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

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Chapter 8

General discussion

General discussion

The aim of adaptive radiation therapy is to achieve adequate dose delivery by compensating for interfraction anatomical variations. In cervical cancer radiation therapy, the possible large day-to-day anatomical variations require an online adaptive strategy to deliver optimized dose distributions by correcting for both systematic and random errors. In the Academic Medical Center, adaptive radiation therapy with concomitant chemotherapy has been introduced recently as the standard treatment strategy for patients with locally advanced cervical cancer.

In this thesis, we have aimed at optimizing adaptive radiation therapy in cervical cancer to improve the treatment efficiency and reduce radiation-associated toxicities. The preceding chapters addressed our solutions to optimize adaptive radiation therapy in cervical cancer. Besides improvements in daily target coverage, our solutions for photon therapy as well as proton therapy resulted in significant dose reductions to surrounding healthy tissues.

First, the clinically implemented daily plan selection adaptive strategy was described in **chapter 2** and the dosimetric consequences of this adaptive strategy compared to conventional non-adaptive radiation therapy were demonstrated. A possible solution in the process of adaptive radiation therapy optimization includes improvements on the daily plan selection methodology. Using the image segmentation method demonstrated in **chapter 3**, the daily plan selection procedure can be automated in order to decrease the decision time in the treatment room. Next to an extensive description of our (semi-)automatic bladder segmentation method on CBCT imaging, **chapter 3** also presented a description of the complete validation of the segmentation performance.

Compared to conventionally used X-rays, protons have certain distinct advantages and hold the promise of limited dose delivery to surrounding healthy tissues. Consequently, organ at risk sparing can be improved by applying adaptive proton therapy. The efficiency of proton therapy delivery was improved by selecting the optimal beam configuration in cervical cancer proton therapy. **Chapter 4** presented our solution to objectively compare beam configurations in terms of plan robustness and dose-volume histogram (DVH) parameters. The optimal beam configuration for cervical cancer proton therapy was determined and used to investigate the application of adaptive proton therapy. In **chapter 5**, the application of adaptive proton therapy in cervical cancer was described and the dosimetric advantages of adaptive proton therapy compared to photon-based adaptive radiation therapy were demonstrated.

Next to the application of proton therapy, adaptive radiation therapy in cervical cancer can be further optimized by improving the strategy of target volume definition. The conventional strategy of target definition in cervical cancer was adapted by excluding the non-invaded part of the uterine body based on exact tumor extent delineation on magnetic resonance imaging (MRI). To safely rely on MRI-based definitions, the accuracy of gross tumor volume (GTV) delineation on MRI was validated in **chapter 6**. Also, our solution on the correlation between MRI and pathology data including deformation corrections was demonstrated. Based on the accurate correlations, discrepancies between MRI-based and pathology-based tumor volumes were derived. Next, a

comparison between the conventional target definition strategy and the novel target definition strategy based on MRI was performed in terms of target coverage and OAR dose. The advantages of the novel target definition strategy were demonstrated in **chapter 7** for the application of photon therapy as well as proton therapy.

In this chapter (**chapter 8**), the results presented in this thesis are compared with other solutions in cervical cancer adaptive radiation therapy. Furthermore, future perspectives of cervical cancer treatment including evolutions in adaptive radiation therapy as well as alternative treatment options are mentioned.

8.1 | Adaptive radiation therapy in cervical cancer

The preferred adaptive strategy includes daily re-optimization of the dose distribution based on pre-fraction imaging, however this type of adaptation is not yet feasible due to technical and logistical limitations. Therefore, alternative strategies need to be developed to anticipate on day-to-day anatomical variations in cervical cancer.

In **chapter 2**, the clinically introduced daily plan selection adaptive strategy in cervical cancer radiation therapy was described and evaluated in detail. The adaptive strategy is based on predicting the target deformation pattern before treatment to be able to anticipate on anatomical changes during the course of radiation therapy. Since variations in target shape and position in cervical cancer are mainly caused by bladder volume differences, the target deformation model is determined by multiple pre-treatment CT imaging acquired with large bladder volume differences. Deformable image registration was applied between CT imaging acquired with extreme bladder volumes to derive the patient-specific target shape model. Corresponding to different bladder volume ranges, this full range target volume was divided in target volume subranges and associated treatment plans were generated to form the plan library. Each treatment fraction, the plan corresponding to the anatomy as observed on pre-fraction CBCT imaging is selected manually followed by dose delivery.

