Reducing small bowel toxicity in locally advanced cervical cancer treatment

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Chapter 10

Summary and General Discussion
Summary

INTRODUCTION

The previous chapters of this thesis presented the results of our studies that aimed to provide new solutions to improve the results of radiotherapy in women with locally advanced cervical cancer. These proposed solutions mainly focused on techniques to reduce severe late toxicity after chemoradiotherapy (CRT) by reducing the radiation dose to healthy organs at risk (OAR), particularly to the small bowel.

This chapter starts by providing a summary of the previous chapters which, in turn, forms the basis for a more in-depth discussion. Then, we consider our results in view of the present state-of-the-art radiotherapy in women with cervical cancer and, finally, make some recommendations for future research.

SUMMARY OF THE THESIS

Part I: Current practice

In 2015 we performed a ‘patterns of care’ survey in the Netherlands to investigate the current radiotherapy practice in women with uterine cervical cancer. The results of this study (presented in Chapter 2) indicate that Dutch radiotherapy practice in cervical cancer is in accordance with international standards regarding the most important parameters that are critical to treatment outcome. A particular finding of this study was that, in patients with a small cervical tumour, none of the medical centres excluded (a part of the) uterine fundus to spare the surrounding OAR, i.e. to spare the small bowel.

Part II: Validation of MRI for craniocaudal tumour measurements in cervical cancer

Systematic review

In 2013 we conducted a systematic review of studies that investigated the role of MRI in detecting and measuring involvement of the uterine body in patients with cervical cancer. As described in Chapter 3, only two retrospective and two prospective series were found that share similar accuracy (> 90%) in detecting whether or not there was cervical tumour involvement into the internal ostium of the uterus. No studies were found that reported actual tumour measurements on MRI compared to the ‘gold standard’, i.e. histopathology.
Craniocaudal tumour extension on MRI compared to histopathology

Next, in the retrospective study in Chapter 4, in 21 patients that had undergone radical hysterectomy for early stage cervical cancer, we measured tumour size on MRI (specifically in the craniocaudal direction) and compared those measures with tumour extension on photographs of surgical specimens in combination with the pathologist’s written report. On MRI, the median tumour size was 2.1 cm. Compared with histopathological assessment, MRI underestimated the craniocaudal tumour extension by (on average) 0.4 cm. In three patients the tumour extension was underestimated by more than 1 cm due to: i) diffuse infiltration without clear tumour boundaries, ii) suboptimal spatial alignment between MRI and histopathology, and iii) tumour resembling the cervical internal canal, respectively.

Validating craniocaudal tumour extension on MRI by deformable registration with macroscopic photographs

Chapter 5 describes a novel method to correlate pre-operatively acquired MRI and pathology photographs after macroscopic intersection in cervical cancer. The three-step multi-image registration strategy is based on the boundary structures and internal structures, and included correction for possible large deformations. The inclusion of the deformable image registration step corrected for possible large deformations between in-vivo and ex-vivo organ shapes, and resulted in a median dice similarity coefficient and surface distance error of 0.98 and 0.4 mm and 0.90 and 0.4 mm for the boundary structure and internal structures, respectively. Subsequently, the discrepancy was quantified after accurate correlations. To obtain a 95% gross target volume (GTV) coverage for 90% of the patients, a minimum of 12.0 mm around the MRI-based GTV was needed. As in described Chapter 4, spatial alignment between 2D pathology photographs and MRI slices was a limitation in selected cases due to possible rotations between in-vivo MRI and ex-vivo histopathology. Furthermore, only macroscopic spread could be assessed on the pathology photographs; ultimately, MRI delineation should also be compared with tumour size including microscopic spread.

