bladder	D_{Max} < 105% (47.3Gy)	V_{40Gy} < 60% * V_{30Gy} < 80% *	D_{Max} < prescribed LN dose D_{Max} < 47.3Gy (in areas 10–15 mm outside PTVn)	V_{40Gy} < 60% * V_{30Gy} < 80% *
Rectum	D_{Max} < 105% (47.3Gy)	V_{40Gy} < 75% * V_{30Gy} < 95% *	D_{Max} < prescribed LN dose D_{Max} < 47.3 Gy (in areas 10–15 mm outside PTVn)	V_{40Gy} < 75% * V_{30Gy} < 95% *
SpinalCord	D_{Max} < 48Gy		D_{Max} < 48Gy	
FemoralHead	D_{Max} < 50Gy		D_{Max} < 50Gy	
Kidney	D_{Mean} < 15Gy	D_{Mean} < 10Gy Quantec ** V_{12Gy} < 55% V_{20Gy} < 32% V_{23Gy} < 30% V_{28Gy} < 20%	D_{Mean} < 15Gy	D_{Mean} < 10Gy Quantec ** V_{12Gy} < 55% V_{20Gy} < 32% V_{23Gy} < 30% V_{28Gy} < 20%

Body	D_{Max} < 107% (48.2Gy)		D_{Max} < 48.2Gy (in areas 10–15 mm outside PTVn)	
Duodenum (optional)	V_{55Gy} < 15 cm^3		V_{55Gy} < 15 cm^3	

**Soft constraints that can be used as optimization constraints. They are not supposed to be fulfilled by all patients as they are not based on clinical evidence, but rather around 70-80% of the patients.

2.8.2 Treatment phase:

For the course of EBRT treatment, the patients in both study arms follow a standard drinking protocol prior to their daily treatment. The drinking protocol implies that the patient is to void her bladder 60 minutes before each treatment, then drink two glasses of water (approximately 300 ml) (Appendix 3) and (Oslo University Hospital, 2023a). Prior to every treatment, a CBCT is acquired and registered to the planning CT on bony anatomy to assess and correct patient positioning. Soft tissue visualization on the CBCT is used to evaluate the position of the target volume (CTV) with focus on uterus and cervix. For patients in the control arm the Standard treatment plan is used for every treatment fraction. For patients in the intervention arm the soft tissue anatomy on CBCT, together with visualization of the 95% isodose lines from the three treatment plans in the plan library, is used to select the most suitable PotD plan for that day. The aim in the intervention arm is to primarily choose between the Full and Empty treatment plan, and only consider using the Standard plan as backup if the two other plans does not have optimal target coverage.

2.8.3 Endpoint of the POD study:

The objective of the POD study is to investigate if a PotD strategy results inn less patient reported acute gastrointestinal toxicity. The primary endpoint is patient reported diarrhea during and at the end of EBRT treatment. Secondary endpoints are local control, other acute and late toxicity, and quality of life. The total time consumption for the two treatment arm procedures will also be registered, as the intervention arm is estimated to be more time consuming.

3 Material and methods

3.1 Patients

This is a retrospective project that includes 10 LACC patients treated in the POD study (REK ref. nr 2021/236807) (Appendix 1). The patients have received curative chemo-radiotherapy treatment at OUH during 2022 and 2023. In the POD study, six of the patients were randomized to the intervention arm and treated with PotD, and four in the control arm treated with a Standard plan. All 10 patients have completed their treatment with 25 fractions of EBRT with weekly concomitant chemotherapy, followed by four fractions of brachytherapy. The treatment planning and plan simulation in this project follow local guidelines (Appendix 3) and (Oslo University Hospital, 2023a), in accordance with the POD study protocol.

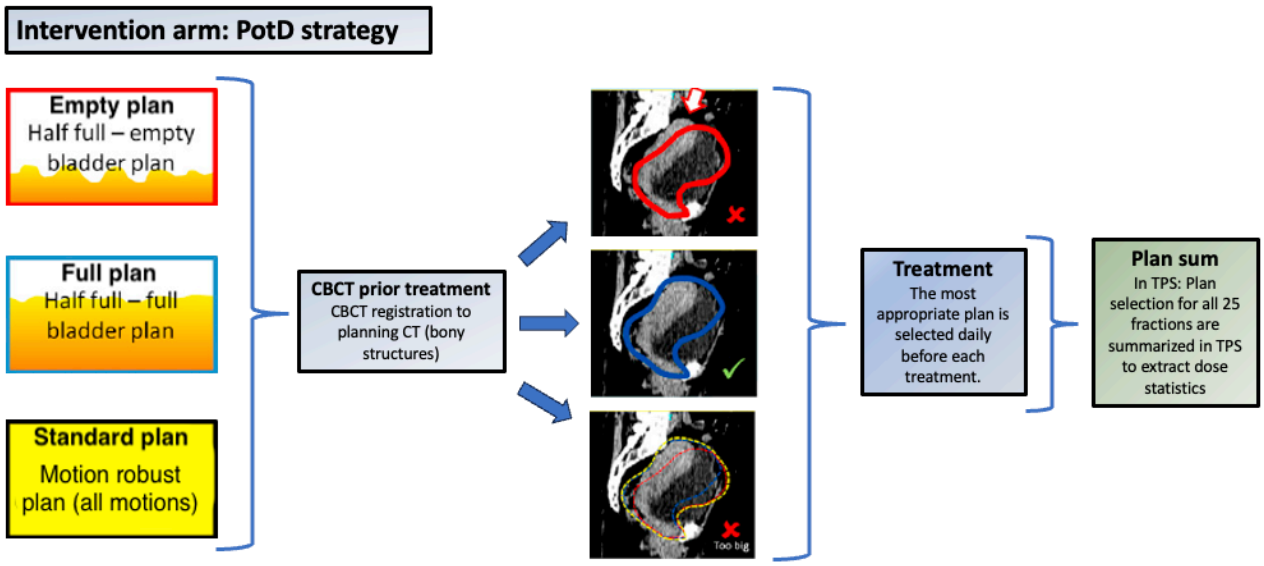
3.2 Project study design

The total dataset in this master's thesis project consists of two planning CTs, one MRI, three treatment plans and 25 CBCTs (one from each fraction of EBRT treatment), for each of the 10 patients. In total, the dataset contains 280 image sets and 30 treatment plans.

This project will investigate if, and to what extent, PotD treatment is able to reduce the total irradiated volume compared to Standard treatment. All 10 patients have completed their radiotherapy treatment either in the intervention- or control arm (25 fractions) and had daily CBCT scans before each treatment for control of patient positioning and soft tissue anatomy (uterus and cervix) in the pelvic region. All CBCT images for each of the 10 patients was imported into RayStation® TPS. Patients in the different POD study treatment arms will not be compared against each other. Instead, two PotD plans, and a standard plan will be compared for all the 10 patients, irrespectively of the treatment they received. Then each patient will serve as its own control, to avoid differences between the treatment arms related to patient anatomy, tumor size, SIB to lymph node(s), and pelvic field vs para-aortic field.