Compared to non-adaptive radiation therapy, the daily plan selection adaptive strategy corrected for day-to-day anatomical variations and resulted in significant improvements in target coverage. Next to the target coverage improvements, we also found a limited dose reduction for rectum and bowel and the clinical relevance of these reductions is expected to be limited. Therefore, the largest area of improvement on adaptive radiation therapy in cervical cancer was found to be the reduction in dose to healthy surrounding tissues while maintaining adequate target coverage.

Optimization of the clinical adaptive procedure

Several aspects of the clinically applied online adaptive strategy in cervical cancer radiation therapy are open for improvements. For instance, the plan library can be personalized prior to treatment

by incorporating besides variations in bladder volume also other patient-specific variations. In addition, improvements of the patient-specific plan library can be achieved during treatment by updating the library of plans based on additional imaging. Currently, the range of target motion is predicted based on two CT images with variable bladder volumes. The prediction error can be reduced by using more than two pre-treatment CT images for model construction or the inclusion of repeat imaging (e.g. CT imaging) during the course of treatment for remodelling [56,120]. However, the introduction and evaluation of additional imaging will increase the clinical workload while the reduction in prediction error is expected to be limited.

Daily plan selection is currently performed manually based on pre-fraction CBCT imaging and the observer is assisted by fiducial markers implanted near the tumor. A fast and automatic plan selection strategy is required to reduce the decision time in the treatment room and consequently limit the effect of intrafraction anatomical changes on dose delivery [45,67,74]. Automatic image segmentation strategies are appropriate candidates to replace manual plan selection procedures. However, the performance of such methodology depends on the CBCT-based segmentation accuracy and the corresponding segmentation time. The reported correlation between bladder volume and the position of the uterus in cervical cancer patients [65,66,73,93] allowed for automatic plan selection based on bladder volume determination. The generic segmentation method presented in **chapter 3** resulted in accurate bladder segmentations on CBCT images acquired within a short period of time. However, the bladder remains a surrogate for the target position and manual verification of the automatic selection procedure based on bladder segmentation is required to avoid incorrect irradiation.

Alternative methods for online plan selection included bladder volume measurements using ultrasound [64], direct segmentation of the target volume based on MRI or CT imaging [76,180,181] and automatic segmentation of fiducial markers used for tumor demarcation [102,103,182]. However, unfortunately all proposed alternatives have limitations in clinical practice. Ultrasound measurements in the treatment room require additional in-room time and might induce additional uncertainties for dose delivery while the bladder volume is still a surrogate for the target position. Methods to directly segment the target volume for plan selection purposes are demonstrated using MRI [180,181] or CT imaging [76], however these methods are not directly suitable using CBCT imaging due to its limited soft-tissue contrast. The segmentation of implanted fiducial markers is applied previously [102,103,182], but a substantial number of fiducial markers is required to accurately determine the daily shape and position of the target volume. Moreover, migration or loss of fiducial markers during the course of treatment decrease the applicability and reliability of automatic plan selection based on fiducial marker segmentation.

8.2 | Proton therapy in cervical cancer

Despite the use of modern techniques, the physical properties of photon beams prevented sharp dose fall-offs around the target volume. In order to achieve less radiation-associated toxicity for cervical cancer patients after radiation therapy, the dose to healthy tissues was reduced by combining the online adaptive strategy with proton therapy. Proton therapy holds the promise to limit dose to surrounding healthy tissues [34], but the delivery of the highly conformal dose distribution is challenging due to the sensitivity of protons to range and position uncertainties induced by anatomical variations. Photon-based radiation therapy is delivered using an advanced rotational IMRT technique (i.e. VMAT) and dose delivery in proton therapy also required an optimized IMPT technique to enable a fair comparison between photon therapy and proton therapy. In order to investigate the actual benefits of adaptive proton therapy, an optimized IMPT technique allowed for a direct comparison between proton therapy and photon therapy both applied using an adaptive strategy.

