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Treatment Planning for External Beam Radiation Therapy with Simultaneous Integrated Lymph Node Boost in Cervical Cancer

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Abstract

Cervical cancer with lymph node metastases has traditionally been treated with external beam radiation therapy (EBRT) to a large pelvic target volume followed by a sequential boost to the affected lymph nodes, and brachytherapy to boost the primary tumor. With modern intensity modulated EBRT techniques (IMRT/VMAT) it has become possible to deliver the lymph node boost dose together with the initial pelvic EBRT as a simultaneous integrated boost (SIB).

The radiotherapy department at St. Olavs Hospital has decided to start using SIB in the treatment of this patient group. This is a study of treatment planning technique, aiming at exploring different aspects of SIB treatment planning for VMAT in the RayStation treatment planning system, assessing the achieved plan quality and presenting recommendations for the department protocol with regards to optimization functions, clinical and auxiliary structures and arc configuration.

5 patients that have received radiotherapy treatment with sequential boost for cervical cancer, each with 1-4 positive lymph nodes, were included in the study. SIB treatment plans with different types of optimization functions and auxiliary structures were created for all patients. The treatment planning aims from the EMBRACE II study protocol, regarded as the current gold standard for cervical cancer radiation therapy, were used for evaluation of the dose distributions along with visual inspection and QA measurements. After a general strategy for structures and objectives had been selected, plans with different arc configurations (1 arc, 2 single arcs or 2 arcs with RayStations dual arc feature) were created and compared.

A general objective set with corresponding auxiliary structures that should be a good starting point for the optimization process for most patients is presented. The SIB treatment plans made with 2 arcs were satisfactory as assessed by medical physicists and verified excellently according to the qual-

ity assurance procedure. Plans made with 1 arc displayed worse conformity of the high dose regions to the target volumes, and were not acceptable for 2 of the 5 patients.

Some challenges in the treatment plan creation were encountered. The clinical goals for the bladder were only achieved for 2 of the 5 patients, hence a change in the department protocol of treatment with empty bladder is recommended. Another issue was that due to the large target volumes, the treatment planning aims allowed significant cold areas. Thorough visual inspection of the dose distributions should therefore be performed. However, this study showed that implementation of SIB for lymph node metastases in cervical cancer is feasible in the current clinical setting at St. Olavs Hospital.

Sammendrag

Livmorhalskreft med lymfeknutemetastaser har tradisjonelt blitt behandlet med ekstern stråleterapi (EBRT) til et stort målvolum i bekkenet, etterfulgt av en sekvensiell ekstern boost til positive lymfeknuter og brachyterapi som boost til primærsvulsten. Med moderne, intensitetsmodulerte teknikker for EBRT (IMRT/VMAT) er det nå mulig å gi den ekstra boostdosen til lymfeknutene samtidig med den innledende, eksterne bekkenbestrålingen som en simultan integrert boost (SIB).

Stråleterapiavdelingen ved St. Olavs Hospital har bestemt at SIB skal tas i bruk som en del av behandlingen for denne pasientgruppen. Dette er en doseplanteknisk studie, med mål om å utforske ulike aspekter ved doseplanlegging med SIB for VMAT i doseplansystemet RayStation, vurdere plankvaliteten, samt gi anbefalinger til nye retningslinjer for avdelingen med hensyn til optimeringsfunksjoner, målvolum, hjelpevolum og feltoppsett.

5 pasienter som har mottatt stråleterapibehandling med sekvensiell boost for livmorhalskreft, hver med 1-4 positive lymfeknuter, er inkludert i studien. Doseplaner med SIB, med ulike typer av optimeringsfunksjoner og hjelpevolum, ble laget for alle pasientene. Dose-volumkrav fra EMBRACE II-protokollen, som på nåværende tidspunkt anses som gullstandarden for stråleterapi av livmorhalskreft, ble sammen med visuell inspeksjon og QA-målinger brukt til evaluering av dosefordelingene. Etter valg av en generell strategi for strukturer og objektiver ble planer med ulike feltoppsett (1 bue, 2 enkle buer eller 2 buer med "dual arc"-funksjonen i RayStation) laget og sammenlignet.

Et generelt objektivsett med tilhørende hjelpevolum, som bør være et godt utgangspunkt for optimeringsprosessen for de fleste pasienter, er presentert. Behandlingsplanene med SIB laget med 2 buer ble vurdert som tilfredsstillende av medisinske fysikere, og verifiserte utmerket. For planene laget med 1 bue var konformiteten dårligere, og dosefordelingen var ikke

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akseptabel for 2 av 5 pasienter.

Enkelte utfordringer i doseplanleggingen ble oppdaget. Dose-volumkravene for blæren ble bare oppnådd for 2 av 5 pasienter, derfor anbefales en endring i avdelingens retningslinjer for behandling med tom blære. En annen utfordring var at dose-volumkravene tillot betydelige kalde områder på grunn av de store målvolumene. Grundig visuell inspeksjon av dosefordelingene er derfor viktig. Denne studien viste imidlertid at innføring av SIB for lymfeknutemetastaser ved livmorhalskreft er gjennomførbart i den kliniske settingen på St. Olavs Hospital.

Preface

This thesis constitute the final work for my master's degree in Biophysics and Medical Technology at the Norwegian University of Science and Technology (NTNU). The work was carried out at the radiotherapy department at St. Olavs Hospital (Trondheim University Hospital) during the fall semester of 2017.

A big thanks to my supervisors, medical physicists Anne Beate Langeland Marthinsen and Josefine Ståhl Kornerup, for all the helpful discussions, thorough feedback and continuous encouragement through the whole semester.

Thanks also to the other physicists at the radiotherapy department for answering my big or small questions, to chief physician Monika Eidem for help with delineation, and to the head of the radiotherapy department, Anne Dybdahl Wanderås.

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Trondheim
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Acronyms and abbreviations

CBCT Cone Beam Computed Tomography

CCW Counterclockwise

CIN Cervical Intraepithelial Neoplasia

CovP Coverage Probability

CTV Clinical Target Volume

CW Clockwise

DD Dose Difference

DTA Distance To Agreement

DVH Dose-Volume Histogram

EBRT External Beam Radiation Therapy

EMBRACE An intErnational study on MRI-guided BRachytherapy in locally Advanced CErvical cancer

EMBRACE II Image guided intensity modulated External beam radiochemotherapy and MRI based adaptive BRAchytherapy in locally advanced CErvical cancer

EQD2 (Biologically) Equivalent Dose in 2 Gy fractions

FDG-PET Fluorodeoxyglucose Positron Emission Tomography

FIGO Fédération Internationale de Gynécologie et d'Obstétrique (International Federation of Gynecology and Obstetrics)

GP Gamma Passing rate

GTV Gross Tumor Volume

HPV Human Papillomavirus

IMRT Intensity Modulated Radiation Therapy

ITV Internal Target Volume

LINAC Linear Accelerator

LN Lymph Node

MLC Multileaf Collimator

MU Monitor Unit

OAR Organ At Risk

OTT Overall Treatment Time

PTV Planning Target Volume

QA Quality Assurance

ROI Region Of Interest

SIB Simultaneous Integrated Boost

VMAT Volumetric Arc Therapy

Chapter 1

Introduction

Cervical cancer is one of the most common types of cancer in women, with around 350 new cases in Norway each year [1, 2]. In almost half the cases, the cancer has spread to regional lymph nodes at the time of diagnosis, and for these patients the recurrence and survival rates are significantly worse [3].

Standard treatment for locally advanced cervical cancer includes external beam radiation therapy (EBRT) to a large target volume in the pelvic area, brachytherapy to boost the primary tumor and concomitant chemotherapy. Any gross disease detected in the lymph nodes is usually treated with an additional EBRT boost dose [4]. Traditionally, the lymph node boost has been delivered as a sequential boost after the primary pelvic EBRT.

In recent years, EBRT using intensity modulated radiotherapy (IMRT) or volumetric arc therapy (VMAT) has made it possible to deliver different doses to specific parts of the target volume with high precision ("dose painting"), making a new option available; simultaneous integrated boost (SIB). Using this technique, the additional boost dose to the lymph nodes is integrated in the same treatment plan and delivered at the same time as the initial external beam fractions [5].

The potential advantages of SIB compared to sequential boosting include reduction of hot spots in normal tissue, and shorter overall treatment time, limiting tumor repopulation and improving local control. Several studies have found that SIB has the capacity to improve the dose distribution [6, 7], and achieve high levels of local control with acceptable rates of acute and late normal tissue toxicities [5, 8].

SIB for treatment of affected lymph nodes is compulsory in the protocol for EMBRACE II, a multicenter interventional study on treatment of locally

advanced cervical cancer [9]. The EMBRACE II treatment protocol is based on comprehensive data from the EMBRACE and Retro-EMBRACE studies [10, 11] which included a large number of patients from a number of clinics, and is at present considered the gold standard for cervical cancer treatment.

At St. Olavs Hospital, lymph node metastases in cervical cancer has until now been treated by sequential EBRT boosting [12]. Based on the available research and the EMBRACE II treatment protocol, the department has decided to implement SIB in the radiotherapy treatment for this patient group. This master's thesis is a study of treatment planning technique, in contribution to the development of a clinical protocol for this type of treatment. The goal was to test the feasibility of SIB treatment planning in the current clinical setting, and highlight potential challenges and benefits with the method for this patient group. Also, this work aims to investigate different strategies for aspects of the treatment planning such as auxiliary structures, objective sets and arc configurations, and present recommendations for the future department protocol based on specific testing using the available software, as well as relevant literature.

Chapter 2

Theory

2.1 Cervical cancer

Cervical cancer is the fourth most common cancer in women, with an estimated 528 000 new cases and 266 000 deaths worldwide in 2012. About 84% of cervical cancer instances and 87% of deaths occur in less developed regions [13]. In Norway, 370 new cases and 79 deaths were reported in 2015 [1, 2].

Virtually all cases of cervical cancer are caused by persistent infection with the sexually transmittable human papillomavirus (HPV). During the last decades, widespread use of screening programs have reduced the incidence of invasive cervical cancer dramatically in developed countries, and HPV vaccination is expected to reduce the occurence further [14].

2.1.1 Primary disease

The cervix is the lower part of the uterus, connecting the uterine cavity and the vaginal lumen (see figure 2.1). The openings into the uterus and vagina are called the internal and external os, respectively. The canal between the internal and external os, called the endocervix, is covered by mucus-secreting glandular cells , while the lower, vaginal part of the cervix, covered by squamous epithelium, is called the ectocervix.

Cervical cancer typically arises from cervical intraepithelial neoplasia (CIN), an asymptomatic, potentially premalignant transformation of squamous cells that emerges 5-15 years preceding invasive carcinoma. Most cervical cancers originate in the squamocolumnar junction, or transformation

zone, where the squamous epithelium of the ectocervix meets the columnar, glandular epithelium of the endocervix [15].
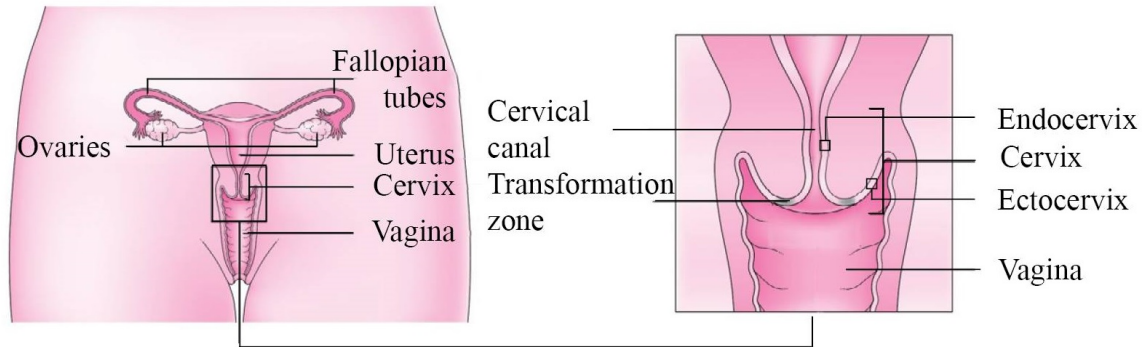

Figure 2.1: Anatomy of the female reproductive system (left) and a closer view of the cervix (right). Adapted from [16].

2.1.2 The lymphatic system

The lymphatic system is a one-way circulatory network consisting of lymphatic vessels, lymph nodes and other lymphoid organs. Its main responsibilities are returning excess fluid from body tissues to the circulatory system, and defending the body against foreign or harmful agents.

Interstitial fluid drains into lymphatic capillaries and becomes lymph, which flows away from tissues in lymphatic vessels, is filtered through the lymph nodes and continues to either the thoracic duct or right lymphatic duct, which drains into the left and right subclavian veins respectively.

Lymph nodes are small, oval masses that tend to group in clusters, for example under the arms (axillary lymph nodes) and in the pelvis (iliac lymph nodes). Lymphocytes, a class of white blood cells that mediate all adaptive immune responses, are concentrated in the lymph nodes. Lymph nodes act as filters for bacteria, viruses and other foreign materials that can be recognized and eliminated by lymphocytes.

The lymphatic system plays a key role in tumor metastasis by providing a pathway for tumor cell dissemination; small lymph capillaries surrounding or invading tumors may take up tumor cells and transport them via larger lymph vessels to regional lymph nodes. The presence of metastatic tumor

cells in regional lymph nodes is an important prognostic factor in many cancers [17].

Lymph node metastases in cervical cancer

Studies on locally advanced cervical cancer have reported lymph node (LN) metastases at the time of diagnosis in 45-47% of the patients [3, 18], and increased frequency of positive LNs with FIGO stage[1][3]. Lymph node status is nowadays most commonly evaluated by FDG-PET imaging, as it offers functional information and can detect disease in normal-size lymph nodes, rather than relying on size criteria only as with CT or MRI [3].

Lymph node regions where metastases from cervical cancer are frequently found are shown in figure 2.2. The pattern of lymph node spread is almost without exception from lower to higher level; pelvic nodes first (first true pelvic and then common iliac), then para-aortic nodes and eventually supraclavicular nodes [3, 20]. For example, none of the two referenced studies found any positive para-aortic LNs in patients without positive pelvic LNs.

For cervical cancer patients, the prognosis depends strongly on the presence and extent of LN metastases. The risk of both recurrence and death increases incrementally based on the most distant level of nodal involvement at diagnosis. Kidd et al. found that the hazard ratio[2]for disease recurrence was 2.40 for pelvic, 5.88 for para-aortic and 30.27 for supraclavicular LN metastases respectively (compared to no lymph node involvement) [3], and Wakatsuki et al. found a decrease in 5-year overall survival (following EBRT with or without sequential LN boost and brachytherapy) from 82.0% to 55.1% if pelvic LN metastases were detected [22].

