Optimization of adaptive radiation therapy in cervical cancer: Solutions for photon and proton therapy
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Chapter 1

General introduction
Chapter 1

1.1 | Cervical cancer

The uterine cervix is the lower, narrow portion of the female uterus and is the connection between the uterine cavity and the lumen of the vagina. As part of the human female reproductive system, the cervix aids in sperm transportation after sexual intercourse to fertilize an egg cell during ovulation. As shown in Figure 1.1, the uterine cervix is located between the urinary bladder and the rectum.

Figure 1.1 | Transverse (left) and sagittal (right) CT slices showing the location of the cervix, uterus, vagina, bladder and rectum in the female pelvic area.

Epidemiology

Cervical cancer is the fourth most common cancer in women worldwide, with an estimated incidence of 528,000 in 2012 [1]. The large majority of this estimated incidence occurs in the less developed regions, including Eastern Africa, Melanesia, Southern and Middle Africa. In Eastern and Middle Africa, cervical cancer is the most common female cancer. In 2012, an estimated 266,000 deaths from cervical cancer worldwide accounted for 7.5% of all female cancer deaths [1]. In the Netherlands, cervical cancer is the sixth most common cancer in women with 729 newly diagnosed cases and 198 cervical cancer-related deaths in 2014 (Figure 1.2). Current curative treatments in the Netherlands resulted in a three-year overall survival rate of 76% [2].

The major risk factor for cervical cancer is an infection with the human papillomavirus (HPV), especially with the high-risk oncogenic HPV types (HPV-16 and HPV-18). HPV infections are mainly transmitted through sexual contact. Although most infections with HPV are self-limiting and cause no symptoms of cervical cancer, HPV vaccination for young adolescent girls together with cervical screening is recommended by the World Health Organization (WHO). In the Netherlands, the national vaccination program includes HPV vaccination for young adolescent girls and female adults between 30 and 60 years old are screened once every five years. Other risk factors for cervical cancer include smoking, long-term use of oral contraceptives, sexual intercourse at a young age and multiple sexual partners.
Tumor staging

Cervical tumors are staged by the International Federation of Gynecology and Obstetrics (FIGO) staging system based on clinical examination [3]. The use of imaging modalities to evaluate the tumor extension is recommended, however not mandatory [4,5]. Compared to other imaging modalities, magnetic resonance imaging (MRI) has been demonstrated to be superior in tumor extent evaluation including parametrial infiltration and vaginal extension [6-9]. For the evaluation of lymph nodes and distant disease, $^{18}$F-fludeoxyglucose ($[^{18}$F]FDG) positron emission tomography – computed tomography (PET-CT) is considered as the most useful modality [10,11]. Early-stage cervical tumors (FIGO stage IB1–IIA1) include clinically visible lesions limited to the cervix or carcinomas with a limited extension (<4 cm) beyond the cervix without parametrial invasion. Locally advanced cervical tumors (FIGO stage IB2, IIA2–IVA) include clinically visible lesions with a substantial extension (>4 cm) or an invasion in parametria, lower third of the vagina, pelvic wall or adjacent organs.

1.2 Cervical cancer treatment

The standard curative treatment for women with early-stage cervical tumors (FIGO stage IB1–IIA1) is surgery and radiation therapy is reserved for women who are medically inoperable. Surgery usually consists of a radical hysterectomy including a pelvic lymph node dissection. Fertility preserving surgery is reserved for young women with very small tumors [12]. Adjuvant radiation therapy after surgery is offered to patients with early-stage cervical cancer who had pathological features associated with high risk or local recurrences [13].
Radiation therapy with concomitant chemotherapy is the cornerstone of treatment for women with locally advanced cervical tumors (FIGO stage IB2, IIB – IVA) [14-16]. The preferred alternative for cervical cancer patients with a contraindication for chemotherapy is radiation therapy with concomitant hyperthermia [17-20]. Hyperthermia is the artificial elevation of the tissue temperature (40°C – 44°C) to enhance radiation sensitivity of tumor cells resulting in an enlarged therapeutic efficacy of radiation therapy [17,19].