Craniocaudal tumour extension in uterine cervical cancer on MRI in a prospective study: the MPAC study

To minimise uncertainties of the previous retrospective study, such as unknown microscopic tumour spread and spatial inaccuracies between MRI and histopathology tumour measurements, in the MPAC study (described in Chapter 6) we prospectively investigated (in 34 surgical patients) the accuracy of MRI to measure maximum craniocaudal tumour size in the direction of the uterine fundus, using three methods which we consider to be complementary: 1) evaluation of MRI by two radiologists compared to histopathology by a pathologist (as described in Chapter 4); to compensate for alterations in uterus shape between pre-operative MRI and the macroscopic surgical specimen, craniocaudal tumour extensions were compared, 2)
direct comparison of MRI and macroscopic photographs based on 3-dimensional (3D) tumour evaluation by a radiation oncologist and a resident, and 3) comparison of MRI and macroscopic photographs after non-rigid registration of the contours of the uterus, uterine cavity and tumour on MRI with digitized photographs of specimen macroscopy (as described in Chapter 5). Results of this study indicate that microscopic tumour spread is within 10 mm of the visible tumour on MRI. The major source of measurement uncertainty was post-surgical change of organ shape and form, which can be reduced by direct post-surgical embedding.

Part III: Reducing small bowel toxicity by changing radiotherapy strategies

Dosimetric advantages of proton therapy compared with photon therapy using an adaptive strategy in cervical cancer

The studies comparing tumour extension on MRI with histopathology gave a reasonable indication of how much of the uninvolved uterine corpus might possibly be excluded from the irradiated volume without challenging tumour control. The subsequent questions were:

➢ How much of the surrounding healthy organs, i.e. bowel and bladder, can be spared by excluding the uninvolved uterus?
➢ How much might that decrease toxicity?
➢ How would exclusion of the uninvolved uterine corpus as a strategy compare to other organ-sparing techniques, such as proton beam therapy?

For these questions (described in Chapter 7), we first investigated the potential dosimetric advantage of image-guided adaptive proton therapy (IGAPT) for OAR, compared to photon-based image-guided adaptive radiotherapy (IGART). Our analysis included: 1) robust optimisation using reported uncertainty values on intrafractional motion, and 2) treatment simulations by recalculating dose distributions according to anatomy of weekly CT. IGAPT was feasible using a library-based plan-of-the-day strategy, while maintaining adequate coverage. Significant reductions in the mean dose to bowel, bladder and rectum were achieved (p<0.01), thereby lowering the probability of small bowel toxicity according to known normal tissue complication probability (NTCP) models.

Reducing small bowel dose for cervical cancer by target definition and using proton therapy: a treatment planning comparison

In Chapter 8, we took small bowel sparing one step further by comparing: i) two external beam techniques, i.e. intensity modulated proton therapy (IMPT) with best
practice photon beam radiotherapy using volumetric arc rotation therapy (VMAT), and by comparing ii) target volumes that include the whole uterus with 'MRI target tailoring' by excluding the part of the uterus that is not involved by tumour, in a 2 x 2 factorial design. To investigate the full potential of this approach, patients with more than 4 cm of uninvaded uterine tissue were included. Results from 11 patients indicate that, compared to VMAT, when including the whole uterus, both IMPT and MRI target tailoring would each yield a 7% reduction in NTCP for ≥ grade 2 acute small bowel toxicity. When combining both IMPT and MRI-target tailoring, the reduction in NTCP could be as high as 16%. A more than 10% NTCP reduction is expected in patients in whom standard VMAT including the whole uterus would result in a high irradiated bowel volume (i.e. with a $V_{45Gy}$ of ≥275 cm$^3$).

Reducing small bowel toxicity by daily online MRI-based replanning: a treatment comparison

Finally, as described in Chapter 9, we performed a dosimetric comparison of MRI-guided strategies with a library of plans (LOP) strategy, taking intrafraction anatomical changes into account. The 14 patients in this study were treated with chemoradiation at our institute and weekly MR images were acquired. The two MRI-guided strategies consisted of treatment plans created on the weekly sagittal MRI with a 3-mm and a 5-mm planning target volume (PTV) margin around the cervix-uterus. The plans in the LOP were based on pretreatment full bladder CT and empty bladder MRI scans. Dose-volume histogram parameters were compared for the target and OAR as delineated on the weekly transversal MRI, which was acquired (on average) 10 min after the sagittal MRI. We found that a 3-mm margin around the clinical target volume (CTV) for PTV results in unsatisfactory target coverage, while a 5-mm margin results in only slightly more dose to the bowel bag. A LOP strategy resulted in a 422 cm$^3$ larger $V_{40Gy}$ and a significantly smaller dose to the bowel. With an online MRI-guided strategy, a 5-mm margin from CTV to PTV of the cervix-uterus is sufficient to account for intrafraction anatomical changes, provided that a new treatment plan can be generated and delivered within 10 min.