Optimization of proton delivery efficiency

We investigated beam configuration optimality in cervical cancer IMPT by comparing configuration-specific Pareto fronts. Without the arbitrariness of individual planning decisions, different beam configurations in IMPT planning were objectively compared using the set of Pareto optimal IMPT plans that reflected the optimal trade-offs between conflicting objectives. In **chapter 4**, a method to automatically approximate Pareto fronts was demonstrated in terms of plan robustness and DVH parameters. In addition, we presented a quantitative comparison and selection between beam configurations in cervical cancer IMPT.

Although the concept of Pareto optimality as an evaluative and comparative tool was previously introduced for radiation therapy purposes [128,130,131,133,183,184], for our purpose it was extended to enable IMPT beam configuration selection. Our presented method on Pareto front approximation included robustness evaluations and therefore became a time consuming procedure. Because only a large reduction in calculation time opens the possibility to a more extensive use of this method or possibly use as a clinical application, improvements in the described method are required. Alternative strategies to derive Pareto optimal solutions are currently under development and already a limited number of (sub)optimal solutions for specific purposes are implemented in commercial radiation therapy software [185].

Rotational delivery techniques in proton therapy are not yet feasible due to technical limitations, but the static field IMPT technique is an excellent alternative to deliver highly conformal dose distributions including the inherent steep dose fall-off outside the target volume. Therefore, beam configuration optimality in terms of DVH parameters and plan robustness is essential to improve the efficiency of IMPT. Although the selected beam configuration was found superior in terms of plan robustness and DVH parameters for all evaluated cervical cancer patients, this configuration

is not necessarily the solution for all patients and therefore it is recommended to derive beam configuration optimality on an individual basis. Similar to solutions presented for photon-based radiation therapy [125,126,186], the optimization of number of beams and corresponding gantry angles should be included in the plan optimization process to obtain patient-specific optimal dose distributions. Preferably, this optimization strategy also includes possible effects of prolonged delivery times [187].

The observed differences between inspected configurations imply the superiority of the four-beam configuration. In clinical practice, the limited advantages of this configuration compared to the three-beam configuration can be diminished during dose delivery. Due to the time needed for dose delivery, additional delivery uncertainties may be induced by intra-fraction anatomical changes. Therefore, a limited number of beams are preferred to preserve high-precision dose delivery in clinical practice.

Adaptive proton therapy in cervical cancer

Using the selected beam configuration for cervical cancer proton therapy as described in **chapter 4**, the application of adaptive proton therapy was compared with photon-based adaptive radiation therapy in cervical cancer. Adaptive treatments for both treatment modalities were simulated using an extensive set of CT images and resulted in adequate target coverage for both treatment modalities. Compared to adaptive photon therapy, the advantages of adaptive proton therapy using the daily plan selection adaptive strategy are presented in **chapter 5**. Besides minor differences in daily target coverage, major differences in delivered dose to surrounding healthy tissues were demonstrated. Moreover, the reduction of dose to bowel and rectum resulted in decreased radiation-associated complication probabilities.

The clinical application of proton therapy relies, even more than for photon therapy, on appropriate image guidance since both inter- and intrafraction anatomical changes can severely deteriorate proton therapy dose distributions. The sensitivity of proton therapy dose distributions to anatomical variation can be decreased by introducing plan robustness with the drawback of not completely exploiting the potential benefit of proton therapy. Although robustness needs to be incorporated to a certain extent in proton plans, an adaptive strategy enabled by appropriate image guidance is necessary to ensure accurate dose delivery.

Volumetric imaging techniques are required for image guidance in proton therapy. Although in-room imaging modalities for proton therapy are confined to mobile (PET-)CT systems or gantry-mounted CBCT systems, modern proton gantries are increasingly equipped with a CBCT imaging system [188-191]. For the application of adaptive proton therapy, online imaging is necessary to perform plan selection in an accurate and fast way. Compared to CBCT imaging, in-room CT imaging acquired with a mobile system will improve the image quality with the drawback of additional in-room treatment time. As a consequence, the improvement of online imaging is of much more importance when an adaptive strategy in proton therapy is applied.