The retrospective treatment planning and plan simulation performed in this project followed different workflows based on which treatment arm the patient was randomized to in the POD study. The two workflows are illustrated in Figure 18 and 19, and are described below:

Intervention arm: Patients in the intervention arm had a complete plan library with two PotD plans (Full plan and Empty plan) and one Standard plan (Figure 18). As part of the PotD strategy, the daily plan selection was based on patient anatomy visualized on daily on CBCT. The Standard plan was already a part of the plan library for patients in the intervention arm, therefore no new treatment plan had to be created in this project for these patients. Instead, 25 fractions of the Standard treatment plan were simulated retrospectively and compared to a plan sum of 25 fractions of the PotD treatment that the patient in the intervention arm received. Both the plan sum and comparison of dose statistics was performed in RayStation® TPS. A plan sum for PotD treatment comprises of a summation of the daily selected treatment plans from the plan library, for each of the 25 fractions in a treatment course. Which plan is chosen for each treatment, as described previously, is individual and based on patient anatomy on daily CBCTs (illustrated in Figure 18). As an example, for one patient, the Full plan was selected for 9 fractions, Empty plan for 11 fractions and Standard plan for 5 fractions. A PotD plan sum in RayStation® TPS for this patient will therefore contain a summation of Full plan x 9, Empty plan x 11 and Standard plan x 5 = 25 fractions. This type of PotD plan sum was created for each of the 10 patients and compared against 25 fractions of treatment with the Standard plan.



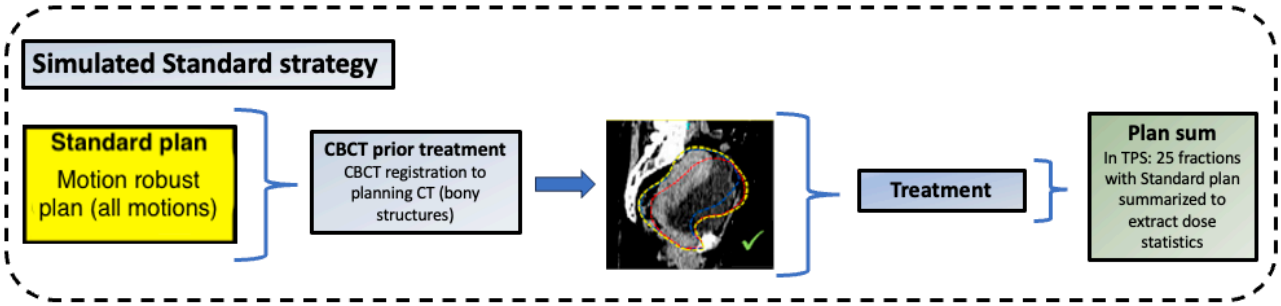
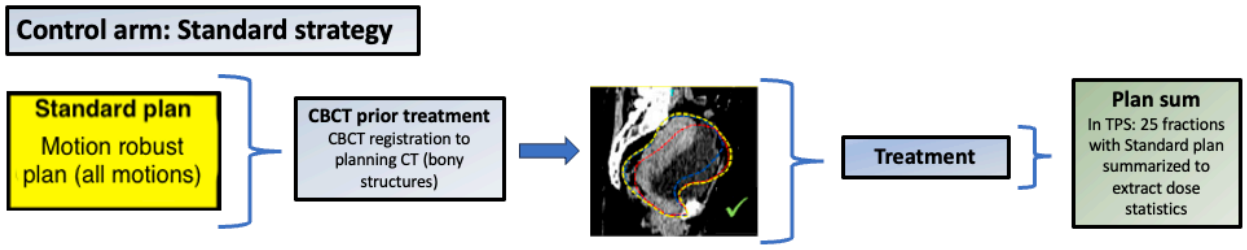


Figure 18: The top figure demonstrates the treatment workflow for patients in the intervention arm in the POD study treated with PotD. The bottom figure (dashed line) demonstrates the simulated workflow if the same patients was only treated with the Standard plan.

Control arm: Patients in the control arm was treated with only one Standard treatment plan. In order to simulate a PotD treatment, new target volumes had to be delineated according to OUH guidelines for radiotherapy planning with PotD (Oslo University Hospital, 2023a). The delineated CTV volumes, DIR and creation of intermediate CTV positions are described previously in more detail in chapter 2.8.1.2 and Appendix 4. Two treatment plans were created retrospectively in order to simulate a PotD treatment (Figure 19); Full plan (covering half full-full bladder volume) and Empty plan (covering half full-empty bladder volume). The PotD plans was created using the same number of treatment fields, position of the isocenter and roughly the same MU, as the already existing Standard plan. The target volume delineation and each of the new treatment plans was evaluated and approved by an oncologist. Based on soft tissue visualization on daily CBCTs that was acquired during patient treatment, and imported into the TPS, the daily plan selection according to the PotD workflow was simulated retrospectively. A plan sum for 25 fractions of PotD treatment strategy (as described previously) was then created and compared to a plan sum for 25 fractions of the Standard treatment plan, that the patients in the control arm received.



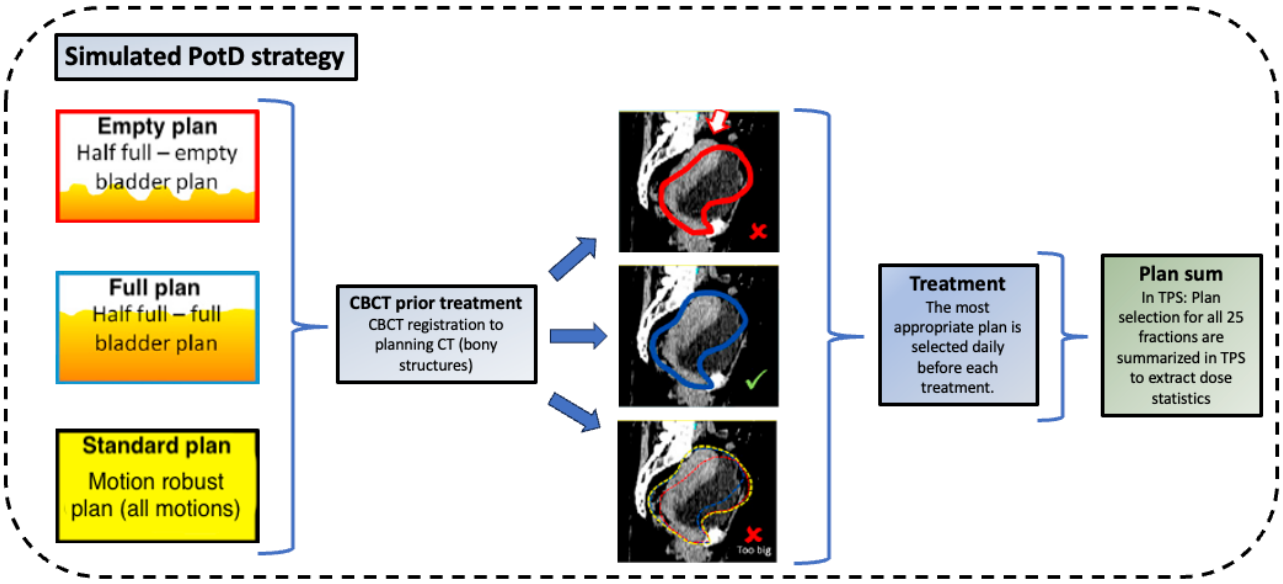


Figure 19: The top figure demonstrates the treatment workflow for patients in the control arm in the POD study treated with a Standard plan. The bottom figure (dashed line) demonstrates the simulated workflow if the same patient group was treated with the PotD strategy.

3.3 Plan comparison and statistical analysis

Radiotherapy treatment plans following the PotD strategy and Standard strategy was compared quantitative. To investigate if there was statistical difference in total irradiated volume between PotD and Standard treatment, data from plan summations was extracted from the TPS. A plan sum of the PotD treatment is individual and will for each patient contain a variation of Full, Empty and Standard plan selected "x" number of times over 25 fractions (illustrated by dashed line in Figure 19). For the Standard treatment, a plan sum will contain only the Standard plan for all 25 fractions. The patients in this project served as their own control, as they all had two PotD plans and a Standard plan each to be used for comparison and statistical analysis, irrespectively of the treatment they received.

