(Un-)certainties in radiotherapy of rectal cancer
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From a historical point of view, surgery has always been the main treatment option for rectal cancer patients. Starting with the Swedish rectal cancer trial [1], addition of radiotherapy in the treatment of rectal cancer has gained ground improving local control. Based on the EORTC 29921 trial [2], the FFCD 9203 trial [3], the Dutch TME trial [4], the German pre- vs. post-CRT trial [5] and the recent MRC-CR07 trial [6], standard of care has now evolved to pre-operative radiotherapy in 5 fractions of 5 Gy for early-stage rectal cancer, and pre-operative chemo-radiotherapy with approximately 25 fractions of 2 Gy in 5 weeks for locally-advanced rectal cancer.

Compared to other malignancies in the pelvis where radiotherapy is the main treatment choice, such as prostate cancer, little has been invested in the accuracy of radiotherapy in rectal cancer. Few studies are available on inter- and intra-fraction setup errors, definition, delineation and shape variation of the clinical target volume (CTV), and finally, no adequate planning target volume (PTV) margins have been defined to account for geometrical uncertainties. The most investigated and published geometrical topics have been influences of bladder volume and orientation of the patient. Supine and prone position and the use of a belly board have been compared on dose received by the small bowel. However, no general consensus has been reached on what orientation should be used, for example, in the Netherlands patients are treated 40% supine, 30% prone and 30% prone with a belly board in the different treatment centers.

Because of the lack on sufficient knowledge on the geometrical uncertainties, or maybe the view that RT is a secondary treatment to surgery, intensity-modulated RT (IMRT) has not been widely implemented for rectal cancer. This is disappointing, since planning studies have shown that use of IMRT can result into equal or better PTV coverage, while reducing the dose to the small bowel [7,8]. Recently Samuellian et al. [9] showed, in a retrospective study on 92 consecutive patients, a clinically significant reduction in acute lower gastro-intestinal toxicity when using IMRT.

In the past few years, a tendency to apply less invasive transanal endoscopic microsurgery (TEM), or no surgery at all in a “wait and see” policy can be observed. These types of treatment rely on adequate (chemo-)radiotherapy to assure local control [10-13], except for TEM surgery in small T1N0 tumors. In the more advanced cases, dose-escalation to the gross tumor volume (GTV) can be used to improve tumor down-sizing and down-staging and broaden the patient group suitable for minimal invasive surgery [12,13]. Ultimately, dose escalation could result in an increase of clinical complete response, after which the “wait and see” policy can be applied to decide on surgery.

With increasing importance of radiotherapy in the treatment of rectal cancer it is also mandatory to increase the knowledge on geometrical uncertainties, providing a base for more accurate treatment using IMRT. The work provided in this thesis aimed to estimate, reduce and compensate for geometric uncertainties in radiotherapy of rectal cancer. The investigated uncertainties include patient setup and orientation, CTV definition and delineation, and shape variation. From derived shape variation uncertainties a PTV margin was derived. Finally the potential margin reduction using adaptive radiotherapy was presented. In this chapter the implications of the provided work and issues for further investigation are discussed.
**Patient setup and orientation**

Supine setup is generally associated with more stability during the irradiation, easier setup and more comfort, while prone treatment, especially on a belly board, is associated with reduced dose to the small bowel [14-16]. In chapter 2 we demonstrated that in the setting of IMRT with very conformal delivery of dose, and a full bladder protocol the use of a belly board still significantly reduces the exposure to the bowel area. The clinical relevance of this reduced exposure of the bowel area was however questioned, because for the majority of patients, cutoff values predicting bowel toxicity [17-20] were not exceeded in any of the orientations. Apparently the use of IMRT and a full bladder protocol is sufficient. Based on these findings use of a belly board was advised for selected patients only with an unfavorable anatomy that would result in a high exposure of small bowel. Comparing prone and supine setup on a flat table we demonstrated that there was no difference in bowel area exposure. For patient comfort and stability, the general treatment of rectal cancer patients should thereby consist of IMRT with a full bladder protocol and supine positioning.