Proton therapy is often used to treat childhood cancer in order to reduce the delivered integral dose, resulting in a lower risk of secondary malignancies as well as an lower risk of radiation-associated late effects [192-194]. Also, the treatment of tumors located close to radiosensitive tissues such as central nervous system tumors and head and neck tumors are preferably treated using proton therapy [122,195]. Although cervical cancer is not one of the primary indications for proton therapy, the potential benefit of proton therapy over conventional radiation therapy is demonstrated in this thesis. Furthermore, adaptive proton therapy enables dose escalation to the primary tumor, possibly in a stereotactic fashion [196], and may be a valid alternative for patients who are not eligible for brachytherapy [124].

8.3 | Target definition improvements in cervical cancer

According to international guidelines, the clinical target volume (CTV) in cervical cancer radiation therapy is recommended to encompass the gross tumor volume (GTV), cervix, upper part of the vagina, lymph nodes and the entire uterus [29,92,146,164,197]. The definition of this structure in current clinical practice is usually performed using (PET-)CT imaging while MRI is often considered as an additional imaging modality to reliably assess tumor involvement in surrounding tissues. In order to improve the conventional target definition strategy, it has been suggested to exclude the non-invaded part of the uterus from the CTV by using MRI for exact GTV definition [6,29]. The inclusion of only the invaded part of the uterus in the CTV resulted in reduced target volumes and enabled high-precision radiation therapy for both photon therapy and proton therapy. In addition, target volume optimization resulted in OAR dose reductions and opens up the possibility for dose escalations in cervical cancer radiation therapy.

Target definition accuracy on MRI

The accuracy of GTV delineation on MRI was validated using pathology data to be able to safely exclude the non-invaded part of the uterus from the CTV. **Chapter 6** demonstrated a method to correlate in-vivo MRI and ex-vivo imaging of surgical specimens. Unlike previously reported correlations between MRI and pathology imaging in cervical cancer [148,154,167], the presented registration method also included corrections for shape deformations between both imaging sets. The presented deformable image registration method resulted in accurate correlations between MRI and pathology imaging and discrepancies between MRI-based GTV delineations and corresponding pathology proven tumor volumes were derived.

The extensive validation of MRI-based GTV definition is necessary to avoid incomplete irradiation induced by incorrect target definition. Therefore, an accurate tissue processing and registration method is required to enable the validation of MRI-based GTV delineations with pathology. In **chapter 6**, anatomical T2-weighted MRI was correlated with retrospectively selected

two-dimensional (2D) pathology images. Although the uncertainty induced by only a 2D-2D correlation was expected to be limited, the recommended three-dimensional (3D) imaging information is currently collected prospectively to improve the validation of MRI-based GTV delineations with pathology [6]. The presented deformable image registration method is expected to be easily extended in order to perform 3D-3D correlations, similar to studies on other tumor sites [152,153,198].

The use of advanced MRI techniques can offer additional information for accurate tumor detection. Instead of only anatomical T2-weighted MRI, the use of diffusion-weighted imaging (DWI) [199,200] or dynamic contrast-enhanced (DCE-)MRI [201,202] can facilitate tumor invasion detection. Furthermore, DWI and DCE-MRI might be used for tumor differentiation or treatment response prediction [203,204]. However, tumor detection using these advanced MRI techniques also needs to be validated before clinical decisions can be taken safely. The demonstrated strategy for tumor delineation validation can also be used to quantify the correctness of tumor definition using DWI or DCE-MRI.