3.3.1 Statistical analysis

Data from the plan summations was collected from dose-volume-histogram (DVH) in RayStation® TPS. The total volume (cm^3) of tissue within the patient to receive radiation dose of 42.8 Gy ($V_{42.8\ Gy}$), 40 Gy ($V_{40\ Gy}$), 30 Gy ($V_{30\ Gy}$) and 20 Gy (V_{20Gy}) was be extracted from DVH for both PotD treatment and Standard treatment. These dose volumes parameters are inspired from Buschmann

et al. (2018) and are also found in OUS guidelines for treatment planning aims to target volumes (Table 2) and organs at risk (Table 3). In addition, the PTV volume (cm^3) for Standard, Full and Empty plan was extracted from plan statistics for each patient.

Statistical analysis was performed in IBM SPSS Statistics for Mac version 29.0.

3.3.2 Wilcoxon matched pair signed ranks test

The analysis was of paired data. For each patient the same data point, volumes receiving a defined radiation dose, was collected from two treatment plans (PotD and Standard), creating paired data. This was also performed for the PTV volume, where the PTV from Standard plan was compared against the PTV volume for Full and Empty plan, respectively. These data are non-parametric and does not follow normal distribution (Aalen et al., 2018, pp. 179-202). Statistical analysis with Wilcoxon matched paired signed rank test was performed, where a p-value of <0,05 was considered significant (Pallant, 2020, pp. 221, 240-242) This analysis could answer if there are any significant differences in PTV volume and total irradiated volume, between Standard- and PotD radiotherapy treatment for LACC patients.

3.4 Research ethics and privacy

The patient selection in this master's thesis project consists of 10 patients included in the POD study. The POD study is a prospective randomized controlled trial for Plan-of-the-Day approved by the Regional Ethics Committee (REK ref. no. 2021/236807) (Appendix 1). This project is a preliminary project within the POD study. All 10 patients have provided a written consent to participate in the POD study (Appendix 2).

The dataset used in this project has been pseudo anonymized and is stored in RayStation® TPS where access is restricted for selected employees at OUH with username and password. Any collected data for analysis is stored digital in a secure folder for sensitive information at OUH. The encryption key is kept separate from the dataset in a locked cabinet. It was never necessary to retrieve any of the patients' identity or to have insight in their electronic patient record.

All 10 patients have completed their radiotherapy treatment at OUH. Any new treatment plans created for this project was done retrospectively and will not have any effect on the patients' treatment. The new treatment plans will only be used for simulation and comparison and will not be used for clinical radiation treatment.

4 Results

A total of 10 patients were included in this project. Six of the patients were randomized to the intervention arm (PotD) in the POD study, and four in the control arm (STD) (Table 4). Four out of 10 patients (40%) had pathological lymph node(s) and was treated with SIB. Two patients had pathological lymph node(s) only in the pelvis (internal and/or external iliac) and received SIB dose of 55 Gy. The two other patients had also pathological lymph nodes outside the pelvis (to the common iliac and/or para-aortic) that received 57.5 Gy in addition to 55 Gy to the lymph nodes in the pelvis (internal and/or external iliac). The presence of more than two pathological lymph nodes resulted in para-aortic irradiation for three of the 10 patients (30%). The average PTV volume for all 10 patients was 1415 cm^3 (range 1124 – 1906 cm^3), and the average tip of uterus (ToU) motion was 5,1 cm (range 4 – 7,1 cm). Replanning was performed for five patients (50%). Of these five patients, four patients were in the intervention arm.

Table 4: Description of patient cohort; PotD: Plan-of-the-Day; STD: Standard treatment plan; Full: Full plan; Empty: Empty plan; ToU: tip of uterus; SIB: simultaneous integrated boost; LN: lymph node.

Subject ID	Treatment arm	PTV volume (cm^3) STD	PTV volume (cm^3) Full	PTV volume (cm^3) Empty	ToU motion (cm)	Para-aortic irradiation (yes/no)	SIB to LN (number)	Dose level to LN (55Gy/57.5Gy)	Re-planning
1	PotD	1647	1518	1499	4.7 cm	Yes	Yes (8)	55 Gy (5) + 57.5 Gy (3)	No
2	STD	1424	1299	1347	4.7 cm	No	No	-	No
3	STD	1494	1354	1303	4.6 cm	No	No	-	Yes
4	PotD	1906	1706	1709	4.0 cm	Yes	Yes (4)	55 Gy (2) + 57.5 Gy (2)	No
5	PotD	1273	1124	1125	5.3cm	No	No	-	Yes
6	PotD	1323	1141	1129	5.4 cm	No	No	-	Yes
7	PotD	1283	1142	1166	4.5 cm	No	No	-	Yes
8	STD	1445	1273	1273	5.8 cm	No	No	-	No
9	PotD	1667	1454	1481	7.1 cm	Yes	Yes (3)	55 Gy	Yes
10	STD	1749	1578	1607	5.6 cm	No	Yes (1)	55 Gy	No

4.1 PTV volume (cm^3)

The boxplot in Figure 20 shows the difference in PTV volume (cm^3) for the Standard plan, Full plan, and Empty plan. The average PTV volume was 1521 cm^3 (range 1273 – 1906 cm^3), 1359 cm^3 (range 1124 – 1706 cm^3) and 1364 cm^3 (range 1125 – 1709 cm^3) for the Standard-, Full- and Empty plan, respectively. A Wilcoxon Matched Pair Signed Ranks Test revealed a statistically significant (p <0.005) reduction in PTV volume for Full and Empty plan, compared to Standard plan. The average reduction in PTV volume was 162 cm^3 (range 125 – 212 cm^3) between Standard plan and Full plan, and 157 cm^3 (range 77 – 197 cm^3) between Standard plan and Empty plan.