With imaging equipment on the treatment machines, such as electronic portal imaging, kV- or MV-Cone-beam CT or Tomotherapy, inter-fraction setup errors have been shown to be fairly small (0.1-0.4 cm SD), while daily online setup correction is clinically feasible [21-24]. After online setup correction, the stability of the patients during treatment becomes the most important factor determining setup uncertainty. The presented intra-fraction setup errors (chapter 6) were for patients treated prone on a flat table with SCRT. Intra-fraction setup errors were small compared to other uncertainties, such as shape- and delineation variation. Only in the left-right direction errors were $\bar{\Sigma}=0.24$ cm and $\sigma=0.22$ cm, which was about twice as much as observed in supine position [25]. This finding was probably due to the lack of bony support in the abdomen when lying in prone position. Since we now treat our patients in supine position intra-fraction setup errors will be negligible.

**Clinical target volume definition**

The Dutch consensus guidelines on CTV definition for early-stage rectal cancer (chapter 4) were based on the evidence based guidelines of Roels et al. [26]. The Dutch guidelines were developed by summarizing the guidelines and reviewing the definition of each CTV region in a consensus meeting. The only major adaptation was a stricter delineation around the sphincter complex, similar to the RTOG atlas [27], because the consensus was that local recurrences do not frequently occur in the ischiorectal fossa region.

The most important goal of developing the guidelines was to reach a nationwide uniform definition of the CTV, minimizing treatment differences between patients treated in different hospitals. We have shown that inter-observer delineation variation was indeed reduced using guidelines and a delineation atlas (chapter 4).
Where CTV delineation guidelines mainly depend on for distance of the tumor to the anal verge [26, 27], other clinical factors are more predictive for local control. We have shown that the few patients with a recurrence after a negative CRM and node negative disease at pathology all recurred in the mid- and caudal part of the pelvis, independent of SCRT (chapter 5). Based on these findings we concluded that for these patients the extent of the CTV at the level of the promontory, S1 and S2 does not add in the prevention of local recurrences, and can therefore be omitted. The idea of lowering the cranial border of the CTV was earlier suggested by Syk et al. [28,29] and by Chien et al. [30] in a response to Yu et al. [31]. Unfortunately, these studies had only few patients with local recurrences (33 and 36, respectively) and data presented was not randomized between RT and no-RT. The findings provided in this thesis are therefore important evidence to further explore the possible reduction of the CTV based on prognostic factors. Ideally, a randomized trial comparing a standard CTV with the reduced CTV and local control as primary outcome would be needed, but such a trial would demand for inclusion of too many patients to be practical, due to high local control.

In a recent discussion on implementing the recommendations of chapter 5 in the Netherlands an important comment was raised. The proposed cranially reduced CTV is defined based on bony anatomy, whereas currently the CTV definition is based on soft tissue. Patterns of local recurrence are probably more dependent on anatomic soft-tissue borders than bony anatomy. As an alternative approach the cranial border could be lowered to the level where the rectum turns into the sigmoid colon. At this level the transition from mesorectum to presacral space is located, which is a more acceptable anatomical border for local spread. An important demand for adapting the CTV definition to prognostic factors is a clear statement on mesorectal fascia (MRF) threat and node negativity from the radiologist. The latter is the more challenging part, with a specificity of approximately 80% on MR [32-34], compared to over 90% specificity for assessing the MRF threat [35-37].

The delineation guidelines of Roels et al. [26] were based on a review of local recurrence sites in literature. For further specification of the CTV definition, ideally randomized trials comparing treatment with and without RT (such as in chapter 5), or comparing different CTV definitions should be used. The chance that these trials will be launched in the near future is however small, since addition of RT has been established as the standard of care. As an alternative a pooled analysis of the major randomized trials could be done. However, most trials lack a 3D analysis of recurrence patterns, and the difference in CTV definition between the trials is generally not large and based on bony anatomy instead of soft tissue.

Clinical target volume delineation
We have shown that CTV delineation variation is a substantial uncertainty that can be reduced significantly using delineation guidelines and an atlas (chapters 3 & 4). Residual delineation variation was, however, disappointing with differences in CTV borders between observers still in the order of centimeters, rather than millimeters.
There are several options to further reduce delineation variation. Following a Belgium rectal cancer project, CTV delineation could be reviewed in a central expert institution to monitor CTV delineation and establish a learning curve by giving feedback [38].