2.2   External beam radiation therapy

Several modalities including photon, electron, proton, neutron and light ion beams are used for external beam radiation therapy (EBRT) worldwide, in addition to internal radiation techniques such as brachytherapy and intraoperative radiation therapy. However, the majority of radiation therapy

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[1]Fédération Internationale de Gynécologie et d'Obstétrique (International Federation of Gynecology and Obstetrics, FIGO) staging for carcinoma of the cervix uteri [19].

[2]The hazard ratio indicate the risk of an event occuring in one group compared to another (control) group.
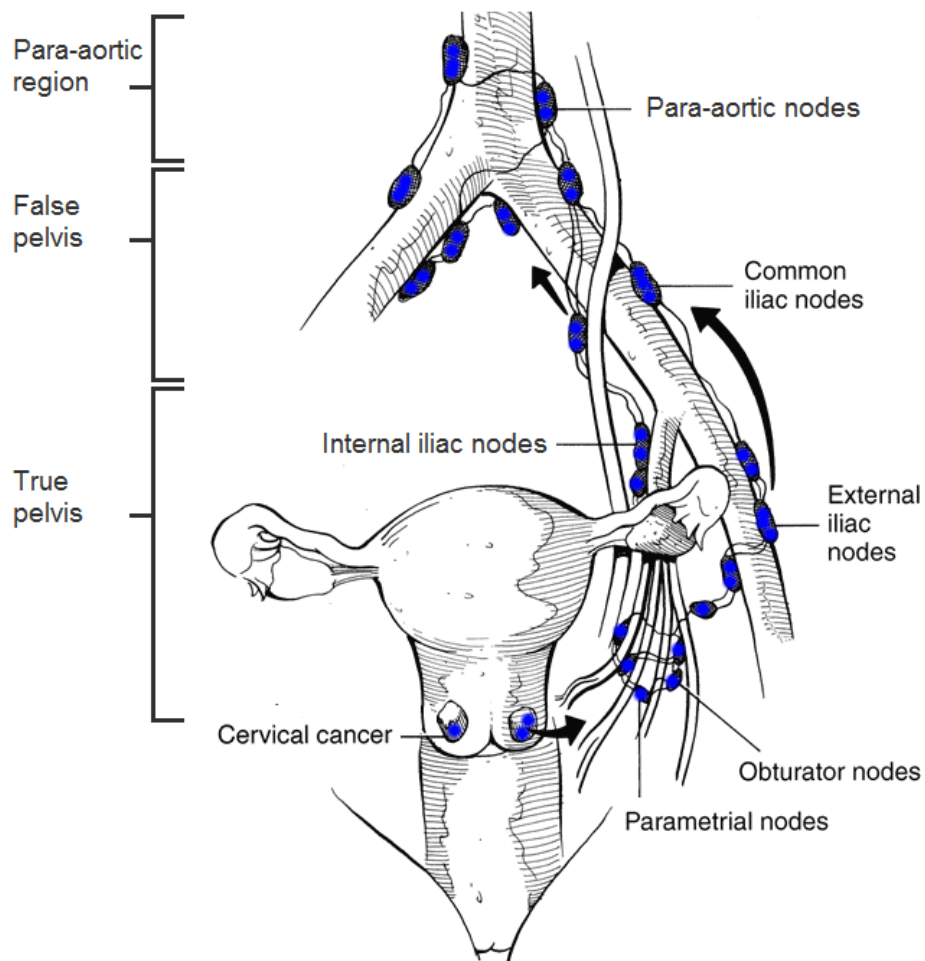
Figure 2.2: Lymph node regions commonly involved in cervical cancer. The arrows indicate the direction of spread. Adapted from [21].

treatments are EBRT with photon or electron beams produced in a linear accelerator.

2.2.1 The linear accelerator

Linear accelerators (linacs) for medical applications accelerate electrons through interactions with a microwave frequency electromagnetic field to energies ranging from 4 to 25 MeV. The monoenergetic electron beam can either be

used directly for treatment of superficial lesions, or imparted on a high density (e.g. tungsten) target to create photons through bremsstrahlung. The photon beam will contain a spectrum of energies, with maximum photon energy equal to the electron energy used. Photon beams of 6, 10, 15 or 18 MV are most common in EBRT treatment.

For photon therapy, the radiation field is shaped by the fixed primary collimator and two pairs of independently movable secondary collimator jaws, providing a range of rectangular field sizes. Modern linacs also have a multileaf collimator (MLC), with tungsten leaves of 0.5 to 1 cm width that can move independently at rapid speed (3-6 cm/s) to shape the radiation field [23].

2.2.2 Intensity modulated radiation therapy

Intensity modulated radiation therapy (IMRT) is a modern radiotherapy technique, where the prescribed dose is shaped to the target volume by modulating the beam intensity and the MLC shape for each beam segment with varying gantry angles. While IMRT refers to radiation delivery through a number of fixed beam segments, VMAT is a subtype that incorporates continuous gantry rotation while the radiation field is modulated through MLC movement and variations in dose rate, thereby reducing the treatment delivery time.

The improvement in conformity of radiation dose to target volume with IMRT or VMAT compared to 3D conformal radiotherapy allows a dose escalation to the target volume and/or a dose reduction to surrounding normal tissue structures [24].

Vergalasova et al. compared IMRT and VMAT for treatment of gynecological malignancies with SIB, and found that both methods produced acceptable treatment plans, with slightly better dosimetry for IMRT, and shorter treatment time and lower MU for VMAT [25]. In the following, this report will focus on VMAT, as this technique is used for cervical cancer treatment at St. Olavs Hospital.

Arc configuration

While good quality VMAT plans for simple geometries may be achieved with one full or partial arc, more complex geometries may require several rotational arcs to allow the modulation necessary to achieve a satisfactory

dose distributions. As the MLC leaves have a given freedom of movement, the possibilities for modulation of the shape and combinations of intensity levels for each segment increase with multiple arcs [24]. One full arc rotation typically takes less than two minutes.

2.2.3 Monitor units

Monitor units (MU) are a measure of machine output, or "beam on" time, for linacs. By convention, 1 MU equals the amount of charge that correlates with an absorbed dose of 1 cGy in a water phantom at standardized calibration conditions (target depth, source-to-surface distance, field size), recorded in the ionization chamber in the linac head, for a particular beam energy [26].

When the dose rate (MU/min) is constant, the number of MU is proportional to irradiation time. In IMRT/VMAT plans, only parts of the target volume are irradiated at any time, and a downside compared to conformal radiotherapy is increased MU, longer irradiation time and more leakage radiation [27]. A high MU can be a sign that the treatment plan is heavily modulated, and that accurate delivery of the plan may be a challenge.

2.3 Cervical cancer treatment

While early and limited disease can be removed surgically, the standard treatment for locally advanced cervical cancer (FIGO stage IB2-IVA) is combined external beam radiotherapy (EBRT), brachytherapy and concomitant chemotherapy [14].

A dose of 45-50 Gy in fractions of 1.7 to 2 Gy is usually delivered by EBRT to a large target volume in the pelvic area, in order to eradicate any microscopic disease and prevent the cancer from spreading. In case of lymph node involvement, the pelvic target volume is expanded upwards to include nodal regions with a significant risk of lymphatic spread (the elective nodal target) [9].

During the last half of the EBRT course or immediately afterwards, the primary tumor is boosted using brachytherapy to reach a total biological dose (see section 2.3.2) between 75 and 95 Gy. In brachytherapy, a radioactive source with a steep dose gradient is placed inside the uterus and vagina in order to deliver a high dose with good precision to the target volume while sparing OARs nearby [14].

Gross disease in areas not accessible for brachytherapy, such as metastases in regional lymph nodes, the pelvic sidewall or the parametrium, can be treated by additional EBRT boost doses [5].

2.3.1 Lymph node boost

Lymph node boosting in EBRT of cervical cancer implies an increase in the dose to positive nodes compared to the surrounding target volume, due to the presence of macroscopic disease. The boost dose may be given either sequentially (following the radiation of the pelvic target) or simultaneously with the initial EBRT fractions as an integrated boost.

Simultaneous integrated boost

Simultaneous integrated boost (SIB) is a novel method exploiting the possibilities of intensity modulated EBRT techniques. Through intentional dose heterogeneity, boost volumes receive a higher fraction dose within a larger volume treated with a lower dose [5].

SIB has several possible advantages over sequential boosting for lymph node metastases in cervical cancer. The inclusive planning offers more control over the dose distribution, so that potentially overlapping hot spots in two separate plans are avoided. Feng et al. found that SIB significantly reduced hot spots in both the pelvic target volume and OARs, as well as the physical dose to rectum and small bowel [6].

As the number of fractions used to deliver the treatment is decreased, usually by 5-7 depending on the fractionation used for sequential boosting, the overall treatment time (OTT) can be shortened, limiting tumor repopulation [7]. Fewer fractions is also more convenient for the patient and saves resources in the department, and as only one treatment plan is required, time for planning and implementation in the clinic can be saved.

A concern with fraction doses higher than the well tested 2 Gy is the risk of unpredicted normal tissue toxicities due to an increase in biological dose to OARs close to boost volumes, especially if normal tissue unexpectedly enters the areas where boost doses are given. However, Feng et al. found that the EQD2 doses (see section 2.3.2) to rectum, small bowel and bladder were equivalent for SIB and sequential boost techniques, and therefore expect toxicities to be comparable [6]. Boyle et al. found that SIB of 2.2 Gy/fraction was not associated with increased acute or late toxicity [5], and Vargo et al.

concluded that the rate of late adverse events was acceptable [8]. These studies demonstrate that doses of 2.2 Gy/fraction can be safely delivered to boost volumes as an integrated treatment.

Lymph node boost doses

As the expected dose contribution from brachytherapy varies with location of the lymph node, the appropriate boost dose will depend on LN region. Studies have reported brachytherapy doses (EQD2, see next section) of 3.8-6.2 Gy for pelvic nodes and 0.5-1.9 Gy outside the true pelvis (mean $D_{50\%}$) [28], and median near minimum point doses of 3.6-4.7 Gy inside the true pelvis and 0-1.2 Gy outside [29].

In the EMBRACE II protocol (see section 2.4), the following fractionation schedules are suggested to achieve a desired total LN dose of 55-65 Gy EQD2 from EBRT and brachytherapy [9]:

- In true pelvis: 25 x 2.2 Gy = 55 Gy physical dose $\approx$ 55.9 Gy EQD2 from EBRT. A contribution from brachytherapy of $\approx$ 4 Gy gives a total biologically equivalent dose of $\approx$ 60 Gy.

- Outside of true pelvis: 25 x 2.3 Gy = 57.5 Gy physical dose $\approx$ 58.9 Gy EQD2 from EBRT. The dose from brachytherapy is negligible.

2.3.2 Physical and biological doses

While prescriptions for fraction doses and total doses for each modality are given as absorbed physical dose, summation of overall doses from EBRT and brachytherapy are performed using the biologically equivalent dose in 2 Gy fractions (EQD2). EQD2 is used for comparing the clinical effects of radiation delivered using different fractionation regimens, and is defined as

$$\text{EQD2} = D\Big[\frac{\alpha/\beta + d}{\alpha/\beta + 2}\Big],$$

where D is the total absorbed dose and d is the dose per fraction. α/β is the ratio of the parameters α and β in the linear-quadratic model, and describes the fractionation sensitivity of tissues [14]. In biological dose calculations for cervical cancer radiation therapy, $\alpha/\beta = 10$ Gy is used for tumor tissue and $\alpha/\beta = 3$ Gy is used for normal tissue [9].

2.3.3 Overall treatment time

A multivariate analysis of 488 patients in the Retro-EMBRACE study (see next section) showed that the effect of shortening the overall treatment time (OTT) by 1 week was equivalent to a 5 Gy dose escalation for the high risk clinical target volume [18]. The aim in the EMBRACE II treatment protocol is to keep the OTT below 50 days, with use of simultaneous integrated lymph node boost and careful timing of the brachytherapy schedule [9].

Figure 2.3 shows examples of possible overall treatment schedules with SIB from the EMBRACE II protocol, as well as a schedule with sequential lymph node boost used at St. Olavs Hospital.
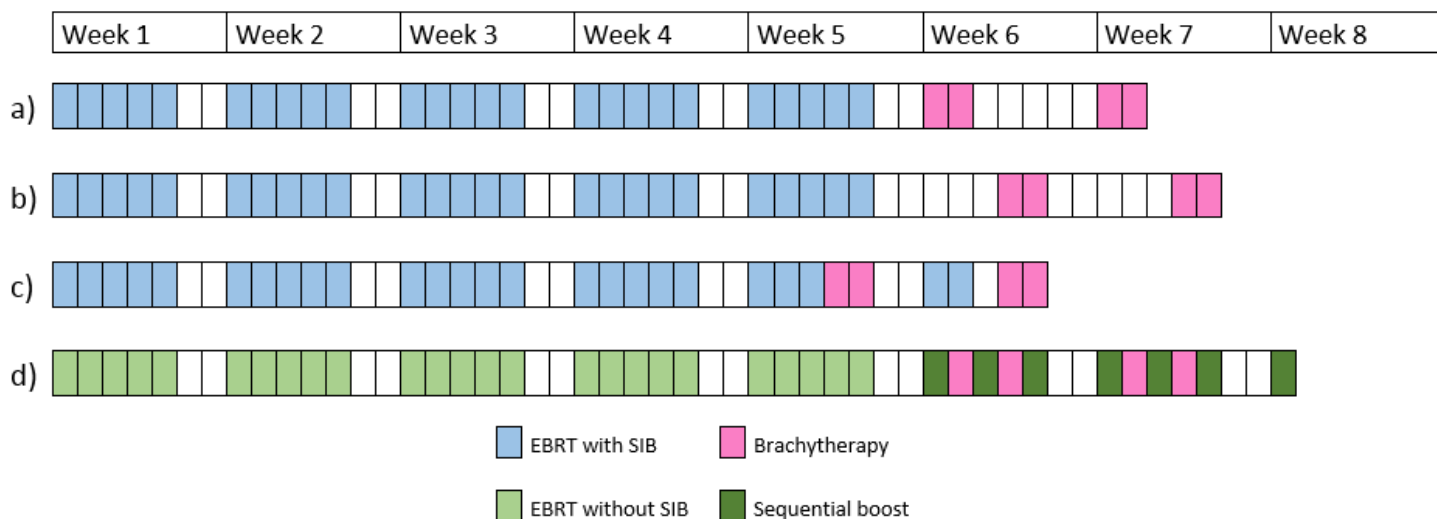

Figure 2.3: Overall treatment schedules for radiotherapy of cervical cancer with lymph node boost. a) and b) are examples from the EMBRACE II treatment protocol giving OTTs of 44 and 47 days. c) is an example from the EMBRACE II protocol for small and/or well responding tumors, giving an OTT of 40 days. d) shows a typical treatment schedule with sequential boost used at St. Olavs Hospital, giving an OTT of 50 days (5-7 boost fractions have been applied based on the oncologist's clinical assessment). Each box represents one day, and white boxes represent days when no treatment is given (weekends and break days).