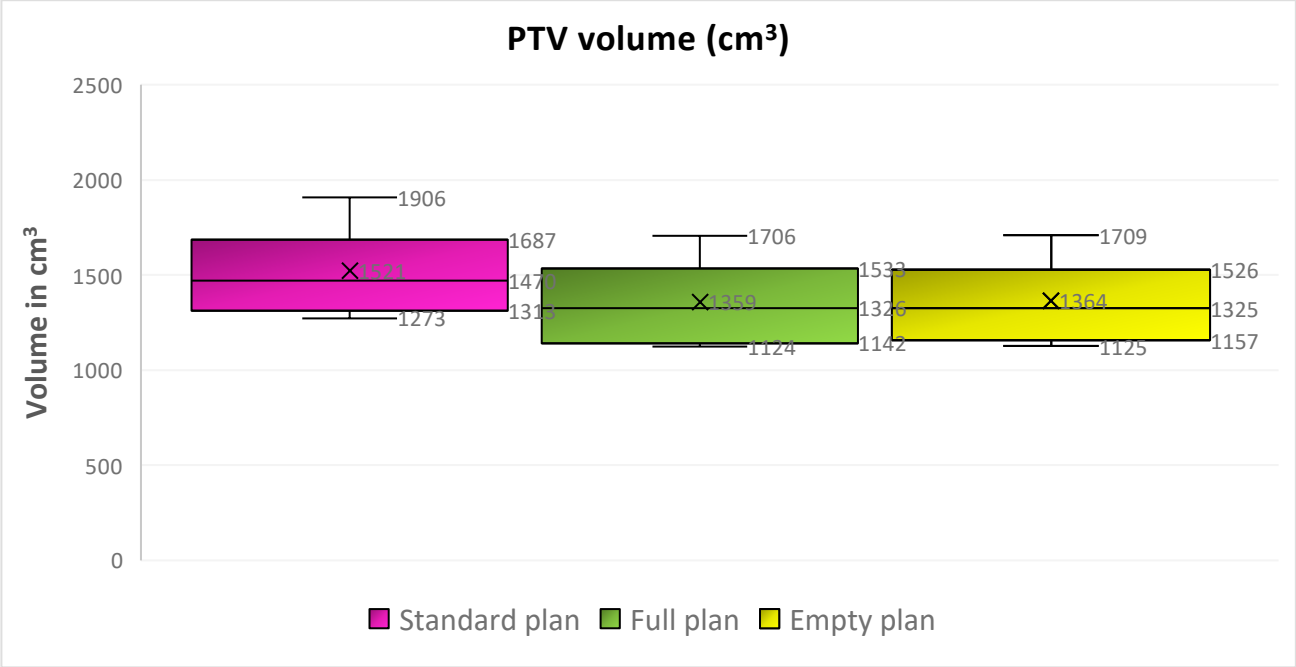


Figure 20: Boxplot of the PTV volume (cm^3) for Standard plan, Full plan, and Empty plan. Colors in the boxplot reflects color coding according to OUH guidelines for PotD (Oslo University Hospital, 2023a).

4.2 Plan-of-the-Day plan selection

In Figure 21 the PotD plan selection for all 10 patients and treatment fractions is demonstrated. The patients were each treated with 25 fractions of EBRT, resulting in 250 fractions in total. The Full and Empty plan was selected 42% (105) and 41.6% (104) of the treatment fractions, respectively. Standard plan was selected for 41 fractions (16.4%).

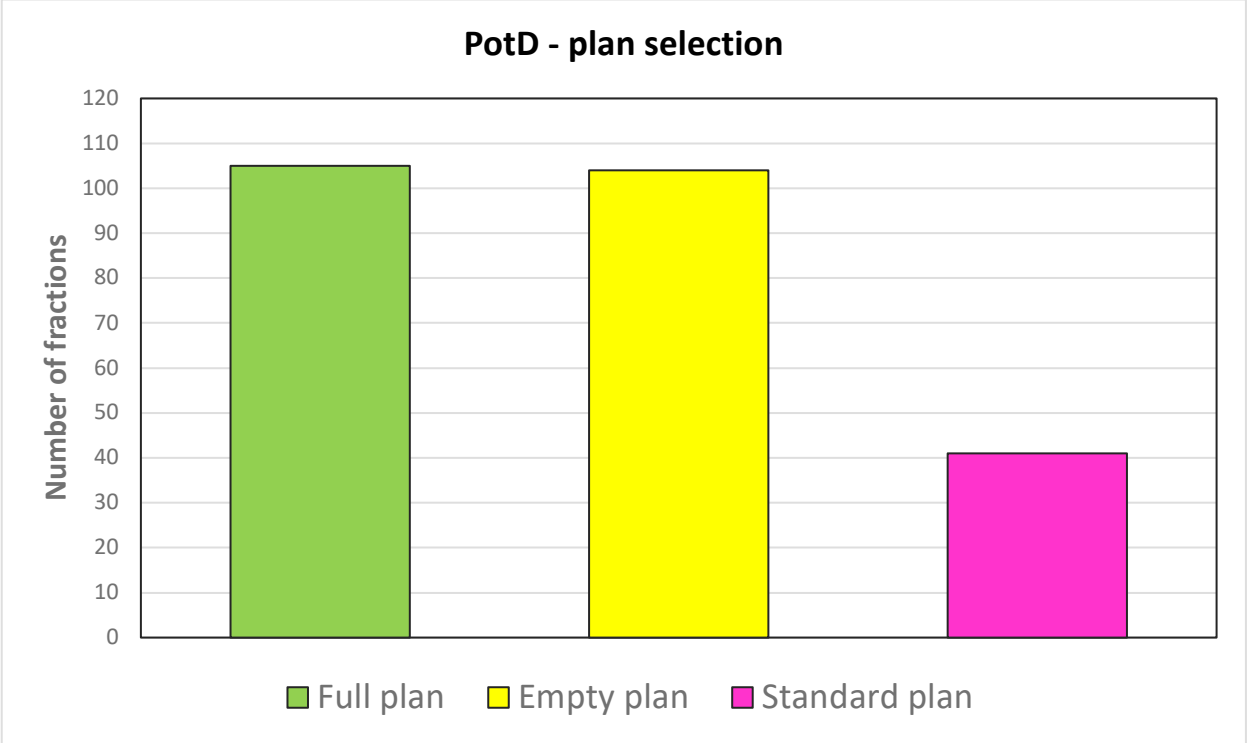


Figure 21: Summarized PotD plan selection frequency for the total treatment course for all 10 patients (25 fractions for each patient = 250 fractions in total). Colors in the column chart reflects color coding according to OUH guidelines (Oslo University Hospital, 2023a).

Figure 22 shows the weekly PotD plan selection frequency during each of the five treatment weeks, summarized for all patients. Full plan was selected more frequently during week one and two (44% and 46%), compared to Empty plan (26% and 36%) and Standard plan (30% and 18%). Empty plan was selected most frequently during week three, four and five (54%, 50% and 42%). The selection of Standard plan was most frequent in the first week (30%) and was then reduced to 18%, 2%, 12% and 20% for week two, three, four and five respectively. Replanning was performed for five patients (50%) after the first week, four of these patients was in the intervention arm in the POD study and treated with PotD (Table 4). New treatment plans were on average ready for treatment for the 8th

fraction (7 – 9). For the one patient in the control arm that needed replanning, the simulated PotD plans (Full and Empty plan) for the same patient did not need replanning.