DISCUSSION

Introduction

The studies described in this thesis aimed to reduce an undesired radiation dose to OAR, particularly to the small bowel, in patients who undergo curative CRT for locoregionally advanced cervical cancer. To reduce acute and late toxicity by target tailoring, the following questions were posed:

1) Is it necessary to include the whole uterus during external beam radiotherapy (EBRT)? Even if elective radiotherapy of the endometrium is necessary, we could apply elective radiotherapy to the uterine body by means of brachytherapy. This implies a smaller margin for intra- and interfractional organ motion that can reduce the dose to the surrounding normal organs.
2) In the aim to exclude the uninvolved uterus during EBRT to save OAR (whereby we base our target volume on tumour size and extension as visualised by MRI), what margin is required to safely cover invisible microscopic disease?
3) How can we identify specific patients who would benefit from this approach?
4) How can we change current radiotherapy strategies in order to reduce small bowel toxicity?

Current practice

Our ‘patterns of care’ survey conducted in 2015 revealed that, in patients with a small primary tumour, none of the participating centres considered to exclude (a part of the) uterine fundus to spare OAR, in particular to spare the small bowel.

Margin for invisible microscopic disease on MRI

Systematic review

In 2012 we conducted a systematic review of the (then) current knowledge on measuring cervical tumour size on MRI. In other words: the aim was to investigate how accurate MRI is in predicting tumour size compared to histopathology as reference standard. The quality of the methodology and the data were assessed in a standardised manner using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool[147]. At that time, no papers had been published which compared tumour size measurements on MRI with histopathology in corresponding spatial direction as reference standard. However, we identified four studies that described the accuracy of MRI in detecting internal ostium involvement (yes/no). After analysis of the available papers, high summary estimates for accuracy were found, indicating
that MRI is an accurate imaging modality to detect internal ostium involvement. Limitations of our review were the low number of studies with small numbers of included patients, particularly in the two prospective studies that were included.

**Retrospective analysis**

After completion of the systematic review, in 2013 we started to generate our own data by (retrospectively) analysing tumour size on MRI compared to histopathology in 21 patients treated between May 2012 and February 2013. Patients had both pre-operative MRIs and evaluable photographs of the surgical hysterectomy specimen. In order to minimise differences in measurements between MRI and histopathology, measurements were performed in a spatially similar craniocaudal direction, i.e. the size of the tumour reaching from the cervical portio into the direction of the uterine fundus, parallel to the uterine internal canal. Analysis revealed that the median tumour size was slightly underestimated (by 4 mm) on MRI compared to histopathology. However, the range of differences between MRI and histopathology was larger than expected. In three cases, the difference in craniocaudal tumour extension was ≥ 10 mm. Further analysis of the outlying cases provided the following explanations: i) in one case the tumour resembled the endocervical tissue and was not recognised by the radiologist, and ii) in the other two cases, the tumours were perfectly distinguishable on MRI; however, the difference in craniocaudal tumour size could be explained by a difference in the shape of the uterus between in-vivo MRI and ex-vivo histopathology, probably caused by post-operative change in tumour shape of the surgical specimen. A limitation of our study (and of validating MRI for this purpose in general) was that only patients with early stage cervical cancer (FIGO stage I-IIA) could be included, since only these patients are treated with surgery in our centre.

**Deformable registration**

In order to overcome alterations of tumour shape between in-vivo MRI and ex-vivo histopathology, deformable registration was used to project macroscopic pathology photographs on MRI. First, delineations of the whole uterus, uterine cavity and tumour were performed by two radiation oncologists. The deformable registration was performed in three steps, starting with rigid registration. In the subsequent steps, two clear anatomic boundaries were used to improve deformable registration. First, the whole uterus as a boundary and subsequently the uterine cavity were matched. Hereby, the soft tissue lying in between was deformed to fit using B-splines-based deformable registration. The registration was evaluated and found to be accurate, with an induced uncertainty of 1 mm. After registration, an underestimation of the GTV on MRI was found. In order to encompass 95% of the GTV in 90% of the patients, a 12-mm margin would be needed. An important limitation that became more obvious in this particular study (but was also present in the retrospective study described above), was that 2D pathology photographs were correlated to a 3D MRI image stack,
from which only one slice was manually selected. This assumes that both images were in the same plane, whereas they were not in exactly the same plane. In fact, the 2D photographs were a 2D representation of a 3D object, thereby neglecting depth.