The accuracy of GTV definition on MRI becomes more and more valuable with the increased introduction of MRI in the radiation therapy workflow. Next to pre-treatment MRI for target volume definition, additional offline MRI during the course of radiation therapy is increasingly applied for alternative treatment adaptation strategies or tumor response monitoring. For both purposes an offline evaluation of the supplementary MRI is required, but the incorporation of MRI-based decisions in the online clinical workflow will result in difficulties in terms of treatment efficiency and clinical workload. The introduction of a MRI-only radiation therapy workflow has been investigated to facilitate the inclusion of MRI-based decisions during the course of treatment next to the elimination of integral dose from CT imaging [205,206]. Radiation therapy requires high geometric precision and the MRI-only workflow allows for an accurate relation between the reference MRI and MRI findings during treatment. The introduced MRI-cobalt-60 system [207] or the scheduled introduction of the MRI-linac, a linear accelerator with an integrated MRI system [208], offers new possibilities regarding online adaptive radiation therapy possibly within a MRI-only framework.

Consequences of target volume definition improvements

For both photon therapy and proton therapy, **chapter 7** demonstrated the potential benefit of excluding the non-invaded part of the uterus from the CTV in terms of target coverage and OAR dose. The GTV was defined using anatomical T2-weighted MRI and the target volume was created by adding the required radiation therapy safety margins. Compared to the use of conventional target volumes, the improved target volumes resulted in reductions of OAR dose while maintaining adequate target coverage. MRI-based target volume definition combined with the application of proton therapy resulted in even less OAR dose and substantially decreased the small bowel toxicity probability for individual patients.

The additional use of MRI for target definition enabled the GTV to be more precisely delineated in order to limit the volume of surrounding tissue that is intentionally irradiated. The direct consequence of MRI-based target volume definition is the volume reduction due to the exclusion of the non-invaded part of the uterus. As a result, the highly mobile uterine corpus is completely or partly excluded from the target volume and will diminish the interfraction anatomical variation of the target volume. Nevertheless, day-to-day anatomical variations will induce changes in target shape and position and an adaptive treatment strategy is desirable. Only a part of the patients will have limited invasion into the uterine body, resulting in a large subset of patients that will benefit from an adaptive strategy.

Even though the benefit of improvements in target volume definition was demonstrated, the actual clinical outcome and toxicity in terms of tumor control, radiation-associated side effects and quality of life need to be studied. Clinical evidence, preferably based on randomized control trials, is essential to convince radiation oncologists and patients that at least similar tumor control with minimal complications can be achieved without irradiating the whole uterus.

8.4 | Future perspectives

Online adaptive radiation therapy in cervical cancer is necessary for optimal dose delivery in the presence of day-to-day anatomical variations. Although actual improvements in overall survival and treatment related toxicity need to be investigated prospectively, this thesis demonstrates improvements in adaptive radiation therapy in cervical cancer. Several solutions including different treatment modalities were addressed to optimize online adaptive radiation therapy. To achieve additional advancements in treatment outcome, improvements in dose delivery precision is desired while minimizing the dose to surrounding healthy tissues. Next to the developments in radiation therapy, alternative treatment options can improve treatment outcome for patients with locally advanced cervical cancer.

Adaptive radiation therapy

The main area of improvement in the process of adaptive radiation therapy is related to daily imaging. Current adaptive strategies in radiation therapy often rely on CBCT imaging, but the present quality of CBCT imaging limits the advancements in treatment adaptations. Although the quality of CBCT imaging is improved by optimizing reconstruction algorithms and post processing methods [55,209-212], alternative online imaging modalities with superior image quality are required to take adaptive radiation therapy to the next level. The use of in-room imaging using a CT-on-rails system offers diagnostic image quality with the drawback of increased overall treatment times and additional integral dose [213]. Furthermore, increased overall treatment times will provoke interfraction anatomical changes. With the superior image quality of MRI compared to

(CB)CT imaging, the introduction of MRI guidance during radiation therapy opens the possibility for advanced adaptive strategies. The first commercial system for MRI-guided radiation therapy has been clinically introduced [207,214]. This system combines online MRI and cobalt-60 radiation therapy and allows for treatment adaptations including online dose calculation. However, online plan adaptation resulted in largely increased treatment times. Also, the decay of the radiation source need to be taken into account and a regular source replacement is required. In the near future, the introduction of a linear accelerator with an integrated MRI system, the MRI-linac, offers new possibilities regarding online adaptive radiation therapy [208,215]. The clinical introduction of this system opens the possibility for sophisticated adaptive strategies to be implemented including online re-optimization and dose escalation [85,216]. Due to the substantial interfraction anatomical changes, cervical cancer patients will probably benefit from adaptive radiation therapy using online MRI guidance. In the near future, cervical cancer patients will receive external beam radiation therapy including online adaptations using the MRI-linac.