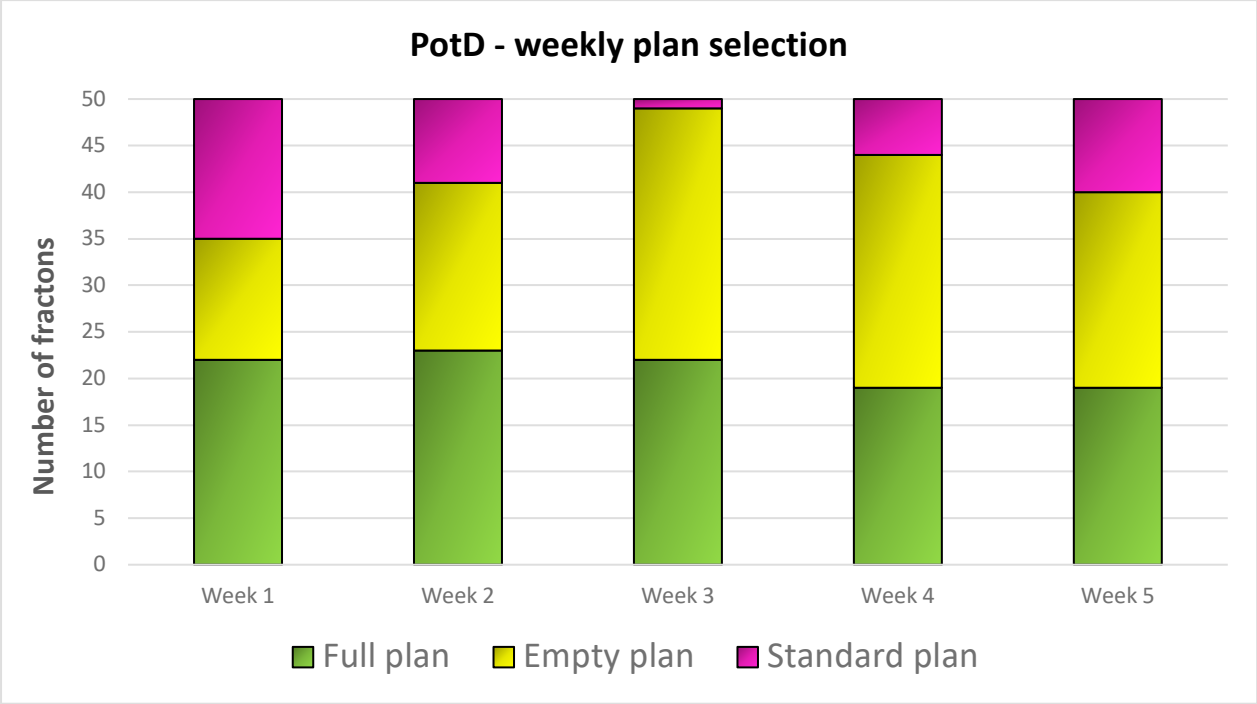


Figure 22: Weekly PotD plan selection frequency summarized for all 10 patients (5 fractions over 5 weeks for each patient, in total 50 fractions per week). Colors in the column chart reflects color coding according to OUH guidelines (Oslo University Hospital, 2023a).

Figure 23 shows the PotD plan selection per patient over the course of EBRT treatment (25 fractions). For five patients the Full plan was selected most frequently, while for the remaining five patients the Empty plan was most frequently selected. The Standard plan was selected for eight patients, and on average for five (out of 25) fractions. For two patients, ID 6 and 9, the Standard plan was selected over 30% of the total treatment fractions (9/25 and 8/25 fractions). For two other patient, ID 1 and 8, the Standard plan was never selected during their treatment course.

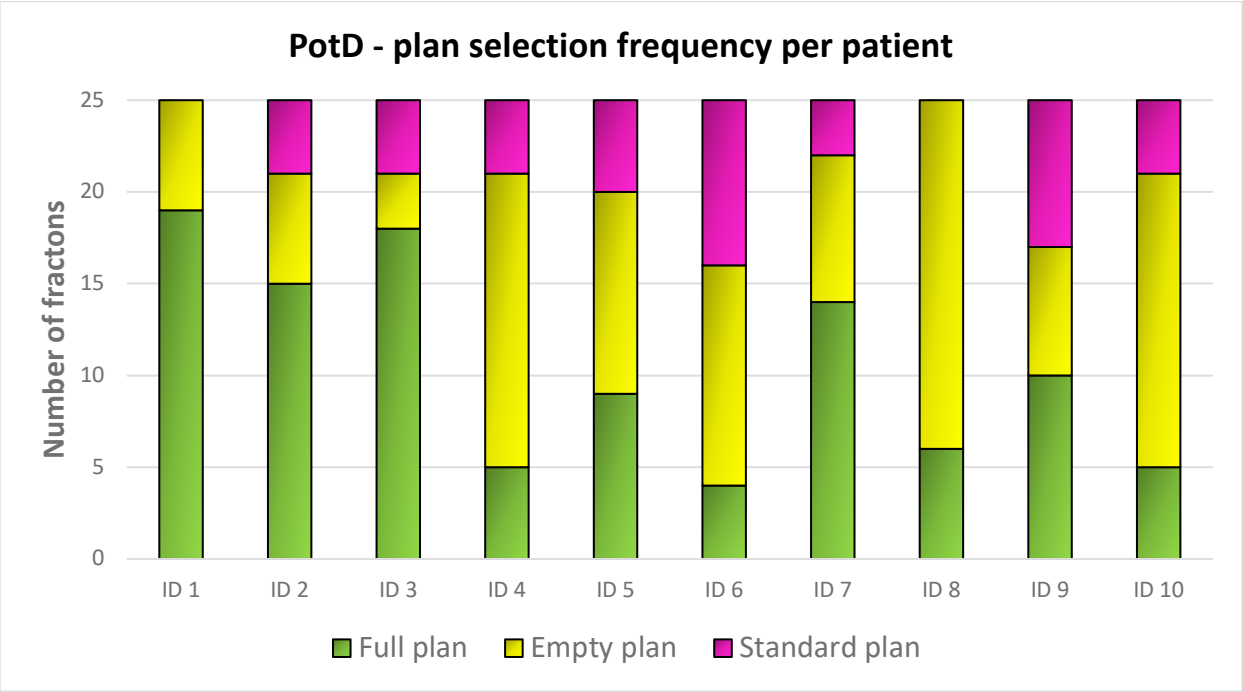


Figure 23: PotD plan selection frequency per patient for the whole treatment course of 25 fractions. Colors in the column chart reflects color coding according to OUH guidelines (Oslo University Hospital, 2023a).

4.3 Total irradiated volume (cm^3)

The boxplot in Figure 24 shows the difference in total irradiated volume between Standard and PotD treatment for several dose levels. The volume of the 95%-isodose (42.75 Gy) was on average reduced with 141 cm^3 (range 102 – 209 cm^3) with the PotD treatment compared to the Standard treatment. The volume of the 40 Gy-, 30 Gy- and 20 Gy-isodose was on average reduced with 119, 111 and 156 cm^3, respectively, with PotD treatment.