**Prospective analysis**

Lessons learned from the former retrospective studies were applied to a prospective validation study in 34 patients with early stage cervical cancer. Before treatment, and following informed consent, patients underwent a 3T MRI with T2-weighted and diffusion-weighted imaging (DWI), to reduce ‘the tumour-resembled-the-endocervical-tissue’ cases to a minimum. The craniocaudal tumour size on MRI was evaluated using three complementary methods (Table 6. A1).

1. Microscopic craniocaudal tumour extension was evaluated by an experienced pathologist and compared to MR images that were evaluated by two radiologists. In this method, the radiologists kept in mind in which direction the pathologist would have measured. Results show that MRI would underestimate tumour extension within a 10-mm margin, except for three cases in which alterations in shape between MRI and hysterectomy probably caused a >10-mm difference. In these three cases, due to alterations in shape, the compared tumour size was not measured in the same direction despite the efforts of the radiologists and pathologist (see Chapter 6, Figure 6.4, 6.A3 and 6.A4). In the fourth case, where after conisation no tumour was recognised on MRI, the >10-mm difference was caused by occult microscopic tumour beyond the resection margin.

2. To further minimise the above-described uncertainties due to alterations in uterus shape between MRI and hysterectomy, a radiation oncologist and a resident evaluated craniocaudal tumour extension on both MRI and macroscopic photographs, to ensure measurements of both modalities in almost the same plane; they found a maximum underestimation of tumour extension on MRI of 6 mm. A drawback of this method is the bias introduced due to both modalities being evaluated by the same observer. Furthermore, only macroscopic data were evaluated, whereas microscopy is considered to be the ‘gold standard’.

3. We repeated the three-step deformable registration method (described earlier) and found that a 10-mm margin was required to encompass 95% of the GTV in 90% of the patients. Again, this method was accurate but limited to the comparison of visualisation of the 3D tumour (including depth) on a 2D photograph that was compared with an MRI slice.
The main limitation of the above-described methods is the uncertainty of the direction in which the tumour size is measured, which needs to be the same to provide a reasonably acceptable comparison. In method 1, the radiologists and pathologist are not biased by each other, but each miss information about the exact direction of the measurement. In methods 2 and 3, the 2D photograph still limits acceptable measurements due to uncertainty of the exact plane of measurement. Ideally, these limitations will be avoided by comparing 3D pathology data with a 3D MRI stack, while measurements by experts can be performed in an unbiased way. Embedding whole-mount sections of the uterus may allow this to become possible. Moreover, this method is likely to further reduce the uncertainty margin for microscopic extension.

**Recent literature**

Since we began our prospective analysis, other groups have published results of similar research comparing MRI and histopathology in patients with cervical cancer. For example, Sanuki et al. (2013) measured maximal tumour extension along the uterine cavity on microscopy and compared this with MRI. The authors found that all tumours would be covered if a 10-mm margin were used around the GTV delineated on MRI [107]; remarkably, the authors do not mention the difficulties that we experienced in measuring the tumour in precisely the same direction. Xie et al. (2015), in a subgroup of 318 early stage cervical cancer patients with squamous cell carcinoma (SCC), found that a margin of only 5 mm around the GTV was sufficient to include all microscopic tumour extension in craniocaudal direction towards the uterine fundus [191]. These authors found that, in SCC, microscopic spread in the direction of the fundus is uncommon. However, lymphovascular space invasion (LVSI) and tumour size >4.5 cm were identified as risk factors for more extensive microscopic spread [191]. Data from these studies are similar to our data and also correspond well to the margin of 5-15 mm from high-risk CTV to low-risk CTV recommended by the GEC-ESTRO for image guided brachytherapy (IGBT) [57,58].