Addition of other imaging modalities, especially MR, after image fusion with the planning CT could potentially further reduce the delineation variation. MRI is generally accepted as the best imaging modality to estimate the distance from the tumor to the MRF, due to better visibility of both the tumor and MRF compared to CT [35, 36] (Fig. 10.1). Use of MR for target volume delineation has already been proven favorable in prostate and head and neck cancer [39]. Potential problems occur when the anatomy surrounding the rectum deformed substantially between the CT and MR scan. In this situation deformable registration algorithms are needed to equalize the anatomy between both and optimally use the complementary imaging information [40].

Finally auto-segmentation has the potential to produce unambiguous CTV delineations, since it relies less on visual interpretation of images. Auto-segmentation is, however, currently not advanced enough for reliable CTV delineation in rectal cancer. In prostate cancer, for example, auto-segmentation has been shown to produce good to excellent delineations of the prostate and bladder, but for the rectum itself results were often not acceptable [41]. With less visible anatomical borders for the CTV in rectal cancer, especially for the lymph node regions, auto-segmentation will likely be even more inaccurate.

The provided work on shape variation of the CTV (chapters 6, 7 and 8) was totally based on delineation of target volumes on repeat CT and CBCT images. To minimize the influence of delineation variation in these studies, the planning CT and repeat scans were delineated by one observer per patient. The planning CT delineations were first discussed in a group of observers and subsequently used as example for delineation of the repeat scans. The intra-observer variation for this approach was shown to be acceptable, in the order of 0.2-0.3 cm SD (chapter 7).
Clinical target volume shape variation

Literature on target volume shape variation is scarce, and available studies are either on post-operative patients, ignore inter-patient variation, do not divide shape variation in systematic and random errors, or ignore heterogeneity of shape variation [24, 42-44]. All available studies are based on data acquired during CRT, prone positioning and provide shape variation only for a part of the CTV.

In this thesis the knowledge on CTV shape variation was extended by investigating shape variation in SCRT, and comparing variation between prone and supine positioning (chapters 6, 7). We also described CTV shape variation for the entire CTV, instead of the mesorectal part only, and were able to compare shape variation between SCRT and CRT (chapter 8).

When evaluating the results of the different studies it is clear that CTV shape variation is substantial, with systematic errors up to 1.0 cm SD. Shape variation was also heterogeneous, and differences exist between SCRT and CRT. In patients treated with CRT a time trend in rectal volume was present resulting in a mean reduction of the CTV size towards the end of the treatment (chapter 8). Positioning patients prone or supine on a flat table did not influence the shape variation.

The results for the mesorectal part of the CTV based on CBCT data (chapters 6 & 7) showed slightly smaller systematic and random errors compared to the repeat CT data (chapter 8). The significant difference in systematic shape variation at the upper anterior edge of the mesorectum between male and female patients in the CBCT data (chapters 6 & 7) was not confirmed in the repeat CT study (chapter 8). In the CBCT studies the average delineated mesorectum length was approximately 10 cm, while for the rCT studies the delineated mesorectum was on average 13 cm. This 3 cm difference might be the reason for the observed differences between the studies. Also the image quality of the CT scans is superior to the CBCT scans (Fig. 7.1) for which we tend to rely more on the repeat CT data. For logistical purposes it is, however, more convenient to use CBCT, i.e. advances in CBCT image quality are necessary.

The most comparable study in literature is by Nuyttens et al. [42], describing variation of the anterior border of the CTV in repeat CT data of patients treated with CRT, although mostly post-operative. Their results were confirmed with the repeat CT data (chapter 8), showing large and heterogeneous shape variation. The similarity in results also indicates that shape variation might be comparable between pre- and post-operative RT patients.