Next to the improvements in photon-based radiation therapy, the treatment of cervical cancer using protons is expected to result in large advantages in treatment outcome. In the Netherlands, proton therapy facilities will become available soon and the clinical introduction of proton therapy opens the possibility for adaptive proton therapy in cervical cancer. Although cervical cancer is currently not one of the main indications for proton therapy, a selection of patients eligible for proton therapy is recommended using a model-based approach [172]. As demonstrated in this thesis, adaptive proton therapy has the potential to largely reduce radiation-induced side effects in cervical cancer. However, advanced image guidance is necessary to guarantee appropriate dose delivery in proton therapy and benefit from this treatment strategy. Moreover, the limited clinical experience on proton therapy compared to photon therapy requires a close collaboration between national and international specialists in radiation oncology to successfully introduce adaptive strategies in proton therapy. In clinical practice, the enhancement of adaptive proton therapy is hindered by the limited availability of in-room imaging (i.e. CT-on-rails imaging system or CBCT imaging system) in proton facilities. Long term developments will combine proton therapy and MRI to apply the preferred treatment modality with a promising online imaging technique [217-219]. Preferably, MRI-guided proton therapy also includes online re-optimization techniques in order to adapt cervical cancer radiation therapy instantaneously and individualize treatments by response monitoring and dose escalation.

Alternative treatment options

The standard curative treatment of patients with locally advanced cervical tumors consists of radiation therapy with concomitant chemotherapy. Besides the optimization of radiation therapy techniques, improvements in treatment outcome are being investigated by advancing current treatment techniques or exploring alternative treatment options.

For instance, hyperthermia in addition to radiation therapy is the preferred choice for cervical cancer patients with a contraindication for chemotherapy. Compared to radiation therapy alone, the combination of radiation therapy with hyperthermia improves local tumor control and overall survival in patients with locally advanced cervical tumors without affecting acute or late toxicity [17,19]. These results imply possible additional improvements in treatment outcome when combining radiation therapy, chemotherapy and hyperthermia as one combined treatment strategy.

A different treatment modality for locally advanced cervical cancer is the application of immunotherapy. This therapy aims to treat and even prevent cancer by activating the immune system of the patient. The cancerous cells are killed selectively and this process is provoked by administering tumor-specific antibodies or targeting tumor-associated antigens. The systematic and targeted character of immunotherapy results in a high potential candidate for cervical cancer treatment and advancements in immunotherapy for cervical cancer are currently under investigation. Moreover, both radiation therapy and hyperthermia stimulate the release of tumor antigens which may enhance the efficacy of immunotherapy. In future, cervical cancer patients might benefit from a combined treatment consisting of radiation therapy with concomitant chemotherapy, hyperthermia and possibly immunotherapy.

8.5 | Conclusions

In conclusion, the results of a number of studies to optimize adaptive radiation therapy in cervical cancer have been addressed and several solutions for both photon therapy and proton therapy have been investigated. It was shown that the daily plan selection adaptive strategy in cervical cancer radiation therapy enabled corrections for interfraction anatomical changes in order to achieve maximal tumor control with minimal complications. Moreover, the simulation studies on the application of adaptive proton therapy showed the ability of high-precision dose delivery in the presence of anatomical variations and resulted in substantial improvements in organ at risk sparing. For cervical cancer patients with a limited tumor invasion into the uterus, high-precision radiation therapy may be further improved by adaptations in target volume definitions using advanced pre-treatment imaging. Target volume definition based on MRI combined with the use of proton therapy, possibly delivered using an adaptive strategy, showed large potential improvements in treatment outcome in terms of radiation-induced toxicity.