A limitation of all the studies on this topic is that only patients with early stage disease can be subjected to histopathological validation of tumour extension. However, in the near future we will probably no longer obtain histopathological data on locally advanced cervical cancer. Therefore, it is debatable whether we should restrict ourselves due to this limitation, or whether we should carefully draw conclusions from these best available data. Most important is to eventually correlate target tailored strategies with both the possibly higher risk of a uterine recurrence, but a lower risk of normal organ toxicity. For instance, studies of patients treated with trachelectomy show that patients with tumours ≥ 2 cm have a higher risk of recurrence, which typically occurs regionally and not in the uterine corpus [133,219]. Other more recent studies on trachelectomies also indicate that LVSI is the most important independent risk factor for recurrence after surgery [192,193]. Although
this topic remains controversial for cervical cancer, the uncertainty of microscopic tumour extension is well investigated for other tumour origin sites. For example, similar margins were found for head and neck cancer, breast cancer, non-small cell lung cancer, prostate cancer, and thyroid cancer[153,172,230–236].

Another cause of measurement inaccuracy is shrinkage of the tumour during fixation (generally 10% in any direction), whereas on MRI the size remains unaffected[237]. Our data indicate that, compared to microscopic pathology, MRI underestimates tumour extension. Therefore, we estimated that a safety margin of 10 mm is required to cover 95% of the tumours. If we also compensate for 10% tumour shrinkage, the required safety margins need to be correspondingly 10% wider, i.e. an extra 3 mm in case of a 30 mm tumour.

Proton therapy

Due to its favourable dose deposition, protons may offer more conformal radiation delivery than conventional photons. A particular advantage of proton therapy is the negligible dose deposition behind the target volume, whereas EBRT is associated with a substantial dose deposition behind the target volume. This higher dose conformity of proton therapy makes it more challenging to cover the tumour during motion, i.e. due to intra- and interfractional tumour motion. Therefore, geometrical uncertainties of the anatomy are taken into account during optimisation in the so-called robust optimised treatment planning. In 2014 we made a comparison (that was as fair as possible) between image guided adaptive proton therapy (IGAPT) with robust optimisation and image guided adaptive radiotherapy (IGART) with EBRT, both using a plan-library plan-of-the-day strategy. In an IGAPT and IGART strategy, daily anatomical variations are monitored with online imaging and, depending on the anatomy on a specific day, the best fitting plan of the library is chosen for the fraction delivery of that day. In our study, day-to-day variations were simulated using weekly CT imaging. While maintaining adequate internal target volume coverage, despite simulated intrafractional motion, results showed significant and clinically relevant dose reductions to the rectum, bladder and bowel. Next, in 2015 we applied an identical proton therapy treatment planning approach in 11 patients with a substantial unininvaded part of the uterus. As described below, comparisons were made with another 'MRI-target tailoring' approach in a 2 x 2 factorial design. Concerning proton therapy treatment planning, significant reductions in the surrounding OAR were again achieved. To estimate the clinical benefit, we used a model-based quantification of the normal tissue complication probability (NTCP) by Roeske et al.[95]. We then predicted that each technique (proton beam and target tailoring) would yield a 7% reduction of ≥ grade 2 acute small bowel toxicity in all patients. Moreover, we identified a patient group that would benefit most from proton therapy,
i.e. patients who, with a conventional technique, would have received 45 Gy or more to > 200 cm$^3$ of the delineated bowel bag. Based on the NTCP model of Roeske et al., in these high-risk patients we predicted a $\geq$ 10% reduction in small bowel toxicity from proton beam therapy[95].

**Recent literature**

Robust optimisation for proton therapy treatment planning using uncertainty values has been used in earlier studies and was also used in our research[84,85]. However, to our knowledge, no other groups included state-of-the-art IGAPT with recalculation of dose distribution using additional imaging obtained during treatment[198,200–202]. Marnitz et al. confirmed the value in sparing OAR with proton therapy; the authors investigated intensity-modulated radiotherapy (IMRT) vs. intensity-modulated proton therapy (IMPT) in patients with locally advanced cervical cancer and also found significant reductions to surrounding OAR.

**MRI-tailored target definition**

As foreseen by others, IGART is the present state-of-the-art radiotherapy for women with locally advanced cervical cancer[80]. Imaging by MRI will be of increasing importance for cervical cancer staging, radiotherapy target delineation, and target tailoring. In the future, MRI will also be important for online position verification during radiation delivery, or at least influence CBCT position verification significantly[238].