2.4 The EMBRACE studies

EMBRACE is an international observational study on MRI-guided brachytherapy in locally advanced cervical cancer [10]. More than 1350 patients treated in 27 centers between 2008 and 2015 were included, among them 37 patients from St. Olavs Hospital. The main goals were to introduce MRI-based 3D treatment planning for brachytherapy in a multicenter setting, and collect data to correlate dose volume parameters for the CTV and OARs with treatment outcome. Details of the EBRT and chemotherapy treatment were also reported.

Retro-EMBRACE is a retrospective data collection project [11]. Data from patients treated with image-guided brachytherapy before startup of EMBRACE in each respective center was collected, and used for analysis while the EMBRACE data matures. 852 patients were included in Retro-EMBRACE.

A number of articles have been published based on the data from the EMBRACE and Retro-EMBRACE studies, and a consecutive study called EMBRACE II with interventions derived from the EMBRACE and Retro-EMBRACE evidence has been initiated with an accrual period from 2016-2019 [9]. The aim of this study is to implement advanced radiotherapy techniques (image-guided, intensity modulated EBRT and image-guided adaptive brachytherapy) and simultaneous chemotherapy for patients with locally advanced cervical cancer according to comprehensive guidelines, in order to achieve an outstandingly high level of local, nodal and systemic control as well as a high quality of life. Due to its extensive research foundation, the EMBRACE II treatment protocol is at the moment regarded as a benchmark for treatment of this patient group.

Some interventions in the EMBRACE II protocol that are of particular relevance to this project are:

- Systematic utilization of IMRT/VMAT and daily image guidance.

- Standardized dose prescription for EBRT of 45 Gy in 25 fractions, 5 days a week, as the dose de-escalation from 50 Gy (traditionally used in many centers, also at St. Olavs Hospital) to 45 Gy has the potential to reduce morbidity.

- Simultaneous integrated boost in case of lymph node involvement.

- Maximal overall treatment time of 50 days, including both EBRT and brachytherapy.

2.5 EBRT treatment planning for cervical cancer with SIB

The general aim in radiotherapy is to deliver a dose sufficient to eradicate disease in the target volume, while not exceeding the tolerance of normal tissues nearby.

In VMAT treatment planning, a very large number of parameters can be adjusted to achieve a satisfactory dose distribution. Computerized inverse treatment planning using appropriate optimization algorithms is therefore required. In inverse treatment planning, a series of aims, or optimization functions, characterizing the desired dose distribution in both target volumes and normal tissues are defined, and the optimization engine works iteratively to determine the MLC shapes and fluence patterns that best fulfill the aims [24].

2.5.1 Clinical structures

Radiotherapy treatment is prescribed by the oncologist according to a set of structures delineated on 3D images (usually a treatment planning CT). To exploit the sophisticated modern intensity modulated radiation techniques, 3D delineation of target and normal tissue structures with high precision is required.

A general definition of target volumes for EBRT has been made by the International Commission on Radiation Units and Measurements [24]:

- GTV: Gross tumor volume. The demonstrable extent of the tumor, evaluated by clinical examination, anatomical imaging and/or functional imaging.

- CTV: Clinical target volume. GTV + suspected microscopic extension of malignant disease.

- ITV: Internal target volume. CTV + internal margin*, taking into account uncertainties in size, shape and position of the CTV within

the patient. Optional tool for help in PTV delineation when internal uncertainties are large and/or independent of external (set-up) uncertainties.

- PTV: Planning Target Volume. CTV + margin to account for the net effect of all geometrical uncertainties (set-up variations*, organ motion etc.), to ensure that the planned absorbed dose is actually delivered to all parts of the CTV with a clinically acceptable probability.

* Internal and external (set-up) margins should be added quadratically and not linearly to avoid unacceptably large total margins.

An overview of the clinical target structures defined in the EMBRACE II protocol for EBRT of cervical cancer with lymph node boost is given in table 2.1. The organs at risk that should be delineated are bladder, rectum, sigmoid colon, bowel and femoral heads, and in case of para-aortic irradiation, also kidneys and spinal cord.

2.5.2 Auxiliary structures

In order to meet the planning aims for a clinical structure it can sometimes be advantageous to assign optimization functions to regions different from the structure itself. For this purpose, auxiliary structures can be derived. An example, suggested in the optimization guide from RayStation [30], is *ring ROIs*: To achieve a sharper fall in the dose close to a target - both in normal tissue and in larger target volumes around boost PTVs - without introducing cold spots in the PTV, a ROI of about 1 cm around the PTV with a max dose objective slightly lower than the prescribed target dose can be created.

Other examples are structures with a small help margin (in addition to the PTV margin) in cases where achieving a certain dose level is critical also at the border of a target volume, and structures where an overlap region is removed to give full priority to another ROI in this region. If a target volume and an OAR overlap and it is desired to favor target coverage, an auxiliary *out-volume* for the OAR can be derived which includes only the parts outside the target volume.

One auxiliary structure is suggested in the EMBRACE II treatment protocol: CTV-T HR with a 10 mm margin. This volume is likely to receive a significant dose from brachytherapy, and for correct summation of OAR doses from EBRT and brachytherapy and to avoid hot spots in OAR walls

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that are likely to receive a considerable brachytherapy dose, a max dose aim for CTV-T HR + 10 mm could be applied.

2.5.3 Coverage probability planning

Coverage probability (CovP) planning has been proposed as a means to achieve lower OAR doses when boosting LNs in cervical cancer patients [29]. CovP is based on the probability distribution of finding the GTV-N at a specific point in the PTV-N, and aims for a heterogeneous target coverage where underdosage is allowed at the edges of the PTV-N while the dose at the center is higher than prescribed. This strategy has been shown to be highly robust if daily image guidance based on bony fusion is performed, and significantly lower doses to bowel and pelvic bones and a higher dose to the central GTV-N were achieved with only a minor reduction in the CTV-N coverage. Also, geographical misses would have limited dosimetric consequence in a SIB setting as the LN targets are embedded in the pelvic PTV receiving 45 Gy. CovP has consequently been implemented in the EMBRACE II study protocol [9].

2.5.4 The RayStation treatment planning system

The RayStation treatment planning system (by RaySearch Laboratories AB, Sweden) is used for EBRT treatment planning at St. Olavs Hospital. A review of some features in RayStation relevant to this study follows [31].

Arc configurations and dual arc

For VMAT treatment using one or more full arcs it is common to avoid ambiguity in the definition of gantry angles by making each arc move counterclockwise (ccw) from 178° or 179° to 182° or 181°, or clockwise (cw) from 182°/181° to 178°/179° or similar.

In optimizations of 1 arc, one fluence map is first generated at every 24° around the arc. Two MLC openings that form each fluence map are created, and each of them are copied to every control point in one direction (2°-4° apart depending on beam settings). These MLC openings are used as a starting point for the continued optimization.

With 2 arcs, one moving counterclockwise (ccw) from 179° to 181° and the other clockwise (cw) back from 181° to 179°, the initial control points

at every 24° for each arc would thus be only 2° apart. The resulting MLC openings used as a starting point would be very similar for the two arcs given the same collimator angle. However, the 2 single arcs can have different collimator angles, giving an extra degree of freedom.

The dual arc feature in RayStation automatically creates a second arc moving in the opposite direction of the original arc. Now 4 MLC openings will form each fluence map (for the first arc only), and the two that are most similar will be assigned to each arc. The second arc will have the same collimator angle as the original arc and this can not be altered.

According to the RayStation user manual, using the dual arc feature should generally result in improved plan quality with less modulation and improved QA results compared to 2 single arcs with identical collimator angles. It is, however, unclear whether the impact of different collimator angles could partly or completely make up for this in a configuration with 2 single arcs.

Optimization functions

In inverse treatment planning, the planner defines a set of optimization functions (objectives) and assigns weights corresponding to their relative importance. After every step in the optimization, weighted values representing how far the planned dose distribution is from achieving each individual optimization function makes up the total objective function. The goal of the optimization process is to minimize the value of the total objective function.

A selection of the available optimization functions in RayStation is described in table 2.2.

2.6   Quality assurance

Quality assurance (QA) for VMAT includes initial commissioning of the linac and treatment planning system as well as regular controls, and patient specific QA to ensure that the linac is able to accurately deliver the planned treatment. This last step is especially crucial for VMAT treatments as the continuous changes in gantry angle and speed, dose rate and MLC shape makes both delivery and dosimetric evaluation complex. Therefore, routine QA of VMAT plans typically involves delivery of the treatment plan to a

phantom - a device that measures samples of the delivered dose - and comparison of the measured and planned dose distribution [32].

Two main concepts complement each other when comparing two dose distributions. For each measurement point, the following parameters can be calculated:

1. Dose difference (DD): Difference between the measured and calculated dose. Suitable in regions with low dose gradients. Where the dose gradient is high, a small inaccuracy in position could lead to a large DD. A typical passing criterion for the dose difference is 3% of the planned dose.

2. Distance to agreement (DTA): Distance between the measurement point and the nearest point in the calculated dose distribution with the same dose. Suitable in regions with high dose gradients. A typical passing criterion for the distance to agreement is 3 mm.

Because of their individual shortcomings, the DD and DTA methods are often used in conjunction, by evaluating them individually for each measurement point and requiring each point to pass either one of the tests. In the gamma method, they are combined into an abstract quantity called the gamma index, giving a single quantitative measure for evaluation of treatment plan quality. Input passing criteria are used for normalization of DD and DTA values, so that a gamma index of ≤ 1 becomes the criterion for each point to pass the test [33]. Figure 2.4 shows an example of how the gamma method works.

The gamma passing rate (GP) is the percentage of evaluated points that pass the gamma test. At St. Olavs Hospital, a GP of $> 90\%$ with 3%/3 mm criteria is normally required for successful verification.

Table 2.1: Definitions of target structures for EBRT of cervical cancer with SIB to lymph nodes from the EMBRACE II treatment protocol [9].

Clinical structure	Definition
GTV-T	The initial gross tumor volume of the primary cervix tumor.
CTV-T HR (high risk)	GTV-T and any remaining cervix.
CTV-T LR (low risk)	CTV-T HR, the entire uterus and parametria, and margins of 20 mm into the vagina and 5 mm towards bladder and rectum.
ITV-T LR	Margins from CTV-T LR depend on clinical judgement of internal target motion and the level of image guidance applied in the specific center.[*]
CTV-E	Elective nodal region, including relevant vessels and pathological lymph nodes in the true and false pelvis for all patients with LN metastases. For patients with ≥ 3 positive LNs, or any positive LNs at the common iliac level or higher, the para-aortic region is also included (see figure 2.2).
ITV_45	ITV-T LR + CTV-E.
PTV_45	ITV_45 with an isotropic margin of 5 mm.[**]
GTV-N(#)_55/57.5	Individual gross tumor volume for each pathological lymph node, numbered from the most inferior. The dose level is determined according to the assumed dose contribution from brachytherapy, as described in section 2.3.1.
CTV-N(#)_55/57.5	In principle equal to the corresponding GTV-N, but an individualized margin (usually ≤ 3 mm) can be applied in special cases to account for e.g. different appearance on CT and MRI, or possible progression before treatment starts.
PTV-N(#)_55/57.5	The corresponding CTV-N with an isotropic margin of 5 mm.[**]

[*] Multiple image series with different combinations of bowel and bladder filling give useful information about the range of internal motion of the CTV-T LR. It is recommended to perform an empty bladder scan in addition to a treatment planning CT with comfortably filled bladder.

[**] A margin of 5 mm is considered appropriate when using daily image guidance and couch correction according to fusion on bony anatomy.

Table 2.2: Optimization functions (objectives) in RayStation 6 (only those used in this study are included) [31].

| Objective type	Input parameter(s)	Description
Min dose	Dose level	The objective is met when the dose is greater than or equal to the specified dose in all parts of the ROI.
Max dose	Dose level	The objective is met when the max dose in the ROI is less than or equal to the specified dose.
Min/max DVH	Dose level, Volume (%)	The objective is met when at least/only the specified percentage of the ROI receives more than the specified dose.
Min/max EUD	Dose level, Parameter A	The EUD (equivalent uniform dose) function equals a mean dose objective when A is set to 1, with cold and hot spots given equal weight when trying to achieve a uniform dose. If A>1, high doses are given higher weight, and if A<1, low doses are given higher weight.
Dose fall-off	High dose level, Low dose level, Low dose distance, Adapt to target dose levels (true/false)	Automatically assigns max dose levels in the ROI depending on the distance from the target. The max dose limit falls off linearly from the border of the target to the low dose level at the specified low dose distance and greater distances. If the dose fall-off function is defined for an organ ROI which overlaps a target ROI, the voxels within the target ROI are disregarded. In plans with multiple target dose levels, "Adapt to target dose levels" can be applied, so that the high dose level is adjusted according to the high dose level of each target.
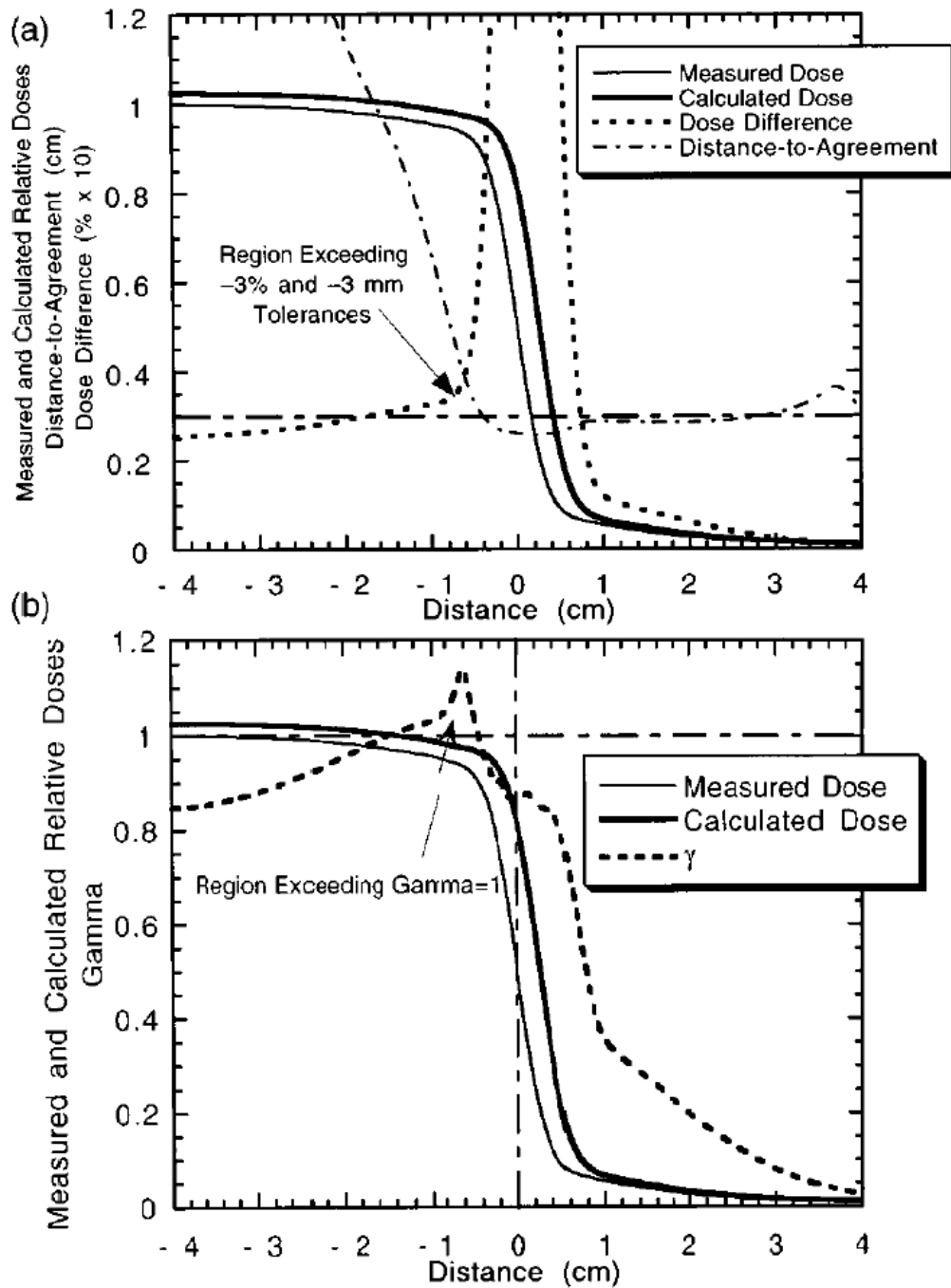
Figure 2.4: Illustration of the gamma method for a situation with a 0.25 cm spatial shift and a 2.5% normalization difference between the measured and calculated dose. Panel a) shows the dose, dose difference (DD) and distance to agreement (DTA), with the arrow pointing out a region where the passing criteria (illustrated by the horizontal line) for both parameters are exceeded. Notice that the DTA is highest where the dose gradient is shallow, while the DD peaks where the gradient is sharp. Panel b) shows the corresponding gamma index (dotted line), with the arrow pointing out a region where the dose distribution fails the gamma test. From [33].