**Radiation therapy**

Radiation therapy uses ionizing radiation to kill malignant cells and is generally applied with a curative intent. To restrain uncontrolled cell growth, the cell deoxyribonucleic acid (DNA) is damaged by ionizing radiation in order to cause cellular death. Instead of delivering a single fraction of high radiation dose, the total amount of prescribed dose is divided into multiple fractions in order to maximize the effect of radiation on tumor cells. Fractionating the dose allows healthy cells to activate their self-repair mechanisms in between fractions which repair the DNA damage. The repair mechanisms in tumor cells are usually less efficient compared to healthy cells, resulting in cell death after irradiation. The difference between therapeutic effectiveness and toxicity defines the therapeutic window of radiation therapy and fractionated treatments are applied to enlarge this therapeutic window.

Radiation therapy can be delivered by addressing the radiation to the tumor from outside the body (i.e. external beam radiation therapy) or by directing the radiation from inside the body (i.e. brachytherapy). In cervical cancer, radiation therapy is offered in a combined strategy: external beam radiation therapy and subsequently brachytherapy.

Brachytherapy, also known as internal radiation therapy, aims to irradiate the tumor locally by using radioactive sources that are placed temporarily or permanently inside or close to the tumor. In brachytherapy for cervical cancer, an applicator is placed temporarily in the vaginal vault and uterine cavity (intracavitary brachytherapy) and the radiation sources are loaded into the applicator. Since the brachytherapy sources are placed near to the tumor, a very high radiation dose can be delivered to the tumor whilst minimizing radiation exposure to surrounding healthy tissue [21]. Brachytherapy can be applied using either low-dose rate (LDR) sessions or as a fractionated high-dose rate (HDR) session. Despite the absence of significant difference when considering overall survival, relapse-free survival, local control rate, recurrences, metastasis and treatment-related complications [22], the use of intracavitary HDR for all clinical stages of cervical cancer is currently more popular than LDR due to shorter treatment times and improved accuracy of source and applicator positioning. As an alternative, a pulsed-dose rate (PDR) scheme can be applied in which short pulses of radiation are given during the course of treatment, typically lasting 24 till 48 hours [23].
1.3 | External beam radiation therapy

External beam radiation therapy is the most common form of radiation therapy in which the radiation is directed at the tumor from outside the body. External beam radiation therapy can be applied using beams of energetic X-rays, protons, neutrons or positive ions. The most commonly applied form of external beam radiation therapy, photon therapy, utilizes beams of high-energy X-rays and is usually delivered using a linear accelerator (Figure 1.3). The gantry of the linear particle accelerator can rotate around the treatment table on which the patient is positioned and allows radiation delivery from different directions. The complete procedure of external beam radiation therapy consists of patient imaging and target definition, radiation therapy planning and actual dose delivery. Photon beams are characterized by a relatively short build-up region to maximize dose deposition and the depth of maximum dose deposition is determined by the beam energy. After the build-up region, the energy deposition is decreased exponentially with increasing tissue depth (Figure 1.4). To limit dose deposition outside the target volume, the radiation dose is generally focused to the target volume by using multiple beams from different directions.

![Figure 1.3 | A linear accelerator with an integrated kV-CBCT system used for clinical radiation therapy.](image)

In particle therapy, beams of energetic protons, neutrons or positive ions are used for cancer treatment. Proton therapy is the most commonly applied form of particle therapy in current clinical practice. Also in the Netherlands, proton therapy will become clinically available in the near future.
In proton therapy, beams of energetic protons are used to irradiate the tumor. Compared to radiation therapy using photons, the penetration depth of the charged particles in proton therapy is determined by the final energy of the emerging proton beam (Figure 1.4). The maximum energy deposition is near the end of the proton range and known as the Bragg peak, while beyond the Bragg peak the dose drops to zero for protons. Due to the energy deposition profile, radiation therapy using protons holds the promise to provide a highly conformal dose distribution including sharp dose fall-offs around the target volume. A complete utilization of the physical characteristics of protons will result an advantage of proton therapy over conventional radiation therapy using high-energy X-rays [24].