The work provided in this thesis adds to the limited data available on CTV shape variation in literature. Hopefully similar studies will be conducted in the near future to confirm our findings. Especially deformable image registration based studies with accurate tissue correspondence between different scans would be welcome to evaluate the model used for shape variation in this thesis. For example repeat MR images with high soft-tissue contrast could be used for validation.
PTV margins
Planning target volume margins are designed to take geometric uncertainties into account and assure a certain dose to the CTV for a certain percentage of the patient population [45, 46]. These margins are thereby balancing the risk of geometric target miss with normal tissue complication. Known margin recipes for calculation of PTV margins are defined for rigid translational geometric uncertainties, not for shape variations.

There are only two studies available in which an estimate of the required PTV margin has been made for pre-operative RT of rectal cancer, including shape variation [24, 43]. In both studies important shortcomings can be identified, hampering the clinical applicability of the derived margin. As described earlier, both studies averaged the shape variation over all measurements, all patients and over the whole surface, ignoring the heterogeneity of shape variation and the effect of systematic and random errors. In the study of Tournel et al. [24] the PTV margins were estimated by adding the Gaussian distributions of the intra-fraction setup errors and the shape variation errors, while ignoring systematic components of both distributions. The 95% confidence interval of the total Gaussian distribution was taken for the PTV margins, assuming 95% physical target coverage of all treatment fractions in the population. However, by not dividing the uncertainties into systematic and random components, and not applying different weights to the systematic and random errors to calculate the required PTV margin, resulting margins are an underestimation.

In the study of Brierly et al. [43] the PTV margin recipe for rigid geometric uncertainties of van Herk et al. [45] was applied to systematic and random shape variation errors which were underestimated because of averaging. The provided PTV margins of less than 0.8 cm are therefore to our opinion insufficient for appropriate target coverage.

The approach in this thesis (chapter 8) was to define the PTV margins locally, resulting in larger margins where the shape variation was also larger, and vice versa. The margin recipe was established by accumulating CTV dose using simulated dose distributions (chapter 8). With the planned dose distributions in the ART study (chapter 9), we have shown that the derived margins also assure sufficient CTV coverage with clinically applicable IMRT plans.

With a maximum anterior PTV margin for the upper-anterior region of the mesorectum of 2.4 cm and 3.2 cm for CRT and SCRT, respectively, derived margins were substantially larger than the current clinical uniform 1 cm margin. These margins were, however, derived based on strictly delineated CTVs according to the guidelines (chapter 5), while in clinical practice the generous anterior border for the mesorectum, as proposed by the RTOG [27], is applied. Interestingly, the strictly delineated CTV plus the larger margin resulted in PTV volumes which were approximately 20% smaller than the generously delineated clinical CTV plus 1 cm margin. When visually assessing the differences between the clinical PTVs and the proposed PTVs, the volume reduction was mainly achieved at the level of the prostate, bladder cervix and uterus. Interestingly, the clinical PTVs tended to be somewhat smaller at the level of the small bowel, implicating a current lack of coverage. With clearly defined CTV delineations, and validated PTV margins target volumes for rectal cancer RT are likely to be more reproducible, smaller and more accurate.
It is important to note that the proposed margins only account for shape variation errors. Other uncertainties, such as setup and delineated errors, should also be incorporated in the PTV margin. With online setup correction, only intra-fraction instability is an important error source. With intra-fraction setup errors being small compared to shape variation, influence on CTV coverage was also shown to be small, using simulations (chapter 8). Incorporation of delineation uncertainties is much more complex, since generally the gold standard CTV is not known. Observers who delineate always too small or always too large will have a different effect on cure and toxicity of a patient. I do not think that just adding the derived standard deviations for delineation variation to the shape and setup variation in the margin concept is sufficient and acceptable to overcome this problem. For rectal cancer this would result in a further increase of the required margin to beyond 4.0 cm, while clinical evidence on local control is generally good and not suggesting under dosage. As suggested by Weiss and Hess [49], it would be more beneficial to focus on strict delineation guidelines, multimodality information and multi-disciplinary discussions with radiologists and diagnostics to reduce delineation variation.

Another point of discussion is the need to cover the entire CTV ensuring the 95% minimum dose for 90% of the patients. As the CTV is constructed out of the GTV and an elective target volume, for which a substantial part might not contain any tumor cells, coverage might also be reduced. Since data on probabilities of tumor cell distributions is lacking it is not trivial to decide for which regions in what patients the treatment planning constraints can be relaxed.