Chapter 3

Material and methods

3.1 Patients

5 patients that have recently received radiotherapy treatment for cervical cancer at St. Olavs Hospital were included in the study. All data was anonymized before the study began, and some adaptions were made retrospectively to the delineated structures to make the findings more clinically relevant. The department protocol is to perform the planning CT scan as well as the EBRT treatment with an empty bladder. Efforts are also made to avoid air in the rectum. In accordance with current practice in the department, the density of the rectum was set equivalent to water if air was visible on the planning CT images.

3.1.1 Delineation of clinical structures

There were some differences between the delineated structures used for the actual treatment of the patients (according to the current department protocol) and the clinical structures defined in the EMBRACE II treatment protocol (see section 2.5.1):

- A CTV-T HR was not defined, only a CTV-T corresponding to the CTV-T LR.

- No ITV was defined, instead a PTV_45 margin of 7-8 mm from the CTV-E and 12 mm from the CTV-T was used.

- The margins for nodal targets were not consistent between patients. The total GTV-N to PTV-N margins varied from 12-18 mm.

- Sigmoid colon and bowel were not delineated.

With respect to limited availability of physicians for delineation it was decided to use the existing target structures, while sigmoid colon and bowel were delineated by an oncologist for this study.

3.2 Treatment plan optimization

VMAT treatment planning was performed using the RayStation 6R treatment planning system (by RaySearch Laboratories AB, Sweden).

3.2.1 Treatment planning aims

The dose constraints from the EMBRACE II protocol for EBRT of cervical cancer with SIB to lymph nodes are summarized in table 3.1. These were used as clinical goals in the treatment planning process.

It should be noted that the dose-volume recommendations for the bladder are based on a protocol with comfortably filled bladder, while planning and treatment at St. Olavs Hospital is performed with an empty bladder.

In certain cases, some clinical goals were inherently impossible to fulfill because patient anatomy caused them to conflict with other goals. The main priority was to fulfill all clinical goals for the target volumes and those listed as hard constraints, while the focus for the remaining OARs was fulfilling all clinical goals reasonably achievable for each patient.

When the goals for an OAR could not be achieved due to a conflict with target volumes, attempts were made to keep the dose within the organ as low as possible while maintaining the desired target coverage.

3.2.2 Selection of structures and objectives

In order to become familiar with the treatment planning system, a simple set of objectives for the clinical structures based on the aims in table 3.1 was used as a starting point for the first rounds of optimization. As challenges with achieving the aims appeared or inspection of the dose distributions revealed cold or hot spots in specific regions, the objectives were adjusted or new ones

Table 3.1: Treatment planning aims from the EMBRACE II protocol [9]. Aims categorized as hard constraints are in bold font, while soft constraints (not based on clinical evidence) are in normal font. Absolute values for dose levels are given in parenthesis for easier comparison with other parts of this report.

Structure	Planning aims	
PTV_45	**V95% > 95%**	**(42.75 Gy)**
ITV_45[*]	**Dmin > 95%**	**(42.75 Gy)**
PTV-N#_55	**D98% > 90%**	**(49.50 Gy)**
	Dmax < 107%	**(58.85 Gy)**
CTV-N#_55	**D98% > 100%**	**(55 Gy)**
	D50% > 102%	(56.10 Gy)
PTV-N#_57.5	**D98% > 90%**	**(51.75 Gy)**
	Dmax < 107%	**(61.53 Gy)**
CTV-N#_57.5	**D98% > 100%**	**(57.50 Gy)**
	D50% > 102%	(58.65 Gy)
GTV-T + 10mm[**]	Dmax < 103%	(46.35 Gy)
Bladder	V40Gy < 75%	
	V30Gy < 85%	
	Dmax < 57.5 Gy	
Rectum	V40Gy < 85%	
	V30Gy < 95%	
	Dmax < 57.5 Gy	
Sigmoid	Dmax < 57.5 Gy	
Bowel	V40Gy < 250 cm^3	
	V30Gy < 500 cm^3	
	Dmax < 57.5 Gy	
Femoral heads	**Dmax < 50 Gy**	
Spinal cord[***]	**Dmax < 48 Gy**	
Kidneys[***]	**Dmean < 15 Gy**	
	Dmean < 10 Gy	

[*] This structure was not delineated and the planning aim could therefore not be applied in this study.

[**] This structure is not identical to the "CTV-HR + 10mm" structure suggested in the EMBRACE II protocol, but it has the same purpose (see section 2.5.2).

[***] In case of para-aortic irradiation.

were added, attempting to create robust plans according to the aims in the EMBRACE II protocol.

Creation of auxiliary structures

In attempts to amend specific issues, various auxiliary structures were created and their impact on the dose distribution assessed:

- To restrict high doses to their designated structures by achieving sharp gradients, auxiliary "ring structures" as recommended in the RayStation optimization guide were tested (see section 2.5.2), and the resulting treatment plans were compared to plans made with dose fall-off or dose-volume objectives for the original structures only.

- To test different combinations of objectives for OARs, out-volumes (BladderOut, BowelOut etc.), were created by removing the part of the organ that overlapped the target volume, with an additional margin of 0.5 cm. They were created for bladder, bowel, rectum and sigmoid for all patients, except in cases were the remaining volume was negligible.

Selection of OAR objectives

Two strategies for assigning objectives to OARs were tested, to see if there were any differences in the ability to achieve the clinical goals:

1. Using the built-in dose fall-off function in RayStation (see table 2.2).

2. Defining a set of dose-volume objectives for each OAR and its out-volume (if applicable, see previous section).

One treatment plan with each strategy was made for all patients. These plans were created with 2 full single arcs and collimator angles 5° (ccw) and 25° (cw).

3.2.3   Evaluation of arc configurations

In addition to the plans made with 2 single arcs described in the previous section, plans with 1 arc and a dual arc were created for all patients. These plans were made using dose fall-off objectives for OARs. The objective set used in the plan with 2 single arcs for each respective patient was used as a

starting point, with individual adaptions made both before and during the optimization to achieve as many clinical goals as possible as well as a clinically acceptable dose distribution. After any major change in the objective set, the optimization was reset and started over.

A collimator angle of 25° was used for the 1 arc and dual arc plans. For the plans with 2 single arcs or dual arc, a maximum delivery time of 90 sec was used for each arc. For the 1 arc plans, maximum delivery times of 90, 120 and 180 sec was tested for the first two patients. As some improvement in plan quality was seen when the delivery time was increased to 120 sec, but the actual time used remained around 120 sec even if longer delivery times were allowed, 120 sec was chosen as the maximum delivery time for all 1 arc plans.

As the plans made with 2 arcs were satisfactory, configurations with 3 arcs were not tested.

3.2.4   Beam and optimization settings

Unless otherwise stated, the following settings were applied:

- Beam energy: 6 MV (department practice).

- Leaf motion constrained to 0.5 cm/deg (department practice).

- Iterations before conversion: 7 (default).

- Intermediate and final dose computed automatically.

- Optimization tolerance: 1.000E-6.

3.3   Treatment plan evaluation

The following parameters were considered when evaluating the quality of the treatment plans:

- How many clinical goals could be achieved.

- The number of monitor units (MU) required to deliver the plan.

- QA measurements according to department protocol for VMAT treatment plans (see next section).

- Clinical evaluation: Two medical physicists examined a selection of the treatment plans and evaluated if the dose distributions were clinically acceptable.

- Work flow: Fluency and efficiency of the treatment plan creation, and potential resources required for implementation in the clinic.

3.3.1 QA measurements

Evaluation of the treatment plans included delivery to a Delta$^{4\,PT}$ phantom (by ScandiDos AB, Uppsala, Sweden). The conformity of the delivered dose to the planned dose was evaluated as described in section 2.6.

Chapter 4

Results

Each of the 5 patients included in this study had 1-4 positive lymph nodes. 4 patients had positive nodes in the true pelvis only and 1 also had a positive common iliac lymph node. The mean total target volume (PTV_45) was 1853 cm^3 and the mean nodal boost volume was 145.0 cm^3. A summary of the tumor characteristics for each patient is given in table 4.1.

Table 4.1: Characteristics for each of the 5 patients included in the study. The total target volume is the volume of the PTV_45, and the total boost volume is the volume of the sum of all PTV-N's.

Patient	LNs in true pelvis	LNs outside true pelvis	Total target volume [cm^3]	Total boost volume [cm^3]
1	2	1	1849	128.6
2	2	-	1874	81.0
3	2	-	1532	116.7
4	1	-	1450	25.9
5	4	-	2561	372.8

The following margins had been used for nodal targets: GTV-N to CTV-N margins of 5 mm for 4 patients and 10 mm for 1, and CTV-N to PTV-N margins of 7-8 mm, giving total GTV-N to PTV-N margins of 12-18 mm. Patient 5 had both the largest margins and the highest number of positive lymph nodes, resulting in a very large nodal boost volume.

4.1 Creation of auxiliary structures

An example of the dose gradient inside a lymph node target volume with CovP planning is shown in figure 4.1. Achieving a sharp gradient around the lymph node PTVs proved challenging, resulting in high doses to large areas surrounding the PTV-N's. To amend this, ring structures were created around the PTV-N's as follows: After removing the PTV-N('s), the remaining PTV_45 was split into two separate auxiliary structures; a gradient (ring) volume, **PTV_Grad**, consisting of a 1 cm thick ring around the PTV-N('s), and **PTV_Help45** which includes the remaining parts of the PTV_45 (figure 4.2). Thus, objectives could be customized to the two separate regions within the PTV_45. The effect on the dose distribution is illustrated in figure 4.3.
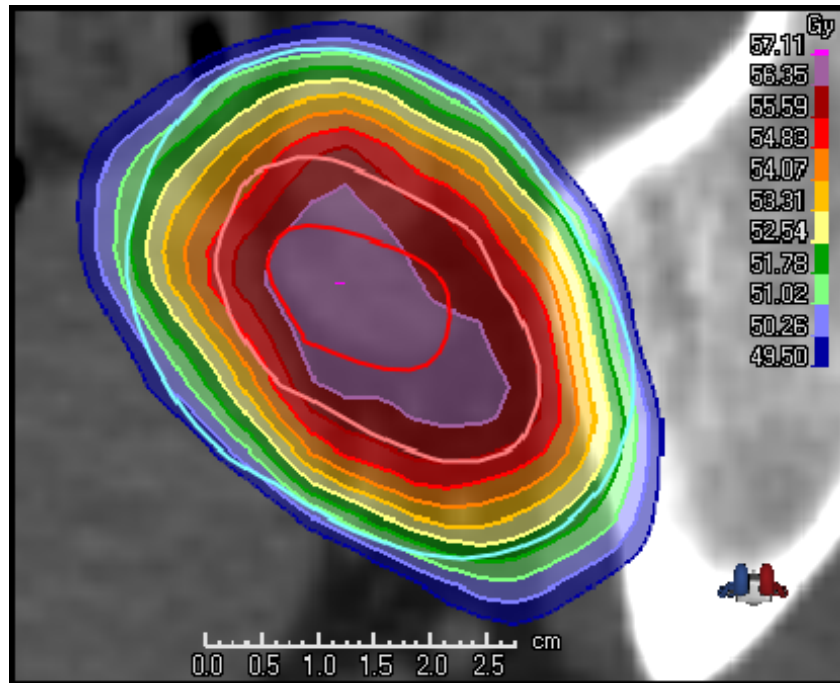
Figure 4.1: Illustration of the dose distribution in and around a lymph node target volume with CovP planning. Dose levels ≥90% of the prescribed LN dose (55 Gy) are shown in color wash. The contours are red for GTV-N_55, light pink for CTV-N_55 and cyan for PTV-N_55.

Other approaches that were tested but found less effective for this purpose

included:

- Dose-volume objectives for PTV_45 only (such as 48.15 Gy to max 10% of the volume).

- A dose fall-off objective for the entire PTV_45 structure.