![Figure 1.4 | Typical example of dose deposition as a function of depth below the body surface for a photon beam and a proton beam.](image)

**Target definition**

Computed tomography (CT) imaging of the patient is one of the first steps in the radiation therapy chain, whereby the patient body, inner organs and tumor are imaged in radiation treatment position. The patient must be in a position that is suitable for both CT acquisition and treatment delivery and reproducible in order to reduce systematic errors during treatment [25]. Cervical cancer patients are often treated in prone position using a belly board device to reduce bowel irradiation [26-28].

Next, the tumor is delineated on the CT imaging by the radiation oncologist. The gross tumor volume (GTV) represents the visible extent of malignant tumor growth. Although the GTV is generally delineated based on the visualized three-dimensional information on (PET-)CT imaging, additional MRI is increasingly used by the radiation oncologist to improve GTV definitions. The clinical target volume (CTV) is formed by expanding the GTV to include subclinical microscopic malignant cells. For cervical cancer radiation therapy, consensus guidelines recommend that the CTV should comprise the GTV, cervix, uterus, upper part of the vagina, parametria and pelvic
nodes [29]. To ensure a homogeneous dose to the CTV throughout the course of irradiation, the planning target volume (PTV) is formed by adding a site-specific (an)isotropic CTV-to-PTV margin. The PTV accounts for geometrical uncertainties and is used to ensure that the prescribed dose is actually delivered to the CTV. Next to the target volumes, also organ at risk (OAR) volumes are delineated on the CT imaging.

**Treatment planning**

The pre-treatment acquired CT image including delineated target volumes and OARs delineations is used for external beam radiation therapy planning. Each pixel of the CT image is assigned a numerical value (i.e. CT number) and converted into relative electron densities to represent corresponding attenuation values, which are displayed using the Hounsfield unit (HU) scale. In radiation therapy planning, the HU information is used to predict the delivered dose along the beam path by calculating the attenuation of X-ray beams. Different dose calculation models are available, including pencil beam models, collapse cone convolution and Monte-Carlo algorithms, with precision versus computation time being the relevant trade-off [30,31]. The conventional forward treatment planning technique is increasingly replaced by the inverse treatment planning technique.

Forward planning is a technique in which the beams are added and adapted manually in order to deliver sufficient radiation dose to the target volume while minimizing the dose to healthy surrounding tissue. The process of forward planning involves the selection of the appropriate beam energy and the manual adaptation of the beams by defining field sizes, introducing attenuating wedges for non-uniform beam intensities and shaping individual leaves of the multileaf collimator (MLC). If the calculated dose distribution is not satisfactory, adaptations to the beams are applied until the determined dose distribution is satisfactory. In contrast to the forward planning technique, the inverse planning technique is designed to minimize the trial-and-error process while producing highly conformal dose distributions. The inverse problem defined by prescribed dose-volume objective functions for the target volume and OARs is solved in order to geometrically shape the beams.

Besides adaptations to the beam geometry, also the intensity of the beams can be modulated independently to produce the desired (non-)uniform dose distribution in the target volume. This advanced type of high-precision radiation therapy is known as intensity-modulated radiation therapy (IMRT). By modulating the intensity and the geometric shape of the beam, IMRT allows for a highly conformal dose distribution, even around concave target volumes. IMRT can be delivered with either a fixed gantry (i.e. static field IMRT) or a moving gantry (i.e. rotational IMRT). Compared to conventional static field IMRT, rotational IMRT techniques (e.g. volumetric modulated arc therapy (VMAT)) decreased treatment delivery time with the addition of further improved OAR sparing [32].
In proton therapy, the CT numbers are converted into proton stopping power values to approximate the loss of particle energy along the beam path. Proton therapy planning is performed using either a scattering technique or a scanning technique. In scattering techniques, proton beams are spread by placing scattering material in the beam path and custom-made collimators and compensators conform the dose to the target volume. Inside the gantry, range modulators or ridge filters are placed to obtain Bragg peaks at different depths. In beam scanning techniques (e.g. pencil beam scanning), a narrow mono-energetic beam is steered by magnets and the target volume is painted in successive layers. Since the depth of each pencil beam is controlled by varying the beam energy, scanning techniques do not require beam-modifying devices. The pencil beam scanning technique enables intensity-modulated proton therapy (IMPT) which is characterized by a highly conformal dose delivery to complex-shaped target volumes by combining heterogeneous contributions of individual beams [33].