Adaptive RT
The concept of adaptive radiotherapy (ART) has been introduced by the Beaumont group in 1997, to either reduce or compensate for the effect of patient specific treatment variation during RT [50]. ART can be focused on treatment effects, such as tumor shrinkage or changes measured on biological imaging [51], but ART can also be focused on geometrical uncertainties, especially the systematic errors [50]. In this thesis, use of single plan adaptation during CRT based on repeat CT images of the first 4 fractions resulted in a significant reduction of the systematic errors, with a reduction from 0.9 cm SD to 0.5 cm SD at the upper-anterior part of the mesorectum (chapter 9). With this reduction, maximum required PTV margins for shape variation could be reduced from 2.4 cm to 1.7 cm resulting in a significant reduction of the volume of bowel receiving 45 and 50 Gy.

Since the birth of the concept in 1997, ART has always been a hot topic in radiotherapy research, because of its high potential. Unfortunately, clinical implementation of ART has always been difficult, requiring a fundamental shift of the infrastructure of the radiotherapy process from the conventional open-loop planning/treatment process to a closed-loop feedback control process [52]. This is also the case for our proposed ideal ART strategy (chapter 9). Acquiring repeat CT images during the first 4 fractions, delineation of the CTV on all scans and re-optimizing a treatment plan on the average CTV is very labor intensive. The associated workload might outweigh the clinical dosimetric benefit. Adapting based on an average CTV over the planning CT and only 1 repeat CT already
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reduced the systematic error substantially. A more practical ART procedure could be to acquire 2 planning CT scan of a patient on different days preceding the treatment and derive an average CTV out of both scans. The reduction in PTV margin would be slightly smaller than the ART_4 procedure, while the workload would be reduced substantially.

Due to the systematic reduction of the rectal volume and the CTV towards the end of CRT treatment, more sophisticated adaptive procedures could potentially further reduce required margins. A plan could, for example, be altered halfway during treatment when repeated in-room imaging has revealed a systematic shape change of the CTV. The easiest adaptation would be to make a new planning CT and create a new treatment plan. As a more technically challenging alternative, the in-room images could also be registered to the planning CT using deformable image registration, providing the option to deform the original planning CT to the average anatomy from the treatment. Reliable deformable image registration for the pelvis should than first be implemented.

Clinical implications

The findings provided in this thesis clearly influenced the clinical practice in our department. Treatment of rectal cancer patients has been changed from prone to supine on a flat table based (chapter 2). This has increased patient comfort and intra-fraction stability. We are currently implementing de delineation guidelines (chapter 4), and adapt the CTV definition in early-stage rectal cancer based on expected CRM and nodal status (chapter 5), not only locally, but also nationally. With stricter delineation of the CTV, we will also introduce the provided evidence-based PTV margins (chapter 8). With these changes we will be able to provide more reliable, accurate and smaller CTV and PTV volumes, essential input for IMRT. The changes will in general result in a reduction of dose to the organs at risk. The IMRT will actually be delivered using intensity-modulated arc therapy, reducing the actual treatment time.

The main missing part is implementation of adaptive radiotherapy (chapter 9). To my opinion, the reduction in required PTV margin and subsequent reduction in bowel exposure does not outweigh the burden of re-scanning, re-delineating and re-planning. In future this could change when re-delineation of the CTV can be automated by deformable image registration and contour propagation. It would also be beneficial if cone-beam CT images could be used instead of repeat CT, since they are acquired for setup correction anyway.

An alternative option to ART is to calculate a library of plans based on the CTV and a series of PTV margins, and subsequently choose the adequate plan for each treatment fraction based on a pre-treatment CBCT. An important advantage of this plan selection approach is that it also takes random shape variation into account, which has been proven to be substantial. Another advantage of plan selection over adapting the treatment plan during treatment is that it is also applicable for SCRT. In the repeat CT study we also acquired CBCT scans on the days of the repeat CT scans. This data will be used to investigate the plan selection approach in the near future. Ideally one would like to re-optimize the treatment plan based on the anatomy from the CBCT scan at every fraction. However, this plan of the day approach can only become clinically applicable when automated fast CTV adaptation and plan calculation is available, in combination with
treatment plan verification. Maybe the development of an integrated linear accelerator with an MRI [53] for image guidance will provide sufficient soft tissue contrast for further explore the “plan of the day” strategies.