The development of MRI techniques as the new ‘kid on the block’ in radiotherapy has gone faster than the actual implementation, validation and acceptance of these imaging techniques. This conservative attitude can best be understood by briefly recapitulating the history of tumour staging in cervical cancer. Up until the late 20th century, clinical examination was the only method available to determine cervical cancer tumour extension and tumour stage[106]. Although abdominal ultrasonography and CT imaging (introduced in the 1990s) allowed a more accurate evaluation of nodal and distant metastases, these imaging techniques contributed little to the assessment of local tumour spread, which could hardly be visualised due to low tumour/normal tissue contrast[67]. Therefore, radiotherapy guidelines traditionally recommended to include the whole uterus in the CTV for EBRT and brachytherapy[68,239]. MRI (slowly introduced around 2010), allowed much better visualisation of the primary cervical tumour. MRI was first introduced in brachytherapy guidelines, by recommending the dose prescription of the brachytherapy boost confined to the visualised tumour, as recommended by the Groupe Européen de Curiethérapie of the European SociétY for Radiotherapy & Oncology (GEC-ESTRO) in the last decade[57,58]. IGABT led to better target coverage
and to a smaller dose to OAR[88]. However, due to uncertainty about possible tumour spread along interconnected vessels and lymphatics in direction of the uterus, most external beam guidelines still recommend to include the whole uterus during EBRT. Additionally, the uterus is subject to movements due to alterations in bowel and bladder content. Therefore, safety margins are applied around the uterus which, inevitably, lead to a substantial dose to surrounding tissue, including the small bowel[92], especially when applied with EBRT. However, since brachytherapy treatment delivery to the uterus is not influenced by intrafractional motion, brachytherapy seems a better modality to deliver a dose to the uterus. More precisely, considering the most recent GEC-ESTRO recommendations with a planning aim of > 85 Gy total dose EQD2\textsubscript{10} to the high-risk CTV, the uterine fundus already receives a brachytherapy dose on top of the 45 Gy from EBRT[57,58,240]. For instance, Sapru et al. (2013) aimed to investigate a cumulative dose to the non-invaded uterus when following the GEC-ESTRO recommendations and found that the uterine fundus receives a median dose of EQD2\textsubscript{10} of 11 Gy[240]. Therefore, by lowering the dose to the uterine fundus with EBRT, we should have a ‘dose margin’ of 11 Gy and brachytherapy also allows to tailor the dose to the uterine fundus. Therefore, lowering the dose to the uterine fundus seems a feasible yet un-utilised opportunity to spare more small bowel.

In 2015, we investigated the dosimetric benefits of lowering the dose to the unaffected uterine fundus in 11 patients with > 4 cm of uninvaded uterine tissue in craniocaudal direction, by excluding the unaffected part of the uterus from the elective target volume, as prescribed by international guidelines[67,68,105,124]. The GTV was delineated using MR images, and a margin of 10 mm to CTV was used to compensate for invisible microscopic spread; this is in accordance with our data and data from others[107,191]. We found a significant reduction in the volume that received 45 Gy of rectum, bladder and small bowel. In our group of patients, applying the NTCP model of Roeske et al.[95] predicted a 7% reduction of ≥ grade 2 acute small bowel toxicity. We also identified patients (55%) in whom this approach would be more beneficial; i.e. patients with ≥ 275 cm\textsuperscript{3} of small bowel that receive 45 Gy are more likely to benefit from the use of either strategy. Additionally, we combined this MRI-tailored target definition with proton therapy, which led to a complementary effect of a further predicted reduction of small bowel toxicity.