- A max dose objective of 46.5 Gy for an auxiliary structure equal to PTV_45, but with PTV-N's with a 5 mm margin subtracted + a dose fall-off objective with a low dose level of 45 Gy in the 1 cm closest to the PTV-N's.
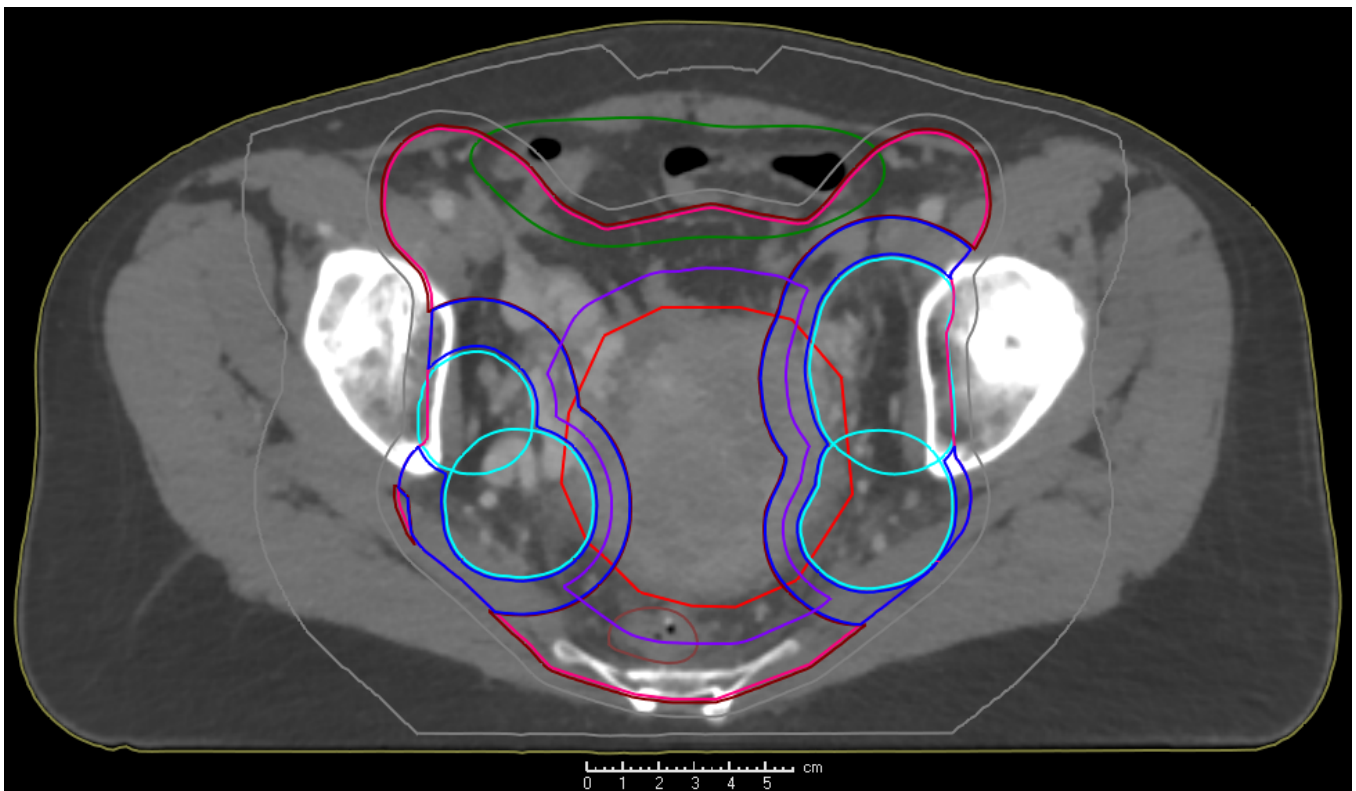
Figure 4.2: Auxiliary structures used in the treatment planning. PTV_Grad in blue, PTV_Help45 in dark red/maroon, NormalTissue in grey and GTV-T + 10 mm in purple. Other structures shown are GTV-T (red), PTV-N#_55 (cyan), PTV_45 (pink), bowel (dark green), rectum (brown) and body (olive).
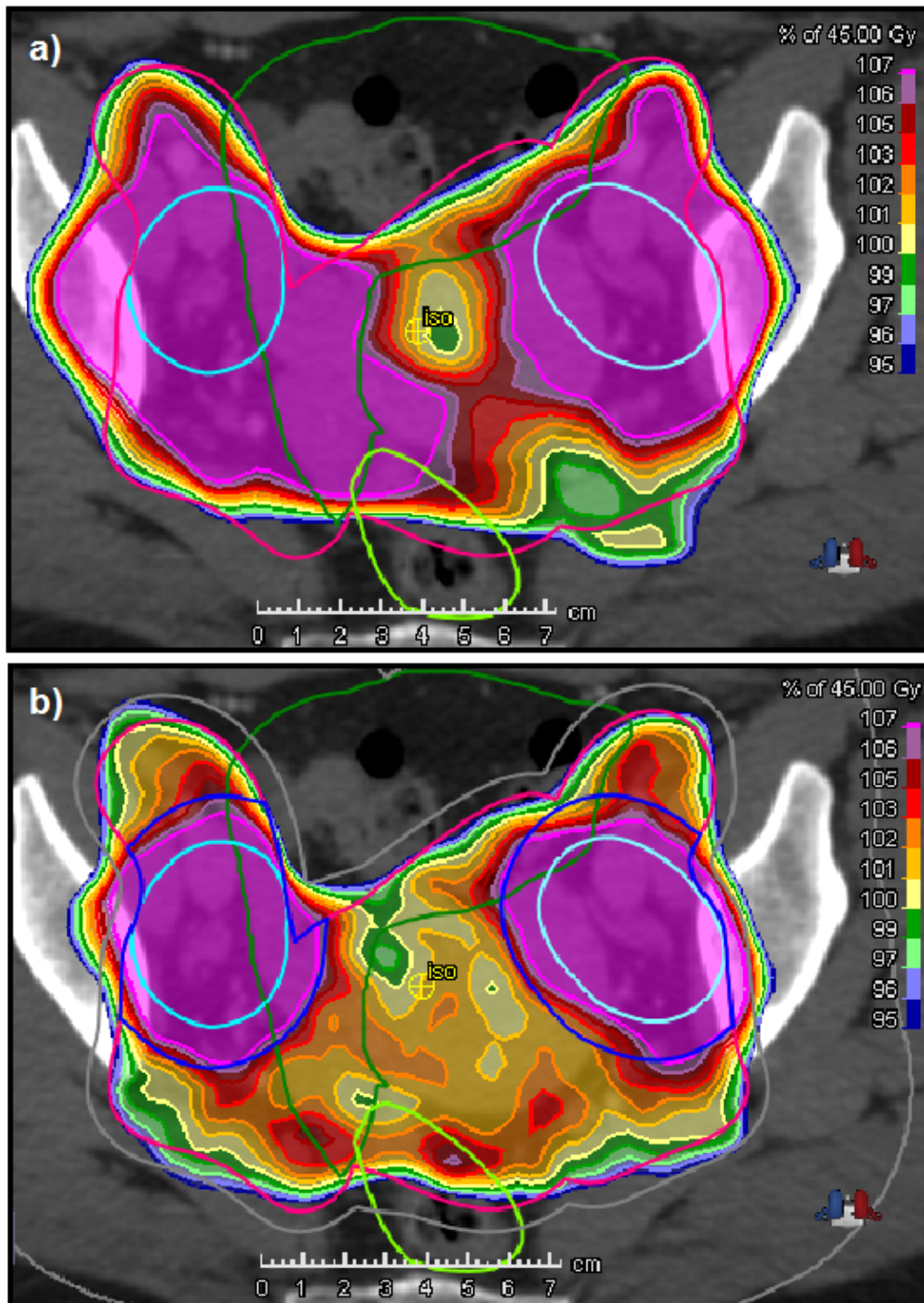
Figure 4.3: Dose distributions showing the improved conformity around the nodal PTVs (cyan) and PTV_45 (pink) after introducing the PTV_Grad (blue) and NormalTissue (grey) ring structures (panel b). In panel a), dose-volume objectives for PTV_45 are used in an attempt to limit high doses 'leaking' around the lymph node PTVs, and a dose fall-off objective on External is used to limit high doses in normal tissue outside the delineated structures. Other structures shown are bowel (dark green) and sigmoid colon (light green).

To achieve a sharp gradient from the PTV_45 to the adjacent normal tissue, two approaches were tested; a dose fall-off objective for External (body + table), or dose-volume objectives for a structure called **NormalTissue**, consisting of a 3.5 cm thick region (ring) starting 0.5 cm outside the PTV_45 (see figure 4.2). The NormalTissue structure made it easier to control the dose distribution and limit high doses outside the PTV_45 (see figure 4.3), and was therefore preferred in the further work.

For one patient, neither approach worked satisfactorily as significant hot spots in normal tissue remained. This could be improved using a combination of both NormalTissue objectives and a dose fall-off on External.

As no CTV-T HR was delineated, the "CTV-T HR + 10 mm" structure suggested in the EMBRACE II protocol to control the dose in parts of OARs receiving a significant brachytherapy dose could not be created. Instead, **GTV-T + 10mm** was used. To avoid conflict with the LN target coverage, PTV-N's with a 5 mm margin were removed from the structure (see figure 4.2). It turned out that the max dose aim of 103% of 45 Gy for this region could not be achieved in any of the plans. Inspection of the dose distributions revealed that the highest doses occurred near the edge of the structure towards the PTV-N's, as shown in figure 4.4.

A list of auxiliary structures used in the optimization process and details on how they were derived can be found in appendix A.1.

4.2 Selection of OAR objectives

Two plans were created for each of the 5 patients, one where the dose fall-off function was used for bladder, bowel, rectum and sigmoid, and one where a detailed set of dose-volume objectives were defined for each OAR and its corresponding out-volume (see section 3.2.2 and figure 4.5).

A summary of the parameters used for evaluation of the plans is presented in table 4.2, and details for each plan are listed in appendix C. The ability to achieve the clinical goals was similar for the two approaches; only for one out of the 120 evaluated goals did the plans differ (the max dose aim for bowel was achieved in the dose fall-off plan only for patient 4). The PTV_45 coverage was slightly higher in all the plans with dose-volume objectives, although the differences were small (0.04-0.23 %) and all values were satisfactory (>98.9%). The dose distributions were evaluated by two medical physicists, who did not find any significant differences and concluded that
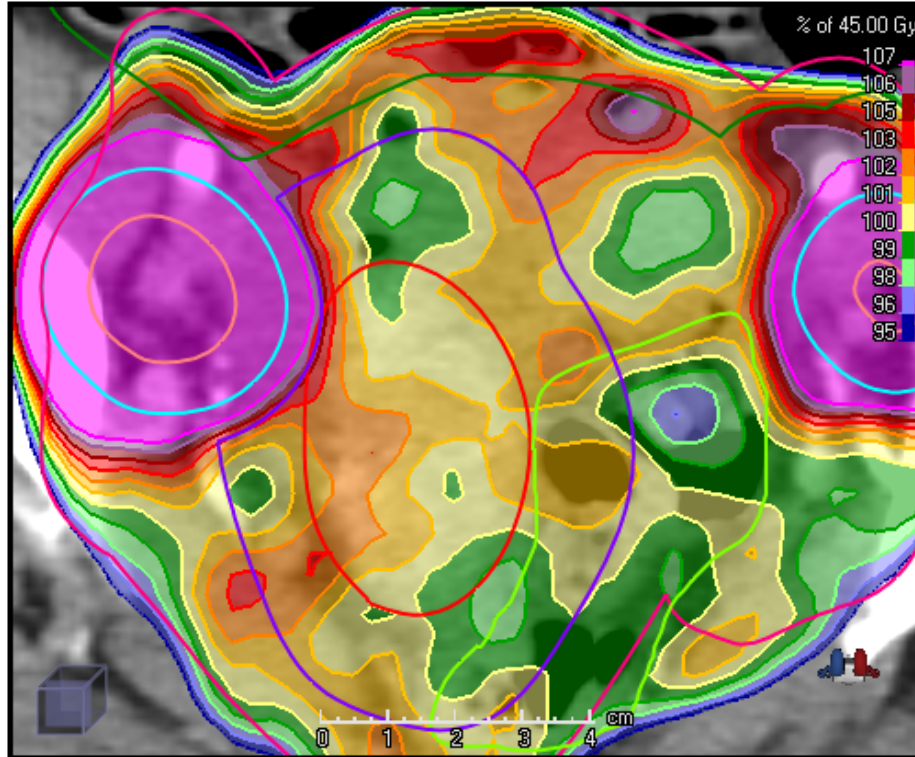
Figure 4.4: Illustration of the "GTV-T + 10 mm" structure (purple), showing how the highest doses in that volume occur right at the edge towards a PTV-N#_55 (cyan). In this section, the part of the sigmoid colon (light green) most likely to receive a significant brachytherapy dose is included in "GTV-T + 10 mm".

both strategies produced clinically acceptable plans.

The number of monitor units (MU) was lower for the plans made with dose-volume objectives for two of the patients, and for the plans made with dose fall-off for three patients. The mean MU was 623 for the dose-volume plans and 555 for the dose fall-off plans. The mean gamma passing rate was slightly higher for the dose fall-off plans, however all plans had gamma passing rates of $\geq 95\%$, well within the clinics acceptance criterion.

The evaluation of plan quality according to the factors mentioned above did not reveal any distinct benefits or disadvantages with either approach. The dose fall-off function is routinely used for treatment planning at St. Olavs Hospital and it requires no auxiliary structures for OARs. Due to considerations of the workflow in the clinic, this approach was therefore chosen
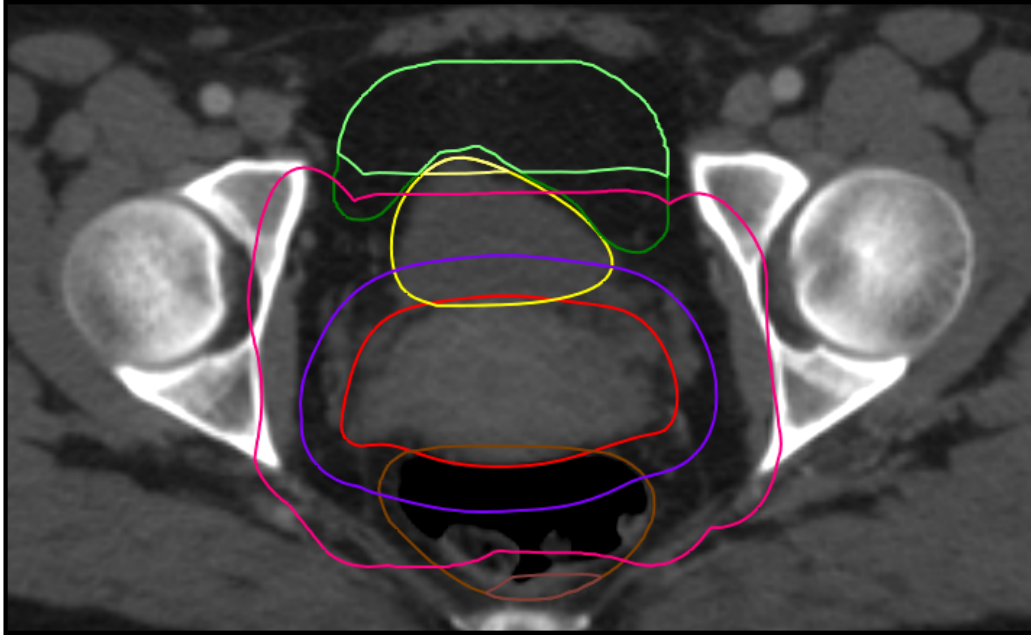
Figure 4.5: Transverse section showing out-volumes for bowel (green), bladder (yellow) and rectum (brown). Contours for out-volumes have a lighter shade than the rest of the organ. This figure also illustrates how the "GTV-T + 10 mm" structure (purple) overlaps the parts of OARs most likely to receive a high dose from brachytherapy, where hot spots should be avoided. Other structures shown are GTV-T (red) and PTV_45 (pink).