Future directions
With rectal cancer being treated in a multi-disciplinary setting, different oncologic specialties anticipate different directions in the future. The actual importance of RT in the future is depending on the type of surgery. If the general surgical approach for all patients will continue to be standardized radical total mesorectal excisions, then better patient selection due to better diagnostic imaging and tumor dependent prognostic factors will possibly allow less RT, to reduce the current overtreatment. If minimal invasive surgery will gain popularity, RT will become more important for rectal cancer treatment. In the following section I will elaborate on RT and minimal invasive surgery, followed by RT response prediction and measurement, and finally overtreatment with RT in TME surgery.

Minimal invasive surgery, “wait and see”
One of the major paradigm shifts in treatment of rectal cancer is the tendency towards minimal invasive surgery, or even completely omitting surgery. These treatments generally result in less morbidity, and for patients in which unfavorable outcome is observed, such as positive resection margins in case of a TEM procedure or local recurrent disease after a wait and see period, there is still a fall-back procedure by doing radical TME surgery. In the minimal invasive setting it is interesting to explore the possibilities and effects of delivering a boost dose to the GTV, while delivering a lower dose to the CTV.

For minimal invasive surgery the transanal endoscopic microsurgery (TEM), introduced by Buess et al. [54] in 1985, is generally used. The TEM as sole treatment is generally only applied for patients with benign rectal tumors, small well differentiated T1 tumors and in the palliative setting [10,11]. Local control, cancer specific and overall survival of over 90% is generally achieved for patients treated with curative intent. When applied to patients with poorly differentiated T1, or with T2/T3 tumors, local control is significantly reduced compared to TME surgery, with up to 50% local recurrences [10,11].

For patient with T2-3 node negative disease, neo-adjuvant (chemo-) radiotherapy followed by a TEM excision seems to be a tempting alternative to neo-adjuvant treatment followed by radical surgery [12-13]. Lezoche et al. [12] showed excellent results in a dataset of 100 patients treated with 50.4 Gy RT in 28 fractions followed by a TEM, with 5% local recurrences, 2% distant recurrence, 89% rectal cancer specific survival and 72% overall survival after 90 months follow-up. The most important factor determining good clinical outcome was down-sizing and down-staging of the tumor after the neo-adjuvant treatment.

To further expand the minimal invasive approach, the most important effect that needs to be achieved is tumor down-staging and down-sizing. Several studies have shown a dose-effect relation in rectal cancer [55-58], implying that dose escalation
might be a suitable option. Dose escalation generally consists of a boost dose given to the GTV while maintaining a standardized dose to the CTV. Several options are available for boost dose delivery, such as contact therapy [58], endorectal brachy-therapy [59] or external beam RT (EBRT). With use of IMRT it is possible to deliver a simultaneously integrated boost (SIB) to the GTV, while giving the standard dose to the CTV [60, 61]. The advantage of SIB over contact- or brachy-therapy is that treatment time is not prolonged and patient burden is not increased, although dose to the organs at risk is potentially higher.

With the results provided in this thesis, the CTV and PTV will generally become smaller compared to current clinical practice. This gain can be used to increase the boost to the GTV while maintaining iso-toxic bowel exposure.

As shape variation of the CTV in rectal cancer is substantial, applying a boost to the GTV will further complicate the radiotherapy, since the positional variation of the GTV within the CTV also needs to be taken into account. In post-operative setting, Nuyttens et al. [42] reported that clips placed at the anastomosis moved in caudal-cranial direction in the order of 1 – 1.5 cm from day-to-day. Vorwerk and colleagues [62] implanted 2-3 gold markers in the tumor region pre-operatively and measured positional variation with 3D vector displacements of 0.99 cm SD with respect to the treatment fields. Based on these data it is clear that a substantial margin is needed to cover GTV motion. The use of implanted fiducial markers is also attractive for image-guided RT, in which it can be used as a surrogate for position deviations of the GTV within the CTV.