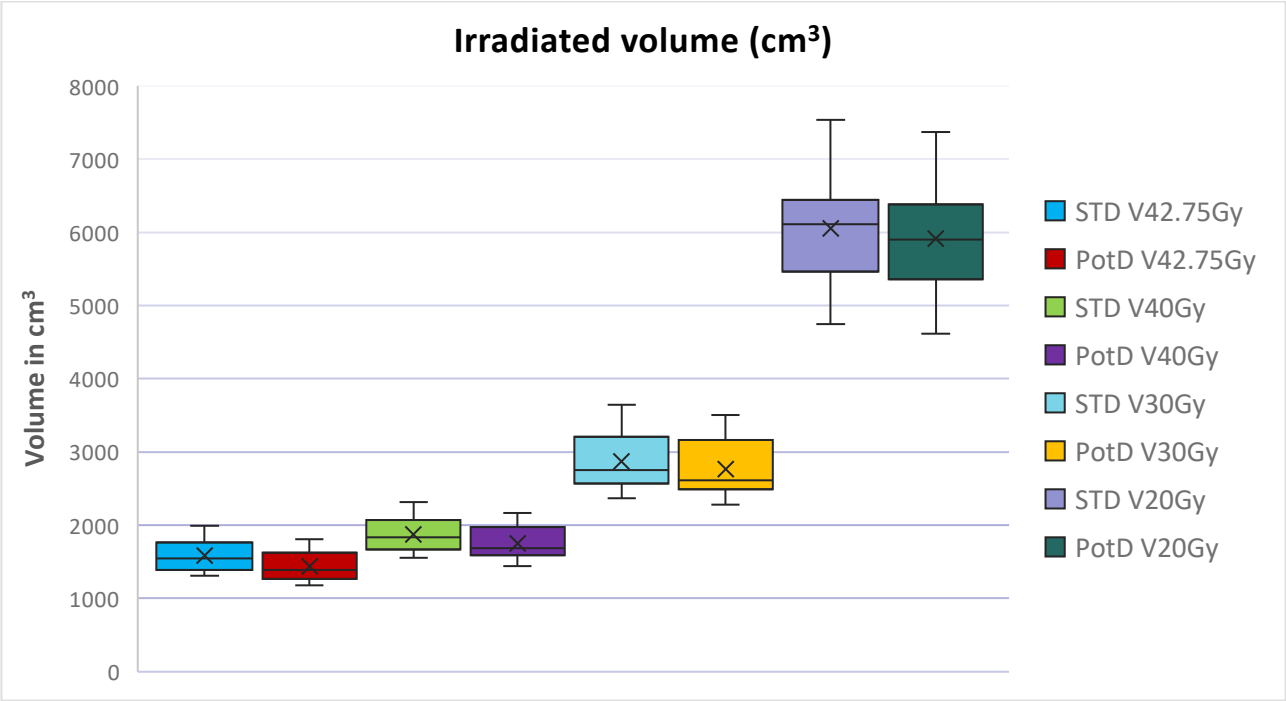


Figure 24: Boxplot showing the difference in irradiated volume between Standard and PotD treatment at different dose levels. STD: Standard treatment plan; PotD: Plan-of-the-Day treatment.

A Wilcoxon Matched Pair Signed Ranks Test revealed a statistically significant reduction in median $V_{42.75\ Gy}$ between Standard and PotD treatment (p <0.005) (Table 5). The median volume (cm^3) was reduced with 154 cm^3 from Standard (Md = 1544 cm^3) to PotD treatment (Md = 1390 cm^3). Significant reduction was also found for the median $V_{40\ Gy}$, $V_{30\ Gy,}$ and $V_{20\ Gy}$, where PotD treatment resulted in 148 cm^3, 146 cm^3 and 209 cm^3 reduction, respectively, compared to Standard treatment.

Table 5: Statistics on total irradiated volume (body) at different dose levels. V_D is defined as the volume (cm^3) receiving the defined dose (Gy) or more. Diff. refers to the median differences between Standard and PotD treatment (Diff. > 0 if PotD > Standard).

			Standard		PotD			
Volume	Parameter	Unit	Median	Range	Median	Range	Diff.	*p*-value
Body	$V_{42.75\ Gy}$	cm^3	1544	1305-1992	1390	1175-1808	-154	<0.005
Body	$V_{40\ Gy}$	cm^3	1834	1554-2312	1686	1442-2163	-148	<0.005
Body	$V_{30\ Gy}$	cm^3	2754	2367-3646	2608	2281-3505	-146	<0.005
Body	$V_{20\ Gy}$	cm^3	6113	4744-7538	5904	4619-7373	-209	<0.007

5 Discussion

In this project a PotD strategy was compared with a Standard single treatment plan for 10 patients included in the POD study at OUH. In the POD study, six of the patients was included in the intervention arm and received PotD treatment. Four patients were included in the control arm and was treated with a Standard treatment plan.

To facilitate the comparison between PotD and Standard treatment in this project, new treatment plans was created and simulated retrospectively, depending on which treatment arm the patients was included in. For patients in the intervention arm, a treatment course (25 fractions) with a Standard treatment plan was simulated. For the patients in the control arm, a PotD treatment course (25 fractions) was simulated. The dataset consists of two planning CTs, an MRI scan, three treatment plans (Full, Empty and Standard plan) and 25 CBCTs per patient. In total, 30 planning image sets, 30 treatment plans and 250 CBCTs was used for treatment planning, simulation, comparison, and analysis.

In this chapter the results from this project, and the clinical relevance, will be assessed and evaluated against scientific studies. The difference in PTV volume, PotD plan selection frequency and difference in total irradiated volume will be discussed in subchapters. Possible future improvements to a PotD strategy, including automatic planning and online ART, will briefly be discussed in the last subchapter.

A Standard treatment plan in radiotherapy has various terms in different clinical studies, e.g., non-adaptive plan, robust plan, motion robust plan, backup plan. They basically mean the same, radiotherapy treatment with one single treatment plan. For simplicity, the term Standard plan is used throughout this chapter.

5.1 PTV volume (cm^3)

In this project, the average PTV volume for the Standard plan was 1521 cm^3 (Figure 20). Compared to the Standard plan, a significant reduction (p <0.005) in average PTV volume was found for both the Full plan and Empty plan, with an average reduction of 162 cm^3 and 157 cm^3, respectively. A

similar reduction in average PTV volume was found in a study by van de Schoot et al. (2017), where the average PTV volume was decreased from 1601 cm^3 for Standard strategy to 1487 cm^3 for the adaptive strategy with PotD, resulting in a decreased average PTV volume of 114 cm^3. A larger reduction in PTV volume was reported in a recent study by Reijtenbagh et al. (2023), who found a theoretical median PTV volume reduction from 841 to 593 cm^3 (248 cm^3) by using a PotD library strategy compared to single Standard plan approach. This is almost 100 cm^3 more than the average reduction found in this project. A possible reason for the larger volume reduction might be a different strategy (and use of margins) for creating PTV in the Standard plan (motion robust backup plan). In the study by Reijtenbagh et al. (2023), safety margin of 15 mm in all directions (10 mm caudal direction) was added to the ITV and elective CTV to create the PTV. In comparison, only a 5 mm margin was added to the same volumes to create PTV for the Standard plan in this project. van de Schoot et al. (2017) added a 10 mm margin from the primary CTV, and 8 mm margin from elective CTV, to create a PTV. The different strategies for creating PTV for the Standard plan, will result in difference in the total PTV volume. As this PTV volume is compared against the PTVs in the PotD strategy, it might explain the differences seen in median PTV volume reduction between this project and the study by Reijtenbagh et al. (2023). The larger the PTV is in the Standard plan, the larger reduction can be found using PotD.

Reducing the PTV margin; i.e. reducing the PTV volume, will result in significant reduction in median dose to OARs such as bladder, rectum and sigmoid as well as for volume of OARs receiving ≥90% of prescribed dose (Lim et al., 2009). Even though Lim et al. (2009) did not investigate PotD, the reduction in average PTV volume is very relevant for the PotD strategy and can hopefully result in similar reductions in dose to OARs. A study by Bondar et al. (2012) showed that using a PotD strategy, compared to Standard plan strategy, significantly reduced the percentage of rectum and bladder volume inside the PTV and therefor better sparing of these organs. This was also reported in a recent study by Reijtenbagh et al. (2023) where PotD strategy lead to a median decrease of 71 cm^3 and 23 cm^3 in PTV overlap with bladder and rectum, respectively, when compared to Standard treatment. In this project a significant reduction in average PTV volume was found for both Full and Empty plan when compared to the Standard plan. As the reduction in PTV volume has been showed to reduce dose to OARs, such as bladder and rectum, it is anticipated that the PotD strategy in this project can result in similar reduction of dose to these OARs. The possible benefits from the reduced PTV volume depends on plan selection during PotD treatment and how frequently Full and

Empty plans are used for treatment. The plan library in the PotD strategy also includes a Standard plan, that can be used as a backup plan if neither Full nor Empty plan cover the target volume (cervix and uterus) seen on CBCT. As the Standard plan has the largest PTV volume, selecting this plan during PotD treatment might counteract some of the potential for OAR sparing.