Recent literature

MRI-tailored target definition remains controversial, probably also due to the risk of compromising high local control rates (86-96%) [88]. However, this control rate should not be compromised by lowering the elective dose in uninvolved uterine tissue without adequate consideration. On the other hand, even before the introduction of IGBT, it was not local control but rather regional nodal metastasis that presented a
greater challenge to radiation oncologists, as further improvements due to chemotherapy seemed to diminish after the introduction of concomitant chemotherapy 20 years ago[134]. Then, to improve locoregional control rates in patients with regional nodal involvement, we probably have to increase the nodal radiation dose[241]. This might only be feasible by reducing the irradiated volume, e.g. by excluding uninvolved uterine tissue. Due to a large margin, this leads to a considerably smaller dose to small bowel. In this thesis we have extensively discussed the probable benefit of image-guided tailoring of the ‘elective’ radiotherapy dose to the uninvolved uterus. Subsequently, we may consider reducing the elective radiation dose to the regional nodal sites, by tailoring the radiotherapy dose to areas that are involved, or are at high risk, as visualised by MRI and/or PET-CT scan[66,112,131]. At present, to our knowledge, there are no further data on the possible benefits of MRI-tailored target definition. However, there is some indirect evidence from trachelectomy studies that that there is a higher recurrence rate in tumours that are >2 cm, which only occurred regionally[192,193,242].

Acute small bowel toxicity is a known risk factor for ≥2 grade II late small bowel toxicity, which is a well-known burden in up to 64% of the patients[44,184]. Although NTCP models of both early and late toxicity are scarce, our results are largely in agreement with the available models. Simpson et al. developed their own NTCP model and found that every 100 ml of small bowel that is spared from the 45 Gy area, results in an expected reduction of grade ≥2 GI toxicity by approximately 50%[243]. This implies that MRI-tailored target definition, or any other strategy that will lower the radiation dose to the small bowel, will lead to a reduction of late small bowel toxicity and to an important improvement in quality of life in these patients. More studies are needed which combine toxicity data and quality of life data with dosimetric indices to develop better NTCP models for pelvic radiotherapy.

**Daily online MRI-based replanning**

Since the end of the 20th century, multiple initiatives worldwide started to develop online MR-imaging mounted on a linear accelerator or Cobalt machine[244–246]. Improvement of online MRI with a better soft-tissue contrast than the present techniques, will also boost IGART. Such online imaging, with real-time plan adaptation with tighter margins around the target volume may allow further sparing of the surrounding OAR[228,247]. Kerkhof et al. (2008) have already reported on the benefits of MR image guidance in cervical cancer patients[123]. Jadon et al. (2014), in a systematic review of the literature, reported that movement of the uterus between each fraction is the major source of organ position uncertainty during cervical cancer radiotherapy; interfraction motion of the uterus may be as much as 4 cm[195]. MRI-based online position verification and replanning may allow safe reduction of the
margin for uterus motion to only 5 mm for intrafraction motion; this reflects similar results of online controlled tumour motion in lung cancer radiotherapy. Further image-guided tailoring can be obtained by plan adaptation in shrinking bulky tumours, with 50% shrinkage (on average) during 4-5 weeks of EBRT; this means that the CTV could be reduced, and may also lead to a smaller dose to the small bowel.

Our analysis of 15 patients with cervical cancer that underwent weekly MRI with a ‘comfortably full’ bladder shows that significant reductions in small bowel toxicity can be expected, especially in patients with an (initially) small bowel volume of ≥ 200 cm³ that receive a dose of at least 45 Gy. Furthermore, our PTV margin of 5 mm was sufficient compensation for intrafractional motion.

Recent literature

Kerkhof et al. (2008) showed that online-MRI with replanning, compared to IMRT with online CBCT position verification, results in a significant dose reduction to OAR. However, since IGART had not yet been introduced into clinical practice, no comparison with IGART was possible; moreover, the authors did not investigate the influence of intrafractional motion during each EBRT session.