Fig. 10.2: Example of lymph node positions on the 9 repeat CT scans for a locally advanced rectal cancer patient in sagittal view of the planning CT scan. Maximum displacements were 0.4, 1.5 and 1.1 cm in left-right, cranial-caudal and anterior-posterior direction, respectively.
To get an impression of lymph node movement within the mesorectum we delineated 9 enlarged lymph nodes in 2 advanced rectal cancer patients from the repeat CT study (Fig. 10.2). Depending on the location of the lymph node, day-to-day motion was in the order of 0.2 cm close to the posterior wall of the mesorectum, while translations up to 1.5 cm were found close to the rectum itself. The movement of lymph nodes will be subject of further investigation.

It is important to realize that treatment using a TEM or “wait and see” after neo-adjuvant (chemo-) radiotherapy makes the rectum itself an organ at risk, because the rectum is not removed at surgery. Tolerance limits for the rectum are extensively studied in prostate cancer patients, but the dose distribution in these treatments is substantially different compared to rectal cancer [63]. In prostate cancer RT only a small part of the rectum is exposed to a high dose (>60 Gy), while in rectal cancer patients the whole rectum will be part of the CTV, receiving a base dose of at least 45 Gy. Some studies on prostate cancer patients suggest that the probability of late rectal bleeding increases when a large part of the rectum surrounding the high dose region receives an intermediate dose of around 35 Gy [64, 65], suggesting a bath and shower effect. Suggestions were made that the rectal mucosal regeneration is affected, which would also be the case for rectal cancer patients. Extensive dose escalation studies should therefore be conducted to validate the tolerance limits of adding a GTV boost, evaluating quality of life and functional outcome.

For patients with locally advanced inoperable rectal cancer minimal invasive surgery or “wait and see” after neo-adjuvant (chemo-) radiotherapy is obviously not a suitable option. However, also in this patient population the concept of dose escalation might be clinically relevant. In operable rectal cancer dose escalation can be used to increase the amount of sphincter saving surgery procedures, reducing morbidity [58] although not all studies were able to prove this effect [5, 66]. For patients with inoperable rectal cancer neo-adjuvant chemo-radiation can be used to reduce tumors such that they become operable in up to 57% of patients [67]. Dose escalation might be used to increase this percentage.

For all treatment settings, reduced PTV volumes (chapter 8), further PTV reduction using adaptive radiotherapy (chapter 9), optimal small bowel exposure reduction using a belly board with a full bladder (chapter 2) and more uniform CTV definition (chapter 3 & 4) will altogether allow for extra dose escalation.

**Imaging treatment response**

The gold standard to accurately assess tumor response after neo-adjuvant RT is obviously pathological examination of the resection specimen. To facilitate the minimal invasive surgery and “wait and see” approaches, alternative and earlier response prediction is needed. Standard imaging modalities such as CT and T2-weighted MR, using morphologic and size-related criteria, can not be used to accurately differentiate responders from non-responders [68]. With functional imaging it is possible to discern the responders from the non-responders during and after neo-adjuvant RT. Especially 18Fluoro-Deoxy-Glucose Positron Emission Tomography (18FDG PET) and Diffusion Weighted MRI (DW-MRI) are used for response prediction. The response prediction consists of measuring
differences between the functional images acquired before treatment, and the ones acquired during or just after treatment.

For $^{18}$FDG PET, the reduction in standardized uptake value (SUV) can be used to predict the pathological complete responders (pCR) with a cut-off of 66% reduction resulting in a 77% positive predictive value and 89% negative predictive value [69]. The additional value of the relative change in SUV next to the clinical tumor data in predicting a pCR was shown by van Stiphout et al., who developed a predictive model for pathological complete remission (pCR) based on a pooled multicenter database of 953 patients [70].

In DW-MRI the apparent diffusion coefficient (ADC), which is a measure to describe the permeability of water molecules within tissue, is used for response prediction. In tumor tissue the water molecules are restricted due to high cell density, resulting in low ADC values. Lambrecht et al. [71], showed that patients with a pCR have significantly lower ADC values before treatment, significantly higher ADC values after 10-15 fractions and also after CRT, indicating that these factors can be used to predict a pCR.