5.2 Plan-of-the-Day plan selection

In this project, the Full and Empty plans was selected 42% (105) and 41.6% (104) of all the PotD treatment fractions, respectively, while the Standard plan was selected 16.4% (41) (Figure 21). For comparison, Reijtenbagh et al. (2023) report in their study that Full plan was selected 75.5%, Empty plan 12.6%, and Standard plan 11.9%. The Empty plan was more frequently selected during the treatment course in this project, than in the study by Reijtenbagh et al. (2023) (41.6% versus 12.6%). This might indicate that some patients in this project had difficulties with bladder filling during treatment. Seppenwoolde et al (2016) reported in their study that for some patients the bladder volume during treatment was never representative of the bladder volume in the planning CT. Even though the Empty plan is part of the plan library and can be selected, guiding patients to strive for a filled bladder through the treatment course is recommended as a filled bladder > 200 ml has shown to help reduce dose to both small bowel and bladder (Wang et al., 2017). A study by Ahmad et al. (2008) found that despite having bladder filling instructions for patients, the bladder volume had a mean reduction of 71% during the treatment course compared to the volume on planning CT. Reductions might occur due to treatment side effects such as radiation cystitis, nausea and diarrhea. This coincides with findings in this project, where the selection of Empty plan was more frequent during week three to five.

The Full plan was more frequently selected during week one and two (44% and 46%) and then reduced to 38% in week four and five (Figure 22). Empty plan was selected most frequently during week three, four and five (54%, 50% and 42%), compared only to 26% and 36% in week one and two, respectively. These findings can be explained by the findings regarding bladder filling in the study by Ahmad et al. (2008) mentioned above. They are also consistent with the results from Heijkoop et al. (2014) where the Full plan was also selected most frequently during the first half of the treatment course (45%) compared to the second half (35%). The Empty plan was selected 51.2% during the second half of the treatment course. Buschmann et al. (2018) also reported in

their prospective study that the Empty plan was more frequently used during the end of the treatment course, from 49% in the first week to 78% in the last week. Both studies, and result from this project show the same tendencies in increased selection of Empty plan at the second half of the treatment course due to systematic reduction in bladder volume as described earlier.

The backup plan was selected in 17% of all the treatment fractions in the study by Heijkoop et al. (2014), which is consistent with findings in this project, with Standard plan being selected 16.4% (Figure 21). In contrast, Buschmann et al. (2018) reported that the Standard plan in their study was used 20 – 30% of the fractions for the first two patients (of 9 patients) but decreased in later patients (Buschmann et al., 2018). This does not correspond to the findings in this project, where the use of Standard plan decreased from 30% the first week to 2% in the third week of treatment, but in the last two weeks, week four and five, there was an increase again with Standard plan being selected 12% and 20%, respectively. The study by Buschmann et al. (2018) specify that a learning effect was observed in their presented data, as the selection of Standard plan for treatment declined after the first to patients.

The reason for reduced selection of Standard plan during the second and third week is that replanning was performed for 50% of the patients (n = 5) after the first week. The high selection of Standard plan during the first treatment week is an indication that the organ motion seen on planning images and the DIR motion model does not encompass the motion seen on daily CBCT. New treatment plans were, on average, ready for treatment for the 8^{th} fraction (range 7 – 9). After replanning, the selection of Standard plan was reduced to 2% in the third week. A study by Reijtenbagh et al. (2023) reported that only 18% (67 of 376 patients) of a fairly large patient cohort needed replanning. Experience with the POD study at OUH revealed that the bladder catheter used for filling the bladder on planning CT also influenced the uterus position on the empty bladder CT scan, restricting the uterus to fall into a natural position. This might have affected the accuracy of the DIR and script-based model to create mid-positions of the CTV, thus not representing the target volume position during treatment. Based on these experiences in the POD study, a new procedure has been implemented where the catheter is removed before the empty bladder scan is acquired. Also, planning CTs with different bladder filling will not always represent the full extent of target volume movement (Seppenwoolde et al., 2016). Some patients will have target volume movement during the treatment course that differs from the planning CT, and these patients will benefit from

replanning based on CBCT anatomy. Replanning can consist of either adapting the already existing library plans, or by adding a plan to the library. In addition, variation in rectal filling can also influence the CTV position, especially the cervix and vaginal canal. Seppenwoolde et al. (2016) recommend that the daily CBCT, in addition to online plan selection, is analyzed offline (after treatment) to identify if the uterus/cervix motion is within the predicted model or if adaptations is needed (replanning).

The need to use the Standard plan was also more frequently at the end of treatment, from 2% in the third week to 20% in the fifth week. The increased use of Standard plan might be caused by tumor regression (shrinking) and organ motion not sufficiently covered by the pre-planned DIR motion model. Significant tumor regression can often occur in cervical cancer, up to 60%-80% of the initial tumor volume, during EBRT (Tanderup et al., 2010). This regression is most prominent in the initial three to four weeks of treatment, but the extent and pattern of regression can vary widely. A study by O'Reilly & Shaw (2016) demonstrated no significant changes in the median target volume on planning CT (211 cm^3) to the first two weeks of treatment, but they noted significant reductions from the third week of treatment (9% reduction) to the final week (18% reduction, range 5%–54%). When the tumor shrinks, there is a potential for OARs to shift into areas where higher-than-anticipated doses of radiation may be administered (Tanderup et al., 2010). Analyzing the reason for selecting the Standard plan more frequently during week four and five should be initiated as a learning process. Perhaps the DIR motion model in the treatment planning phase should be updated, or adaptations of the treatment library initiated during treatment (replanning).

5.3 Total irradiated volume (cm^3)

This project demonstrated that treatment with a PotD strategy led to a statistically significant reduction in total irradiated volume when compared to Standard treatment (Table 5). For PotD treatment, the median $V_{42.75\ Gy}$, $V_{40\ Gy}$, $V_{30\ Gy,}$ and $V_{20\ Gy}$, was reduced with 154 cm^3, 148 cm^3, 146 cm^3 and 209 cm^3, respectively, compared to Standard treatment. The reduction in total irradiated volume is larger than reported in Buschmann et al. (2018), who also found significant reduction with PotD for the volumes $V_{42.75\ Gy}$, $V_{40\ Gy}$, $V_{30\ Gy}$ with a median decrease of 87 cm^3, 74 cm^3 and 65 cm^3, respectively. They also observed that the volume sparing effect of PotD treatment diminished at low doses of 20 Gy, in contrast to the findings in this project, where a significant median

reduction of 209 cm^3 was observed for the same dose level ($V_{20\,Gy}$). The reason for the differences in median volume reduction might originate from different strategies in creating mid-positions of the CTV, as well as the use of internal margins to create the ITV. Given the highly individual approach based on patient-specific anatomy in planning images, variations in delineated target volumes and added margins may account for the observed differences in median volume reduction. A significant reduction in total irradiated volume with PotD is considered positive and beneficial for sparing dose to OARs surrounding the target volume.

Even with the use of PotD, patients still experience acute side effects from the treatment that affect their quality of life (Heijkoop et al., 2017). The acute side effects often occur in the gastrointestinal tract symptoms such as cramps, diarrhea, and incontinence, and for the urinary tract with painful urination (dysuria), increased frequency of urination and incontinence. A part for their study, Seppenwoolde et al. (2021) investigated whether there was a correlation between acute side effects with dose-volume parameters from various external radiotherapy techniques. They found a significant correlation for acute side effects, such as frequent stools, where the volume of bowel receiving 40 Gy was equal or more than 250 cm^3, rectal incontinence where the volume of rectum receiving 40 Gy was 80% or more, and urinary incontinence where the volume of bladder receiving 40 Gy was 80-90%. Among various treatment techniques, PotD demonstrated a reduction in the irradiated volume receiving 43 Gy and for the volumes of bowel and bladder receiving ≥ 40 Gy. A previous planning study reported a decrease in $V_{40\,Gy}$ for bowel of approximately 100 cm^3 with the PotD approach (Seppenwoolde et al., 2016). In this project, the dosimetric analysis revealed that the PotD strategy resulted in a considerable reduction in the total irradiated volume receiving 40 Gy, with a median reduction of 148 cm^3, which is expected to be beneficial for these OARs.