Table 4.2: Comparison of the two approaches for OAR objectives. The evaluated parameters include the number of clinical goals achieved, if the medical physicists considered the dose distribution clinically acceptable, and mean values for PTV_45 coverage (percentage of the volume that receives $\geq 95\%$ of the prescribed dose), number of monitor units (MU) and gamma passing rate (GP).

	Dose fall-off	Dose-volume objectives
Clinical goals	105/120	104/120
Clinical evaluation	✓	✓
PTV_45 coverage (%)	99.25	99.36
MU	555	623
GP (%)	99.3	98.0

for further work with this project.

4.3 Optimization template

A complete list of the structures used in the optimization with colors corresponding to those used in figures in this report can be found in section A.2 in the appendix, and a summary of the objectives used in the optimization process for all patients is given in appendix B. Based on this, as well as the clinical goals listed in table 3.1 and inspection of the DVHs, a suggestion for a general objective set that could be used as a template for this patient group is presented in table 4.3.

When using the dose fall-off function, the appropriate low dose distance, low dose value and weight depended strongly on the patient anatomy.

Additional objectives may be helpful depending on the individual patient anatomy and dose distribution, for example:

- If most of the bladder is inside the PTV_45: Max dose objective of 45.0-46.0 Gy.

- If parts of the bowel are inside a PTV-N: Max dose objective of 56.5 Gy.

- If there are hot spots or significant high dose peaks outside the target volume: Dose Fall-Off 45-20 Gy, 8 cm (weight 10) on the External structure.

4.4 Evaluation of arc configurations

A summary of the parameters used to evaluate the different arc configurations is given in table 4.4. Details for each plan can be found in appendix D. All plans verified excellently with gamma passing rates $\geq 98.8\%$, and the ability to achieve the clinical goals was similar (the only difference was the same bowel max dose goal as mentioned in section 4.2).

Although all the 1 arc plans were successful in achieving the clinical goal for PTV_45 coverage, the coverage was lower than in both plans with 2 arcs for all patients. There were particularly differences in the ability to create a conformal dose coverage in concave regions. While 3 of the plans turned out acceptable, inspection of the dose distributions revealed significant

Table 4.3: Suggested general objective set based on the clinical goals in table 3.1 and experience from the optimizations performed in this study. The structures are described in table 2.1 and appendix A.1, and the objective types are described in table 2.2.

Structure	Objective	Weight
Target related structures		
PTV_Help45	Min dose 44.5 Gy	130
	Max dose 46.5 Gy	100
CTV-N#_55	Min dose 55.3 Gy	100
	Min DVH 56.3 Gy to 50% volume	100
PTV-N#_55	Min dose 50.0 Gy	100
	Max dose 58.6 Gy	100
CTV-N#_57.5	Min dose 57.7 Gy	100
	Min DVH 58.8 Gy to 50% volume	100
PTV-N#_57.5	Min dose 52.0 Gy	100
	Max dose 61.3 Gy	100
PTV_Grad55	Max dose 55.5 Gy	100
	Min dose 45.0 Gy	100
	Max DVH 50.0 Gy to 25% volume	80
PTV_Grad57.5	Max dose 57.5 Gy	100
	Min dose 45.0 Gy	100
	Max DVH 52.0 Gy to 25% volume	80
GTV-T + 10mm	Max dose 46.4 Gy	80
Normal tissue structures		
Bladder	Dose Fall-Off 45-15 Gy, 2 cm[*]	15
Bowel	Dose Fall-Off 45-15 Gy, 5 cm[*]	10
Rectum	Dose Fall-Off 45-15 Gy, 5 cm[*]	5
Sigmoid	Dose Fall-Off 45-15 Gy, 3 cm[*]	5
Femoral Heads	Max dose 50.0 Gy	50
Spinal Cord[**]	Max dose 48.0 Gy	50
Kidneys[**]	Max EUD 10.0 Gy, Parameter A=1	50
Normal Tissue	Max dose 45.0 Gy	80
	Max DVH 38.0 Gy to 5% volume	50
	Max DVH 30.0 Gy to 28 % volume	50

[*] Adapt high dose to target dose levels.
[**] In case of para-aortic irradiation.

weaknesses for two patients. Figure 4.6 shows one section from each of these patients where the 1 arc plan is considerably worse than the 2 arc plans.

Table 4.4: Comparison of the different arc configurations. The evaluated parameters include the number of clinical goals achieved, if the medical physicists considered the dose distribution clinically acceptable for all patients, and mean values for PTV_45 coverage (percentage of the volume that receives $\geq$ 95% of the prescribed dose), number of monitor units (MU) and gamma passing rate (GP). (Note: MU and GP for the plans with 2 single arcs is not identical to table 4.2 as they were measured on two different occasions and some adjustments were made in the plans.)

	1 arc	2 single arcs	Dual arc
Clinical goals	104/120	105/120	104/120
Clinical evaluation	✗	✓	✓
PTV_45 coverage (%)	98.68	99.25	99.36
MU	448	538	559
GP (%)	99.9	99.6	99.7

The difference in PTV_45 coverage was very small between the plans made with 2 single arcs and dual arc, and the dose distributions were overall rather similar (figure 4.6). None of the two configurations stood out as more effective in achieving the aims or easier to use than the other.

4.5 Examples of challenges in the treatment planning

4.5.1 Bladder anatomy and doses

The dose-volume planning aims for the bladder - V40 Gy < 75% and V30 Gy < 85% - could only be achieved for 2 of the 5 patients. For the 3 remaining patients, almost the entire bladder was located inside the PTV_45, and to meet the bladder aims the PTV_45 coverage would have to be sacrificed as showed in the next section. An example of a situation where the planning aims were not possible to achieve is shown in figure 4.7.

The bladder volumes for the patients in this study ranged from 41.0-71.1 cm^3, with a mean value of 57.1 cm^3.
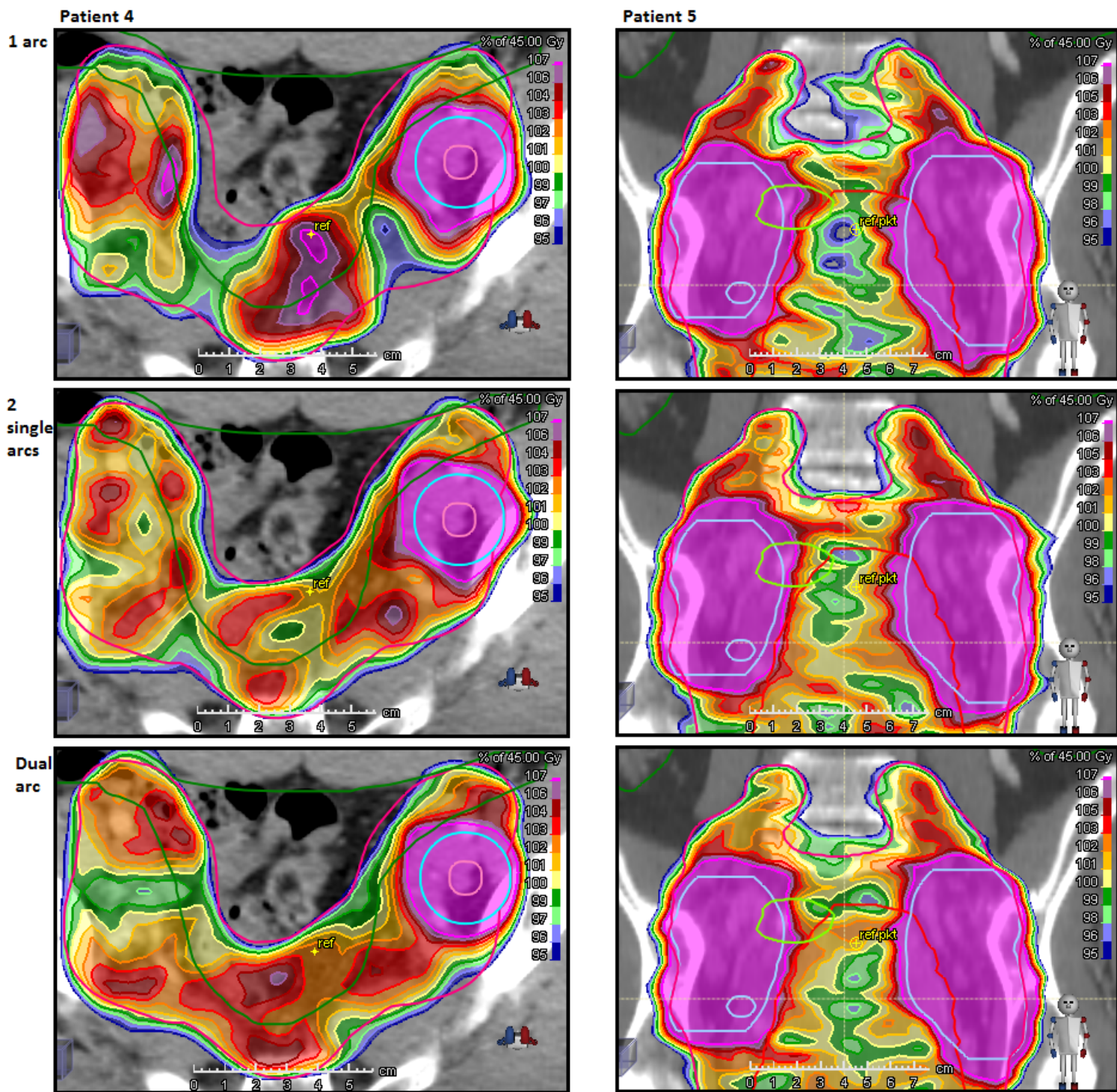
Figure 4.6: Dose distributions for plans made with 1 arc (top), 2 single arcs (middle) and dual arc (bottom). A transverse section from patient 4 is shown on the left, and a coronal section from patient 5 on the right. Sections were chosen to highlight shortcomings in the 1 arc plans. Doses above 95% of the prescribed dose (to PTV_45) are shown in color wash. The contours are red for GTV-T, bright pink for PTV_45 and cyan for PTV-N#_55.
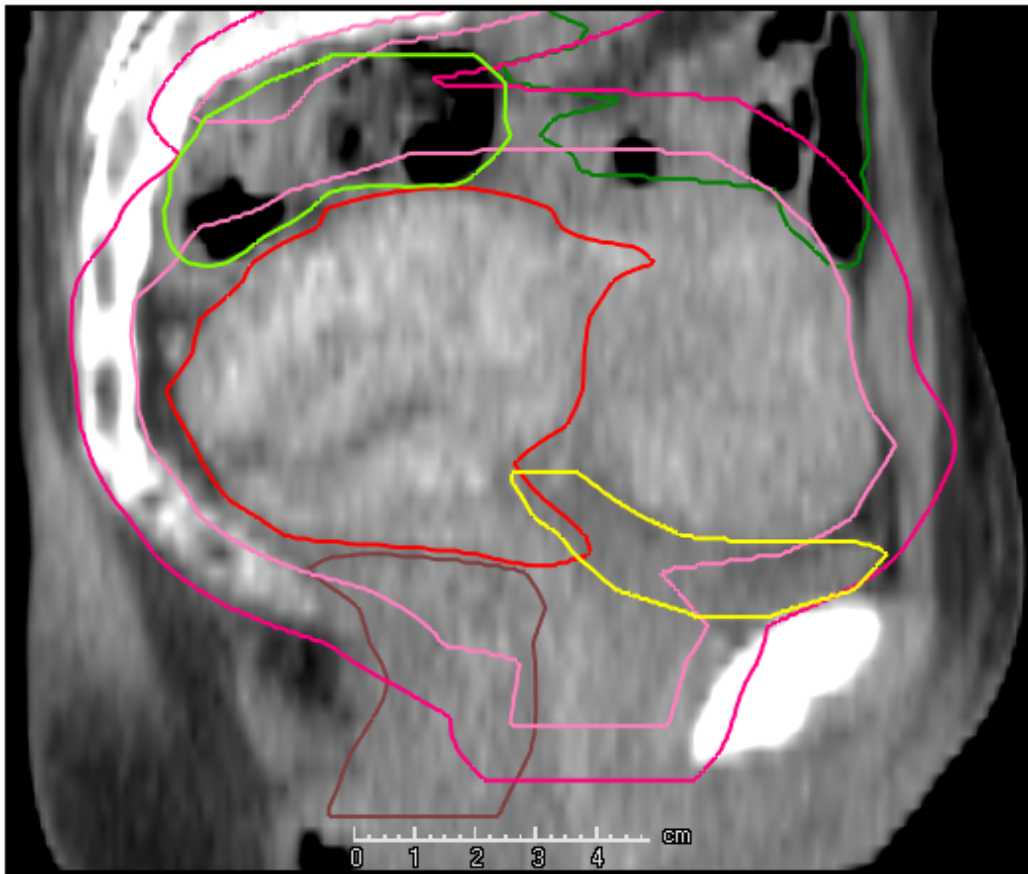
Figure 4.7: Sagittal section from a patient where the dose-volume aims for the bladder could not be achieved. The bladder (yellow) overlaps almost completely with the PTV_45 (bright pink). The flat appearance of the organ was common for the 3 patients for which the aims were not fulfilled.

4.5.2 Target coverage and robustness

For illustration purposes, a plan with focus on achieving as many clinical goals as possible was created for a patient with large parts of the bladder and rectum inside the PTV_45.