Due to the highly localized dose deposition, IMPT has the potential to improve OAR sparing without compromising on target volume irradiation [34,35]. However, a major challenge in proton therapy is that dose deposition is very sensitive to treatment uncertainties [24]. Interfraction motion of the tumor and surrounding organs limit the targeting accuracy and affect the efficacy of IMPT. As a result, the actual delivered dose distribution is not necessarily similar to the high quality dose distribution obtained during treatment planning. In order to fully exploit the potential benefit of proton therapy, it is essential that IMPT plans are robust against treatment uncertainties.

**Image-guided dose delivery**

External beam radiation therapy in cervical cancer is typically delivered in 23 fractions or 28 fractions when the para-aortic lymph nodes are included in the target volume. Prior to each irradiation fraction, patients are positioned on the treatment table identical to the position during pre-treatment CT imaging to be sure that the actual delivered dose matches the planned dose. Using the in-room laser systems, patients are aligned based on the pre-treatment applied skin marks. The internal patient anatomy relative to the skin marks can largely vary between treatment fractions and pre-fraction imaging is required for accurate dose delivery. Image-guided radiation therapy (IGRT) is a technique whereby frequent imaging is used during the radiation therapy course to improve the accuracy and precision of dose delivery [36,37]. Image guidance modalities commonly applied included portal imaging, planar kilovoltage (kV) or megavoltage (MV) imaging using digital reconstructed radiographs and cone-beam computed tomography (CBCT) imaging.

Portal imaging is the acquisition of patient images based on MV radiation beams used for radiation treatment by measuring the beam portion that passes through the patient. Although portal imaging was initially applied using radiographic films, advancements in digital imaging devices resulted in electronic portal imaging devices (EPID). Compared to film-based portal imaging, EPID allows to process the image directly and digitally and can be used for treatment
guidance [38,39]. However, the lack of volumetric information including soft-tissue information limits the use of EPID-based image guidance.

Volumetric imaging using kV-CBCT technology enables internal structure visualization and allows for treatment localization and verification based on three-dimensional images. Since CBCT imaging systems including a kV source and imaging panel have been integrated with linear accelerators (Figure 1.3), pre-fraction volumetric imaging using the CBCT system is increasingly used to guide irradiation. Two-dimensional projection images of the entire volume of interest are acquired by rotating the CBCT system around the patient and these projections are reconstructed into a three-dimensional volume analogous to the pre-treatment CT image. The reconstructed CBCT image is aligned with the pre-treatment CT image and the treatment table is shifted accordingly in order to minimize patient set-up errors. However, straightforward positional corrections are often not sufficient due to anatomical changes or tumor visibility is limited due to the poor soft-tissue contrast.

Even though the introduction of CBCT imaging has enabled soft-tissue visualization, tumor visibility on pre-fraction kV-CBCT images is often limited. To improve tumor localization on CBCT images, fiducial markers are often implanted in or near the tumor before the treatment course. For various tumor sites, different types of surrogates used for tumor localization are reported [40-44]. Also in cervical cancer, different types of tumor demarcations are investigated to improve daily tumor localization on pre-fraction CBCT images [44-46].

In proton therapy, dose delivery is very sensitive to geometric uncertainties and therefore image guidance during the course of treatment is essential. Since portal imaging is not feasible in proton therapy, orthogonal kV-based image-guided techniques have been used routinely [24]. However, target alignment based on two-dimensional imaging does not provide the variation in patient anatomy for accurate image guidance and high-precision dose delivery. Recently, volumetric imaging using kV-CBCT technology is introduced in proton therapy and modern proton therapy gantries are nowadays equipped with a CBCT imaging system.