Future perspective

Our data further corroborate that MRI-tailored target definition in cervical cancer radiotherapy reduces the dose to OAR and may lead to a clinically relevant reduction of acute and late small bowel toxicity. When MRI is used for target delineation in cervical cancer, our results indicate that a clinical uncertainty margin of 1 cm in craniocaudal direction towards the uterine fundus is sufficient to cover microscopic tumour extension. Since this is a new strategy, it remains debatable whether to reduce the external radiotherapy dose to the uninvolved uterine body, and whether it is sufficiently safe to cover the ‘elective’ dose to the endometrium by brachytherapy. Recent data indicate that we have a 11 Gy (± 7.5 Gy) ‘dose margin’, implying that if we treat the uterine fundus by EBRT with only 34 Gy (EQD2), brachytherapy will still increase the ‘elective’ dose to the uninvolved uterine body up to 45 Gy. In the future, better EQD2 dose maps could combine EBRT and brachytherapy dose, giving visual insight into where dose limits have been reached, and where dose escalation is possible. A possible limitation of this strategy would be posed by a patient with a relatively large uterus, in whom the dose margin will be smaller due to the distance to the high dose brachytherapy target volume. This method would probably also be limited by patients with a higher risk of uterine tumour extension due to LVSI, adenocarcinoma, clear cell carcinoma, or large tumours. However, those with reservations about such an approach should be reminded that regional failure is a
greater challenge for cervical cancer radiotherapy than local failure. To improve
regional tumour control we have to increase the radiation dose to unresectable
metastatic lymph nodes; for that matter less ‘elective’ dose to uninvolved regions and
normal organs might be convenient. Another approach to reduce radiation dose to the
bowel without compromising cure rates will be investigated in the prospective ‘EXIT’
study. At the time this thesis was being printed, colleagues from Belgium opened this
new study testing the safety of neo-adjuvant external beam pelvic radiotherapy plus
weekly cisplatin without brachytherapy. During EBRT, the non-involved uterus on
MRI will be EXcluded to further reduce bowel toxicity. Six to eight weeks after
radiotherapy, patients will have a radical hysterectomy[251].

Treatment with proton therapy is a feasible and valuable complementary option to
further reduce the dose to OAR, particularly to the small bowel. However, to justify the
high costs of proton therapy, we need better NTCP models, based not only on acute
side-effects, but (more importantly) also on late complication rates[218]. Our results
suggest that most benefit will be obtained from proton therapy in women with a
relatively large small bowel volume (>200-275 cm$^3$) that will receive 45 Gy; for
instance, women in whom the para-aortic lymph node regions should be irradiated.
The same group of patients will also benefit most from treatment with online MRI in
combination with fast replanning, which will (hopefully) become available in the near
future for cervical cancer; however, online replanning might be available first for the
broad audience, in combination with online CBCT since this technology is already
widely implemented. By using CBCT, some propose a so-called ‘evolutive library’ of
plans for IGART that improves after several fractions[238]. As for MRI-guided
radiotherapy with online replanning, some technical hurdles still have to be
taken[110]. For instance the maximum treatment field-size of an MRI-linear
accelerator may be as small as 22 cm and therefore a more advanced solutions such as
a dual isocenter technique needs to be evaluated[252].

It should be noted that imaging (such as MRI and PET-CT) might never replace clinical
examination under anaesthesia, and these techniques should be used in a
complementary manner. Furthermore, our data suggest that, besides T2-weighted
images, at least DWI with ADC-mapping should be performed to improve tumour
detection. Future studies are needed to validate the value of imaging, particularly MRI,
for target delineation. In this thesis, we correlated MRI and histopathology of
hysterectomy specimens only for craniocaudal tumour extension. To correlate tumour
extension in all directions (particularly in the direction of the parametrium) requires a
different ‘3D whole organ’ preparation of the surgical specimen. Such a novel
approach will not only improve accuracy for radiotherapy, but may also provide
better anatomical information to evaluate ‘nerve sparing’ surgical techniques.
Correlation of such a study with clinical outcome, may also provide more accurate
information on risk factors (e.g. tumour size, LVSI, histological subtype).
In conclusion, underestimation of cervical craniocaudal tumour size on MRI is within 10 mm. This margin with incorporated uncertainty can probably be further reduced when whole-mount uterus sections are compared with MRI. Patients with small tumours and a substantial part of the small bowel near target volumes, will most likely benefit from an approach in which the uninvaded uterus is lowered in elective EBRT target volumes, and/or an approach in which proton beam therapy and/or online replanning are used. The use of either of these approaches allows a smaller dose to be delivered to OAR, in general particularly to the small bowel. Due to the considerable long-term toxicity and risk of regional failure, further investigation of opportunities to reduce the dose to OAR while maintaining/improving adequate dose to tumour sites should start as soon as possible. With the currently available clinical data, together with our research data, this should enable a step forward to improve the prognosis for these predominantly young women with cervical cancer.