The test plan fulfilled all clinical goals for bladder and rectum, and 27 out of 28 clinical goals in total. The reference plan (the plan with 2 single arcs made previously), considered clinically acceptable by two medical physicists,

fulfilled 24 out of 28 clinical goals, with the volumes of the bladder receiving more than 30 Gy and 40 Gy respectively and the rectum volume receiving more than 40 Gy larger than the aims (the max dose aim for the bowel could not be achieved in any of the plans, as the bowel and CTV-N_57.5 overlapped). The PTV_45 coverage (>95% of prescribed dose) was reduced from 99.69% in the original plan to 97.71% in the test plan, still well within the >95% aim from EMBRACE II.

However, inspection of the test plan dose distribution revealed significant cold areas in parts of the bladder and rectum inside both the PTV_45 and CTV_45 (figure 4.8). The medical physicists stated that they would not be comfortable using this plan in the clinic, despite the apparent advantages when considering the EMBRACE II aims.

The volumes of bladder and rectum inside the PTV_45 for this patient was 40 and 54 cm^3 respectively, which combined equals 5.1% of the total PTV_45 volume.
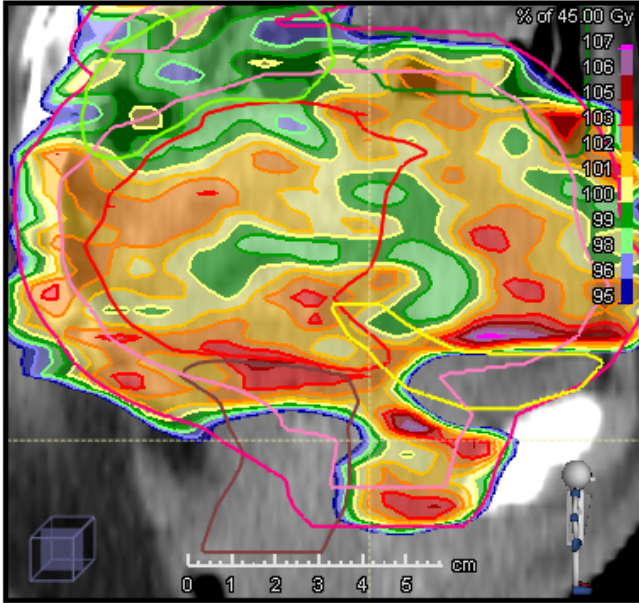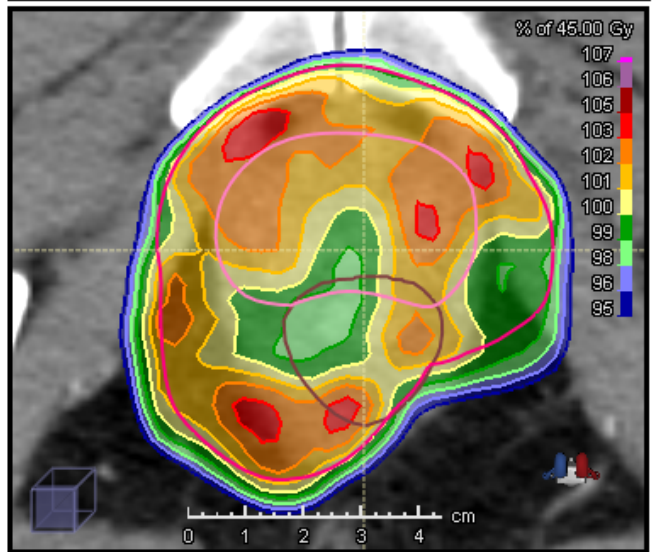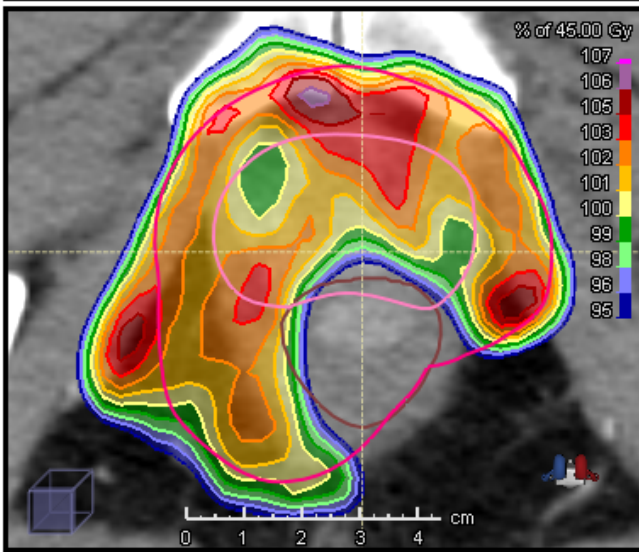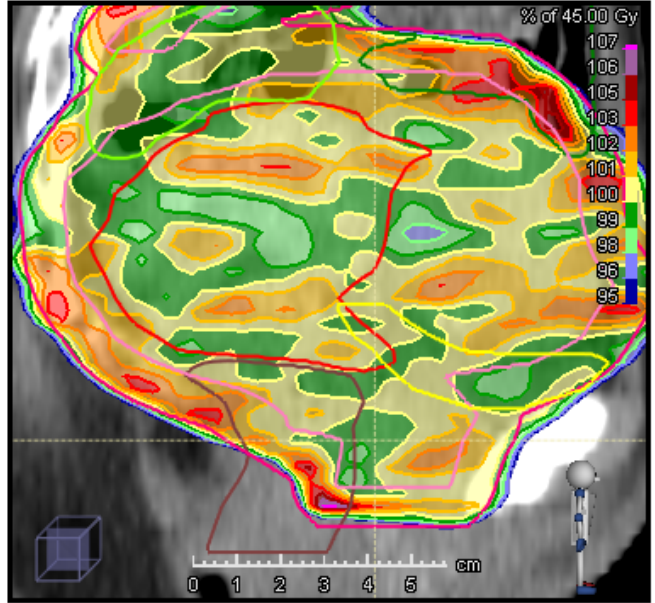
Figure 4.8: Comparison of the dose distributions for the test plan (left) and reference plan (right). The top panel is a sagittal view through the pelvis, and the bottom panel is a transverse view through the middle of the rectum. Doses above 95% of the prescribed dose are shown in color wash. The contours are red for GTV-T, light pink for CTV_45, bright pink for PTV_45, yellow for bladder and brown for rectum.

Chapter 5

Discussion

Implementation of SIB for cervical cancer with lymph node metastases is supported by recent studies. Although this is a rather new technique, both retrospective dosimetric comparisons to sequential boost plans and clinical results from SIB treatment have been published, encouraging future use [5–8].

One of the major benefits of SIB compared to sequential boosting is the decreased number of EBRT fractions used for treatment delivery, making the treatment more convenient for the patient, saving resources in the department and potentially reducing the OTT. Several studies emphasize the importance of OTT in radiotherapy of cervical cancer [18, 34], and according to the EMBRACE II treatment protocol, EBRT and brachytherapy should be completed within 50 days.

Treatment time ≤50 days has been achieved at St. Olavs Hospital also with sequential lymph node boosting (figure 2.3d). However, SIB enables either further reduction of treatment time with integrated EBRT and brachytherapy as in figure 2.3c, or brachytherapy after completion of EBRT as in figure 2.3a-b for a possible decrease in the risk of adverse side effect. By delivering the brachytherapy after the EBRT, the significant tumor regression that often occurs during EBRT can be fully exploited to improve the potential of achieving satisfactory brachytherapy target coverage. This is more significant for large or poor-responding tumors [14].

Delivering the same physical dose in a shorter time with higher fraction doses results in a higher biologically effective dose, as there will be less repair both for target and normal tissues. This could positively influence the tumor control, but it is important to monitor the effect on OAR morbidity. However,

clinical studies have found acceptable rates of adverse effects with SIB despite the increased fraction doses [5, 8]. This is likely because of the precision of IMRT/VMAT combined with the control over the dose distribution offered by integral planning. Also, the required dose gradient is much smaller when building from 1.8 Gy in surrounding tissue to 2.2 Gy in lymph node PTVs than when building from 0 Gy as with sequential boosting, making it easier to create a sharp gradient and avoid excessive doses in surrounding tissue.

Alternatively, a lower physical dose can be delivered in a shorter time to achieve the same biological effect for the tumor, with potential to decrease adverse normal tissue effects.

5.1 Clinical structures

5.1.1 Margins for nodal targets

The total GTV to PTV margin used for the nodal targets varied between 12-18 mm for the patients in this study. This is large compared to reported margins from other centers, such as Aarhus University Hospital (5-10 mm) [29], Bern University Hospital (5 mm) [35] and the University of Pittsburgh Cancer Institute (7-10 mm) [8]. In the EMBRACE II treatment protocol, the margin for nodal targets is 5-8 mm (CTV-N to PTV-N margin 5 mm, GTV-N to CTV-N margin up to 3 mm if the appearance of the boundaries differs on CT and MRI). If a PTV-N is not encompassed by the PTV_45, a margin of 10 mm may be considered [9].

Reduction in the margin for nodal target volumes can spare normal tissue, and in a SIB setting where 45 Gy is delivered to the PTV_45 surrounding the PTV-N's, the consequence of potential misses would be limited [29]. Also, daily CBCT in treatment position and couch correction based on matching on bony structures is performed for cervical cancer treatment at St. Olavs Hospital, limiting set-up errors and reducing the risk of geographical misses. A reduction in the margins for LN target volumes to comply with the EMBRACE II delineation guidelines therefore seems appropriate.

5.1.2 Delineation of target structures

As the structures in the pelvic region (especially the cranial part of the uterus and the OARs) are more mobile than those in the elective nodal region (where

lymphatic vessels usually follow bony structures), different internal margins are appropriate. Current practice at St. Olavs Hospital is to create the PTV_45 by applying a margin of 7-8 mm to the CTV-E and 12 mm to the CTV-T. No ITV is delineated.

The EMBRACE II protocol uses a margin of 5 mm from CTV-E to PTV. For the CTV-T LR, clinical judgement of the range of target motion based on imaging with different modalities and organ filling statuses is used for delineation of an internal target volume (ITV-T LR). A margin of 5 mm is then applied to create the PTV. Image-guided set-up is required for each fraction. In this way, target coverage can be maintained and the dose in large bowel volumes potentially decreased.

Delineating a CTV-T HR structure may not be as essential as no clinical aims are defined for the structure and it is not necessary for creation of the ITV_45. It is however used to create the optional "CTV-T HR + 10 mm" structure.

5.2 Auxiliary structures

Auxiliary ring structures were a useful tool in the optimization process, both around the PTV_45 to limit high doses in normal tissue and around the PTV-N's to allow a lower and more homogenous dose in the remaining PTV_45. The separation of PTV_ 45 into the PTV_Grad and PTV_Help45 structures was helpful, and an advantage compared to other methods tested was that a high weighted max dose objective of for example 46.5 Gy ($\approx$ 103%) could be applied to the parts of the PTV_45 not immediately adjacent to the PTV-N's. This had a positive effect on the dose distribution as shown in figure 4.3.

5.2.1 GTV-T + 10 mm

The "GTV-T + 10 mm" structure was constructed for this study, in an attempt to imitate the suggested "CTV-T HR + 10 mm" from the EMBRACE II protocol in the local clinical setting. The present structure is slightly less extensive than the EMBRACE II structure, still the planning aim (Dmax < 103% of 45 Gy) was not achieved in any of the plans for any patient. Modifications to the structure therefore seems appropriate.

A recommended margin towards PTV-N's in the area is not mentioned

in the EMBRACE II protocol. 5 mm was used in this study (see appendix A.1). As the highest doses occurred close to the PTV-N's (illustrated in figure 4.4), increasing the margin towards PTV-N's to 10 mm would make a significant difference for the max dose in the structure. The desired effect of this structure is avoiding hot areas in OARs, which are mainly located in anterior (bladder, bowel) or posterior (rectum, sigmoid colon) parts of the volume, while most lymph nodes are located lateral to the GTV-T. This alteration would therefore not have a large impact on the effect of the structure (small volumes of the sigmoid colon and bowel would be excluded for some patients).

However, two of the patients did not have any PTV-N's in this region, and the max dose aim was not quite achieved for these patients either. Increasing the weight of the max dose objective or adding a uniformity objective in the optimization may be possible ways of achieving the aim.

Even if some adjustments would be preferable, the current structure with an appropriate max dose objective will make sure that this issue is considered by the optimization algorithm.

5.3   OAR objectives

When comparing the two strategies for OAR objectives, the main point of interest was to examine if achieving the treatment planning aims for OARs would be easier with one of them. No major differences were found, but due to considerations of the workflow in the clinic, the dose fall-off approach was chosen for further work with this project. The dose fall-off function is routinely used in the treatment planning at St. Olavs Hospital, and it requires no auxiliary structures for OARs.

It should, however, be noted that out-volumes with dose-volume objectives performed equally well in terms of achieving the clinical goals, and might make it easier to control the dose levels within an organ. This approach gives the opportunity to fine-tune the dose-volume objectives with focus on desired dose levels, while the dose fall-off only offers a linear approach.

Another challenge with the dose fall-off function is that it can be difficult to determine when the objectives are optimal for the specific patient, as the effect of adjusting the input objectives is not always apparent in the DVH. Thorough slice-by-slice visual inspection of the dose distribution to evaluate any potential for improvement is therefore especially important.

A limitation for both the dose fall-off function and the out-volumes is that they only work outside the target volume. In cases where an entire organ is located within the PTV_45, the organ would thus not be considered in the optimization process at all. If the majority of an organ overlaps the target volume, special care should therefore be taken to avoid hot spots inside the organ, by for example adding a max dose objective.

As a conclusion, the dose distributions and ability to achieve the clinical goals were similar with the two approaches. Dose fall-off objectives may save time in the treatment planning process, while dose-volume objectives offer more control and make it easier to adjust the dose distribution according to specific aims or patient anatomy.

5.4   Arc configurations

Although the ability to achieve the clinical goals was similar for plans made with 1 and 2 arcs, comparison of dose distributions showed that the 1 arc plans were clearly worse in terms of achieving a conformal target coverage. The 1 arc plans were acceptable for some patients, while others had obvious shortages in the dose distribution. For one of the patients (patient 5, figure 4.6) the lack of target coverage between the PTV-N's was especially concerning, as significant cold areas were present in the middle of the GTV-T. The plans with 2 arcs managed to achieve satisfying coverage also in this area. In conclusion, the small benefit in treatment time (and thereby potentially in precision and reduction of leakage radiation) does not justify using only 1 arc for this patient group.

The configurations with dual arc and 2 single arcs both have their advantages; dual arc has more freedom in creating the initial MLC openings that form the basis for the optimization, while the 2 single arcs can have different collimator angles and therefore increased freedom in another way. For this patient group both configurations seem to work well. For other diagnoses where the target volumes are smaller and the anatomy more intricate there may be larger differences between plans made with these two configurations.