1.4 Adaptive radiation therapy

Adaptive radiation therapy (ART) aims to individualize radiation therapy based on patient-specific variations evaluated during the course of treatment. Originally, ART was developed as an offline strategy to correct for systematic errors by re-planning during the radiation therapy course [47-50]. However, this adaptive strategy increased the clinical workload during the course of radiation therapy without accounting for random day-to-day variations [50,51].

The introduction of pre-fraction volumetric imaging has enabled daily soft-tissue visualization and together with possible tumor demarcation by fiducial markers allows for treatment adaptations. In online ART, the dose delivery is adapted directly after imaging according to the observed interfraction anatomical changes. The obvious advantage of online adaptations is
that both systematic and random errors are corrected efficiently. Since adaptations can be applied using various approaches, different online adaptive strategies have been investigated [52-57]. The preferred online adaptive strategy includes daily radiation therapy re-optimization based on pre-fraction imaging. However, such an online adaptive strategy is not yet feasible in clinical practice due to technical and logistical limitations.

A frequently applied practical adaptive approach in radiation therapy for pelvic tumors is the plan-library based plan-of-the-day strategy [58-63]. Also in cervical cancer radiation therapy, this online adaptive strategy holds the promise to compensate for interfraction target motion. Next to daily adequate target coverage, each treatment fraction the dose to surrounding tissues may be reduced. Prior to treatment, several radiation therapy plans are generated corresponding to different target shapes and positions. Subsequently, each treatment fraction the plan best fitting the target shape is selected based on pre-fraction CBCT imaging.

**Challenges in cervical cancer ART**

In cervical cancer radiation therapy, interfraction changes in target shape and position are largely influenced by variation in bladder volume [64-66]. Despite drinking instructions given to the patient, the day-to-day bladder volume may vary strongly during the course of treatment and consequently affects the target position [67,68]. Instead of using large CTV-to-PTV margins to account for target volume changes during cervical cancer radiation therapy, the plan-library based plan-of-the-day adaptive strategy is often selected as the standard treatment strategy. Also in the Academic Medical Center, cervical cancer patients selected for radiation therapy are treated according to the daily plan selection adaptive strategy. Based on multiple CT images acquired before treatment with variable bladder volumes, several target volumes are defined and corresponding radiation therapy plans are generated. Prior to irradiation, the library plan best fitting the target volume as observed on pre-fraction CBCT imaging is manually selected.

Additionally, the adaptive strategy can be applied using proton therapy in order to reduce the dose to healthy tissues. In cervical cancer radiation therapy, the potential benefit of proton therapy is only investigated in a limited number of studies without validating the actual delivered dose [69-71]. Based on planned dose distributions, proton therapy is compared to radiation therapy using photons in terms of dose to the target volume and OARs. Besides the lack of plan robustness assessment, none of the published studies reported on dose distribution recalculation to evaluate differences between both treatment modalities in terms of delivered dose. Alternatively, the definition of target volumes in radiation therapy is currently based on (PET-)CT imaging. The addition of MRI in the process of target definition allows for improvements in target volume definitions and enables a more precise and efficient treatment procedure. However, little is known about the accuracy of target definition using MRI in cervical cancer and this knowledge is required before the actual benefits of target volume optimization can be assessed.
To improve treatment outcome in cervical cancer, adaptive radiation therapy needs to be optimized in terms of treatment precision and treatment efficiency. Besides improvements on daily target localization, the optimization of cervical cancer ART includes the reduction of radiation-associated toxicity without compromising on tumor control. Therefore, the goal of this thesis is to optimize adaptive radiation therapy in cervical cancer in order to improve the precision and accuracy of radiation therapy while minimizing radiation-induced toxicity.