5.4 Project limitations

A previously described, this master's thesis project demonstrated a significant reduction of total irradiated volume with PotD treatment compared to Standard treatment. However, a limitation of this project is a relatively small patient cohort, comprising only 10 included patients. Several other studies have also investigating the effectiveness of PotD on patient cohorts between 10 – 20 patients, but the effectiveness in terms of OAR sparing has not been extensively studied for large patient groups (Buschmann et al., 2018; Rigaud et al., 2018; B. Rigaud et al., 2019; van de Schoot et

al., 2017). A prospective evaluation of PotD based on a large number of patients is required to determine the actual benefits in terms of tumor control and toxicity (Reijtenbagh et al., 2023). This was the motivation for initiating a prospective randomized control clinical trial on PotD with "the POD study" (Appendix 1) at OUH. The primary endpoint of the study is to compare patient reported acute diarrhea between the intervention arm (PotD treatment) and control arm (Standard treatment). The secondary endpoint includes comparison of patient and physician reported acute and late toxicities for the bowel and bladder. This study will help to answer if LACC patients benefits from PotD treatment terms of reduced toxicity.

Another limitation in this project is the lack of actual dose distribution statistics to OARs such as bladder, rectum, and bowel. As daily CBCTs are available for each patient, they could be used, together with DIR and dose accumulation, to estimate daily dose distribution to both target volume and OARs. Buschmann et al. (2018) performed in their study a dosimetric analysis to compare OAR sparing between a Standard plan and PotD. This was achieved by delineating the bladder and rectum, in addition to CTV_LR, on every CBCT scan. The daily dose from the selected PotD plan was then rigidly mapped to the CBCT. For comparison, the daily dose from the Standard plan was also rigidly mapped for every fraction. Using this method, daily DVH values for the bladder, rectum, and CTV_LR was recorded for both PotD and Standard treatment.

A different approach is to use DIR to directly compute doses on CBCT images (Chetty & Rosu-Bubulac, 2019). The process involves calculating doses for each acquired CBCT dataset, which are then mapped back to the planning CT and accumulated using the deformation vector field generated during the deformable registration of the CBCT to planning CT. However, CBCT images may suffer from poor quality due to artifacts and reduced contrast. These challenges affect the ability to establish a reliable conversion from Hounsfield Units (HU) to electron density, that is crucial for accurate dose calculation. Another complication in dose calculations on CBCT arises from the limited cranio-caudal length and field-of-view, posing difficulties in accurate dose computation and deformable mapping for certain anatomical sites. For Varian TrueBeam® linacs, the CBCT field-of-view is 16 cm in the cranio-caudal direction, resulting in CBCTs with limited anatomical information for LACC patients. This CBCT is sufficient for correcting patient setup and assess target volume position for PotD plan selection. However, is does not cover the entire target volume or OARs, a limitation that will affect the dose computation and accumulation. Other factors, such as

tumor regression, variations in normal tissue density and mass, etc., are all significant considerations that influence the accuracy of the deformable dose accumulation and must be carefully considered (Chetty & Rosu-Bubulac, 2019).

Dose accumulation based on CBCT is a labor-intensive procedure, as the target volume and OARs must be delineated on every CBCT scan for each patient. In addition, several factors make accurate dose accumulation difficult for LACC patient. With the allocated time and resources in this master's thesis project, acquiring accumulated dose to specific OARs was not feasible.

5.5 Future improvements to a PotD strategy

5.5.1 Automatic planning

The implementation of a library based PotD approach with multiple plans generated pre-treatment per patient requires an increased planning effort (Buschmann et al., 2018; Sharfo et al., 2016). The conventional manual process for generating treatment plans is time-consuming, and the outcome heavily depends on the planner's efforts, skills, and allotted planning time. This limitation hinders the widespread clinical implementation of library based PotD strategies or imposes constraints on the number of plans in a library. Notably, Sharfo et al. (2016) report in their study that the quality of automatically generated VMAT plans was found to be superior to manually generated plans, and that automatic VMAT plan generation for cervical cancer has been successfully integrated into their clinical routine. With the reduction in workload because of automatic planning, expanding plan libraries to improve OAR sparing has become feasible. A Norwegian study by Funderud et al. (2023) demonstrated a clinical implemented script-based automatic radiotherapy planning for LACC patients, resulting in acceptable target coverage and reduced mean doses to almost all OARs, when compared to clinical manually made plans. The automated script-based plans were also generated four to ten times faster than the manual plans, with an automated plan being created in 30-45 minutes.

5.5.2 Online adaptive planning

Online ART, which includes modifying the original treatment plan based on target volume positional changes in daily online imaging with, is not yet widely implemented in radiotherapy centers

(Holborn & Perry, 2019, p. 229; Lim-Reinders et al., 2017). This is because the clinical application of this approach encounter difficulties due to technological limitations (Lim-Reinders et al., 2017). The process of creating a treatment plan is time-consuming and requires a dedicated team, including radiation oncologists, dosimetrists, radiation therapists, and medical physicists, who must be ready to initiate an accelerated sequence of events for online ART to be practical. This involves daily contouring of OARs and target volumes, re-optimization of beams, and a thorough re-examination of the treatment plan for quality assurance (QA) purposes. Online ART has to be performed with the patient in the treatment position in the treatment room, but the patient cannot be immobilized for an extended period of time as this increase the risk of intrafractional movement. The implementation of online ART should therefore not significantly increase the treatment time. A study by Sibolt et al. (2021) demonstrated the feasibility of clinical CBCT-based online ART for several pelvic sites, with a median duration of 18 minutes between the approval of reconstructed CBCT to treatment delivery. The future clinical impact of online ART will depend on the availability of real-time tools for high quality soft-tissue imaging, rapid countering of target volumes and OARs, deformable soft-tissue modeling and dose accumulation, rapid radiation treatment replanning (automatic replanning) and appropriate QA of new treatment plans (Erickson et al., 2011, p. 359).

6 Conclusion

This project has demonstrated that radiotherapy treatment of LACC patients with a PotD strategy can significantly reduce the PTV volume and total irradiated volume, compared to a Standard treatment. Whether the reduction with PotD results in less patient and physician reported toxicity is currently investigated in a randomized controlled trial, the POD study, at OUH.
Future improvement for the PotD strategy would be the implementation of automatic treatment planning. This has been successfully implemented in other clinics and is a promising method for reducing the increased workload with PotD while maintaining plan quality. To further improve the radiotherapy treatment for LACC patients, development and research in online ART can in the future facilitate daily online replanning directly on the linac, making it possible to ensure target coverage and further reduced dose to OARs and healthy tissue.

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Appendix

Appendix 1: POD study protocol.

Appendix 2: POD study – Form for patient consent.

Appendix 3: OUH guideline for cervical cancer radiotherapy treatment planning.

Appendix 4: OUH user manual for PotD radiotherapy treatment planning.

Appendix 5: OUH guideline for MRI in radiotherapy treatment planning.

Appendix 6: OUH guideline for PET-CT radiotherapy treatment planning of gynecological cancer.

Appendix 7: OUH guideline for fixation and CT for PotD radiotherapy treatment planning.