In case of very challenging anatomies where 2 arc plans are not found acceptable, an alternative in order to improve plan quality could be combining a dual arc with a third arc using a different collimator angle. This was not tested in this study as approaches using 2 arcs provided satisfactory dose distributions for all patients.

5.5 Optimization challenges

5.5.1 Bladder protocol

Achieving the clinical aims for the bladder proved to be a challenge for most patients, and only for 2 of the 5 patients could all aims for the bladder be achieved.

The treatment planning aims from EMBRACE II for the bladder are based on a protocol with comfortably filled bladder, while treatment at St. Olavs Hospital is performed with empty bladder. The relevance of the dose-volume aims is therefore questionable. When implementing SIB treatment planning according to the clinical goals from EMBRACE II, the department should therefore also implement a similar bladder filling protocol.

With increased bladder filling, parts of the bladder and bowel are pushed away from the target volume. An empty bladder protocol may improve reproducibility, especially for patients that experience radiation side effects that impact their ability to maintain a full bladder, but also leads to a considerable loss in bladder and small bowel sparing [36]. Wang et al. found that distension of the bladder significantly reduced the mean dose to bladder and small bowel, as well as the bowel V20Gy, V30Gy and V40Gy, in a comparison of bladder volumes <100 ml and >200 ml [37]. Zhang et al. found a large reduction in V45Gy for both bladder and small bowel with full bladder compared to empty bladder [38].

5.5.2 Target coverage and robustness

The EMBRACE II planning aim for PTV_45 of V95% > 95% seems rather lenient when considering the large target volumes in these patients. 5% of the PTV_45 becomes a significant volume - 93 cm^3 for the mean target volume in this study. For two of the patients, the EMBRACE II planning aim allows underdosage to a volume larger than the entire GTV-T.

Figure 4.8 illustrates how a treatment plan that looks superior in terms of clinical goal achievement represents a concern in terms of robustness, as organ motion easily could cause underdosage in significant target volumes. When considering variations in organ motion and filling status as well as set up variations this could potentially negatively impact the treatment outcome.

Although this example is rather extreme, it illustrates the importance of thorough inspection of the dose distribution, even when the treatment

planning aims are fulfilled.

5.6   Quality assurance

VMAT treatment places high demands on QA as the computerized treatment planning algorithms are somewhat inscrutable and delivery is complex. At St. Olavs Hospital, the QA routines for VMAT include delivery of all plans to a Delta$^{4\ PT}$ phantom and assessment of the gamma passing rate (GP).

All the plans measured in this study had consistently high GP values. The plans were measured on two different occasions, first the plans with different OAR objectives and then the plans with different arc configurations, and between this the phantom went through a repair and new calibration. In the second round of QA measurements the values were outstandingly high. This was somewhat surprising based on the varying dose levels within targets. This result may be explained by the fact that the gradients are not that sharp - in fact, with CovP planning, the gradients around LN targets are deliberately shallow - and with very large targets, the percentage of points in or close to areas with sharp gradients is not that high. The constraint on leaf motion (max 0.5 cm/deg) that is used as a standard at St. Olavs Hospital could also help avoid extreme modulation.

There were some differences in the number of MU between the different approaches tested. The number of MU is an indication of how modulated the plan is. A high degree of modulation is desired in VMAT treatment to obtain a highly conformal dose distribution, as long as the machine is able to accurately deliver the treatment. Therefore, a higher MU is not necessarily a problem as long as the plan verifies well when delivered to the phantom. Robustness might however still be a concern; a small deviation in the set-up or change in internal anatomy might cause severe over- or underdosage in a highly modulated plan with small margins and steep gradients.

5.7   Implementation of SIB in the clinic

The radiotherapy department at St. Olavs Hospital would like to start using SIB for treatment of lymph node metastases in cervical cancer patients. The objective set presented in table 4.3, with its corresponding auxiliary structures, could be used as a starting point for the optimization and should work

well for most patients. However, a limitation in this study is that none of the patients had positive para-aortic nodes, and only one node was located outside the true pelvis. There were, however, no particular difficulties associated with reaching the treatment planning goals for the node with the highest prescribed dose level. Max dose aims for the kidneys and spinal cord would likely be more difficult to achieve if para-aortic LNs were involved.

The EMBRACE studies represent the largest, most systematic investigation of modern radiochemotherapy for locally advanced cervical cancer and more and more institutions will likely start following the EMBRACE II treatment protocol. To fully exploit this knowledge and make comparison easier, using a protocol as similar as possible would be beneficial. In addition to the implementation of SIB, adaptions in aspects of the department protocol such as delineation of clinical structures and bladder filling protocol should be considered. This process needs to involve both oncologists, physicists and radiation therapists.

While this study aimed to find a well functioning method for creation of good quality treatment plans with SIB, taking into account the available knowledge from the EMBRACE studies and other relevant literature, there is undoubtedly many other methods that could deliver satisfactory plans. Testing all possible combinations of settings, structures and objectives (or even just the most obvious ones) is an insurmountable task. Focus has therefore been on developing a method that seems to perform well for most patients.

In addition to testing the proposed objective set on patients with para-aortic lymph node metastases, some aspects of the treatment planning that would be interesting to investigate but were not included in this study due to the limited amount of time include:

- How variations in e.g. rectum filling, uterus position and patient contour (due to weightloss or swelling) might impact the actual patient dose. Especially in areas close to PTV-N's, where fraction doses higher than 2 Gy are administered.

- If the constraint on MLC leaf motion used as a standard in the department (but met with scepticism by RayStation representatives) actually influences the verification results positively or the dose distribution negatively.

Chapter 6

Conclusion

SIB treatment planning for VMAT was successfully performed retrospectively for 5 patients with cervical cancer and lymph node metastases, producing dose distributions that were satisfactory as assessed by medical physicists and verified excellently according to the department's quality assurance procedure.

The effect of different types of objectives, auxiliary structures and arc configurations on the dose distribution was evaluated, and a set of optimization objectives is presented that should be a good starting point for the treatment plan optimization for most patients. Satisfactory treatment plans were achieved using 2 full arcs, while the plan quality was worse for plans made with 1 arc, and not acceptable for 2 of the 5 patients.

SIB is one of a number of interventions in the EMBRACE II treatment protocol, currently regarded as the gold standard for radiation therapy of cervical cancer. To make comparison with the protocol easier and get the most benefit from the comprehensive research behind it, other aspects should be considered for implementation in the department, such as the procedure for delineation of target structures and organs at risk and the bladder filling protocol.

Radiation therapy with SIB for cervical cancer with lymph node metastases is recommended in scientific literature and has a number of benefits, and is shown to be feasible in the clinical setting at the radiotherapy department at St. Olavs Hospital.

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APPENDICES

Appendix A

Optimization structures

A.1   Auxiliary structures

The auxiliary structures used in the optimization process were derived as follows:

PTV_Help45	PTV_45 + 1 mm. Subtract all PTV-N's with a 10 mm margin.
PTV_Grad	PTV_45 - PTV_Help45. Subtract all PTV-N's with a 1 mm margin. One common gradient structure was made around all PTV-N's with the same prescribed dose.
NormalTissue	PTV_45 + 4 cm. Crop towards Body and PTV_45 with a 5 mm margin.
GTV-T + 10 mm	GTV-T + 10 mm. Subtract all PTV-N's with a 5 mm margin.
Out-volumes for OARs	Subtract the part of the organ that extends inside PTV_45, with an additional 5 mm margin.

A.2 List of all structures

Targets		Organs at risk		Other
🟪 CTV_45union		🟨 Bladder		🟪 GTV-T + 10mm
🟧 CTV-E_45		🟨 BladderOut		🟦 PTV_Grad55
🟥 CTV-N1_55		🟫 BODY		🟦 PTV_Grad57.5
🟥 CTV-N2_55		🟩 Bowel		🟥 PTV_Help45
🟥 CTV-N3_57.5		🟩 BowelOut		
🟧 CTV-T_45		🟧 External		
🟥 GTV-N1_55		🟧 Femoral Head dx		
🟥 GTV-N2_55		🟩 Femoral Head sin		
🟥 GTV-N3_57.5		🟫 Kidney dx		
🟥 GTV-T		🟦 Kidney sin		
🟪 PTV_45union		⬜ NormalTissue		
🟦 PTV-E_45		🟫 Rectum		
🟦 PTV-N1_55		🟫 RectumOut		
🟦 PTV-N2_55		🟩 Sigmoid		
🟦 PTV-N3_57.5		🟩 SigmoidOut		
🟦 PTV-T_45		🟪 Spinal Canal		

Figure A.1: Structures used for delineation or optimization in alphabetical order, with colors matching the contours in the figures in this report. The number of lymph nodes naturally varies, here shown for patient 1. For simplicity, PTV_45union is called PTV_45 throughout the report.

Appendix B

Summary of optimization objectives

Table B.1: Summary of objectives used for all 5 patients, showing the range of values used. Objectives from both 2 single arcs (with the dose fall-off approach for OARs) and dual arc plans are included, as both produced satisfactory results and there were only minor differences. See table 2.2 for description of the objective types.

Structure	Objective type	Value(s)	Weight(s)
Target related structures			
PTV_Help45	Min dose	44.5 Gy	100-130
	Max dose	46.5 Gy	100
CTV-N#_55	Min dose	55.3-55.5 Gy	100-130
	Min DVH	56.3-56.4 Gy to 50% volume	100-135
PTV-N#_55	Min dose	50.0 Gy	100
	Max dose	57.8-58.8 Gy	100-130
CTV-N#_57.5	Min dose	57.7 Gy	100
	Min DVH	58.8 Gy to 50% volume	100
PTV-N#_57.5	Min dose	52.0 Gy	100
	Max dose	61.2-61.3 Gy	110-120
PTV_Grad55	Max dose	55.0-55.5 Gy	100
	Min dose	45.0 Gy	100
	Max DVH	48.0-53.5 Gy to 11.5-25.5% volume	80
PTV_Grad57.5	Max dose	57.5 Gy	100
	Min dose	45.0 Gy	100
	Max DVH	50.0 Gy to 12% volume	100
GTV-T + 10mm	Max dose	45.8-46.4 Gy	80-120
Normal tissue structures			
Bladder	Dose Fall-Off[*]	[H] 45 Gy [L] 6-15 Gy, 0.55-2 cm	15-90
Bowel	Dose Fall-Off[*]	[H] 45 Gy [L] 15 Gy, 3-5 cm	10-15
Rectum	Dose Fall-Off[*]	[H] 45 Gy [L] 10-15 Gy, 3-5 cm	3-20
Sigmoid	Dose Fall-Off[*]	[H] 45 Gy [L] 5-15 Gy, 3-5 cm	3-50
Femoral Heads	Max dose	50.0 Gy	50
Spinal Cord	Max dose	48.0 Gy	50
Kidneys	Max EUD	10.0 Gy, Parameter A=1	50
Normal Tissue	Max dose	45.0 Gy	80-100
	Max DVH	37.0-40.0 Gy to 1.5-7.5% volume	50-60
	Max DVH	30.5-33.0 Gy to 22.0-29.0% volume	50-60

[*] Input to the dose fall-off function includes high dose level [H], low dose level [L] and low dose distance. "Adapt high dose to target dose levels" was applied.

Table B.2: Extra objectives used for individual patients due to particular challenges in the treatment planning.

Structure	Objective type	Value(s)	Weight(s)
Bladder	Max dose	45.0-46.0 Gy	50
Bowel	Max dose	56.3-56.5 Gy	80-110
Sigmoid	Max dose	46.0 Gy	50
	Max dose	56.2-56.45 Gy	130-140
External	Dose Fall-Off	[H] 45 Gy [L] 20 Gy, 5-8 cm	10

Appendix C

Selection of OAR objectives

Parameters used for comparison of the two approaches for OAR objectives are reported for all patients. This includes the number of clinical goals achieved (the aim for "GTV-T + 10 mm" that was not achieved for any patient is not included), if the medical physicists considered the dose distribution clinically acceptable, PTV_45 coverage (percentage of the volume that receives $\geq 95\%$ of the prescribed dose), number of monitor units (MU) and gamma passing rate (GP).

Table C.1: Data for the plans made with dose fall-off objectives.

Patient	Clinical goals	Clinical evaluation	PTV_45 coverage (%)	MU	GP (%)
1	24/28	✓	99.69	485	99.9
2	17/22	✓	98.98	493	99.7
3	22/22	✓	99.37	585	100
4	15/18	✓	99.31	582	98.3
5	27/30	✓	98.92	628	98.7
Sum	105/120	✓	-	-	-
Mean	-	-	99.25	555	99.3

Table C.2: Data for the plans made with dose-volume objectives.

Patient	Clinical goals	Clinical evaluation	PTV_45 coverage (%)	MU	GP (%)
1	24/28	✓	99.84	478	99.6
2	17/22	✓	99.03	653	95.0
3	22/22	✓	99.42	722	99.0
4	14/18	✓	99.54	690	96.4
5	27/30	✓	98.96	574	99.9
Sum	104/120	✓	-	-	-
Mean	-	-	99.36	623	98.0

Appendix D

Evaluation of arc configurations

Parameters used for comparison of the three arc configurations that were tested. For explanation of the parameters, see the previous chapter.

Table D.1: Data for the plans made with 1 arc.

Patient	Clinical goals	Clinical evaluation*	PTV_45 coverage (%)	MU	GP (%)
1	24/28	✓	99.37	409	99.7
2	17/22	✓	98.29	435	99.9
3	22/22	✓	98.44	482	99.9
4	14/18	✗	98.53	408	100
5	27/30	✗	98.78	507	99.9
Sum	104/120	✗	-	-	-
Mean	-	-	98.68	448	99.9

* Inspection of the dose distributions revealed minor issues for patient 2 and significant weaknesses for patient 4 and 5, while target coverage and conformity was satisfactory for patient 1 and 3.

Table D.2: Data for the plans made with 2 single arcs.

Patient	Clinical goals	Clinical evaluation	PTV_45 coverage (%)	MU	GP (%)
1	24/28	✓	99.69	485	99.9
2	17/22	✓	98.98	493	99.7
3	22/22	✓	99.37	585	100
4	15/18	✓	99.31	582	98.8
5	27/30	✓	98.92	546	99.8
Sum	105/120	✓	-	-	-
Mean	-	-	99.25	538	99.6

Table D.3: Data for the plans made with 2 arcs using the dual arc feature.

Patient	Clinical goals	Clinical evaluation	PTV_45 coverage (%)	MU	GP (%)
1	24/28	✓	99.69	509	99.5
2	17/22	✓	98.97	537	99.9
3	22/22	✓	99.53	631	99.9
4	14/18	✓	99.61	510	99.4
5	27/30	✓	99.02	608	100
Sum	104/120	✓	-	-	-
Mean	-	-	99.36	559	99.7