1.5 | Outline of this thesis

In this thesis, optimization strategies for adaptive radiation therapy in cervical cancer are presented and solutions for both photon therapy and proton therapy will be addressed. The optimization strategies and potential advantages of adaptive radiation therapy in cervical cancer are the topics of research.

Adaptive radiation therapy is increasingly used to correct for anatomical changes during fractionated irradiation. Several adaptive strategies can be applied, dependent of the available pre-treatment imaging techniques and deformation types. A practical adaptive treatment approach often used in the pelvic area is the plan-library based plan-of-the-day strategy. Before treatment, a library of plans is generated based on pre-treatment imaging and each treatment fraction a library plan is selected based on pre-fraction imaging. Also in the Academic Medical Center, the daily plan selection adaptive strategy is introduced for curative radiation therapy in cervical cancer. The dosimetric evaluation of this clinically applied adaptive strategy is described in chapter 2. Compared to a non-adaptive approach, the advantages of adaptive radiation therapy using the daily plan selection adaptive strategy are presented in terms of target coverage and dose to healthy tissues.

The application of ART using the plan-of-the-day strategy requires daily plan selection. In current clinical practice, after accurate patient set-up the library plan best fitting the target volume as observed on the pre-fraction CBCT is selected manually. Plan selection based on automatic image segmentation holds the promise to reduce the time in the treatment room and decrease observer dependency. A generic method to automatically segment the bladder on pre-fraction CBCT images is proposed in chapter 3. This generic method is designed to segment bladder volumes independent of the treatment position while only available pre-treatment CT data is used to guide the segmentation. In addition, segmentation results are validated by comparing segmented and manually delineated bladder structures.

The challenges to further optimize cervical cancer radiation therapy by combining adaptive radiation therapy with the use of protons are addressed in the chapters 4 and 5. Rotational IMRT techniques are used for photon-based treatments in daily clinical practice, which are not applicable in proton-based radiation therapy. Given certain distinct advantages of protons over conventionally used X-rays, a fixed beam configuration based on a limited number of beams is preferred when
applying IMPT. To select an appropriate beam configuration in terms of plan robustness, target coverage and sparing of surrounding healthy tissues, different beam configuration candidates are objectively compared in chapter 4 using an advanced method based on Pareto fronts.

The application of adaptive proton therapy and the actual dosimetric advantages of adaptive proton therapy in cervical cancer are investigated in chapter 5. Using the selected beam configuration for cervical cancer IMPT, the potential benefit of adaptive proton therapy compared with adaptive photon therapy in cervical cancer is demonstrated in terms of target coverage and dose to OARs.

Target definition for radiation therapy planning is generally performed based on pre-treatment CT imaging. In cervical cancer, the recommended clinical target volume encompasses the GTV, cervix, uterus and upper part of the vagina. The addition of safety margins to the CTV resulted in relatively large target volumes and consequently increased the volume of healthy tissue receiving a substantial amount of dose. Moreover, large target volumes including the entire uterus are prone to anatomical changes during the course of radiation therapy. In order to optimize the target volume, it has been suggested to only include the invaded part of the uterus in the clinical target volume. Since the GTV is poorly visible on CT images, MRI is considered for tumor extent assessment. In order to validate tumor definition accuracy using MRI, a method to correlate surgical specimen imaging and MRI including soft tissue deformations is demonstrated in chapter 6. In addition, discrepancies between MRI-based and pathological-based tumor definitions were quantified.

The consequences of excluding the non-invaded part of the uterine body from the target volume after tumor definition based on MRI is addressed in chapter 7. For both photon therapy and proton therapy, radiation therapy planning is performed based on conventional target volumes and MRI-based target volumes and plans are compared for target coverage and OAR dose. Also, the dosimetric advantages of the improved target volume definition strategy are presented in terms of OAR dose reductions as well as estimated complication probability differences.

In chapter 8, the most important findings presented in this thesis will be summarized. Furthermore, the presented results will be discussed and compared with other solutions to improve cervical cancer radiation therapy. Also, future perspectives on cervical cancer radiation therapy as well as alternative treatment options in cervical cancer will be addressed.