Ultimately DW-MRI and $^{18}$FDG-PET can be combined to predict which patients will have a pCR. Lambrecht et al. [72] showed that using a cutoff point for pre-treatment ADC, in combination with the reduction in SUVmax between pre-treatment and after 10 fractions resulted in a 100% sensitivity and a 94% specificity for predicting a pCR. Functional imaging is therefore a promising tool to predict a pCR without a resection specimen. Although promising, use FDG-PET and DW-MRI is not widespread, mainly because imaging protocols and data analysis should first be improved in order to ensure the very high reproducibility required for treatment adaptation [73].

Another advantage of functional imaging techniques is that they provide extra information about the GTV for the boost. In FDG-PET scans, the GTV can be segmented automatically using a gradient-based method, providing target volumes which correlate well with the GTV volume measured at pathology [40].

**Total mesorectal excision and overtreatment with RT**

Already in the first operated series of Heald et al. [74] it was clear that performing a standardized total mesorectal excision results in high local control with local recurrence rates as low as 6% at 5 years and 8% at 10 years. Based on their experience they concluded that 4 out of 5 patients operated with curative intent could be cured with TME surgery only. The remaining 1 out of 5 patients is the group that benefits from pre-operative RT in terms of local control. However, selecting these patients is the major challenge. In the Dutch TME study local control and rectal cancer specific survival was shown to be significantly better in the RT+TME group compared to the TME alone group at 10 year [4]. Overall survival however, was not different between both groups, because in the RT group patients died more often of non-cancer specific causes. The advantage in cancer specific control was possibly compensated in survival by the effects of the RT induced morbidity, and thus RT induced mortality. The specific causes of RT induced mortality can only be speculated on. The increased secondary malignancies of 14% vs. 9% in RT+TME and TME alone respectively [4], can probably be attributed to the integral dose delivered with RT. Other causes of death showed less difference and are therefore hard to speculate on. With the improvements proposed in this thesis we will be able reach
a better balance between CTV coverage and organ at risk dose. With less irradiation of normal tissue the non-cancer specific mortality of RT might be decreased.

When evaluating subgroups based on TNM stage, patients with TNM stage III and a negative CRM had a significant benefit of RT in terms of overall survival (50 vs. 40%). As indicated by the authors [4], in TNM stage I patients approximately 38 patients had to be irradiated to prevent 1 local recurrence, while for TNM stage III only 10 patients have to be treated to prevent 1 local recurrence. Based on these results, TME without RT should be the treatment of choice in TNM stage I patients. The subgroup data can also be used to speculate that at least addition of RT in TNM stage III patients results in a clinical benefit. However, for patients with TNM stage II, currently treated with SCRT followed by a TME, the lack of evidence in favor of RT feeds the opinion to omit RT in this patient group, especially because increased morbidity with RT is evident.

Recent publications on gene expression and kinase activity profiling revealed the possibility to predict CRT treatment response in vitro [75] and in vivo [76, 77]. Eschrich et al. [78] developed a 10 gene prediction model for intrinsic radiosensitivity, with a sensitivity of 80% and a specificity of 82%. With these kind new biological developments treatment of rectal cancer can evolve from a tumor stage specific to a patient tailored approach.
Chapter 10

Conclusions
The work provided in this thesis aimed to estimate, reduce and compensate for geometric uncertainties in pre-operative radiotherapy of rectal cancer. Based on the provided work, we can conclude that target volume delineation variation and target volume shape variation are the major uncertainties in radiotherapy for rectal cancer. Setup errors were shown to be small, while they can also be easily corrected in an online fashion. To reduce target volume delineation uncertainties we have shown that delineation guidelines in combination with a delineation atlas are an important first step. For early-stage rectal cancer, national delineation guidelines and a digital delineation atlas were established. Target volume shape variation was shown to be heterogeneous, with the smallest variation close to bony anatomy, and the largest at the upper-anterior mesorectum, close to the bladder and small bowel. A planning target volume margin recipe was developed compensating for the shape variation of the target volume. Resulting planning target volumes based on the provided delineation guidelines and PTV margin were shown to be approximately 20% smaller compared to generous delineated clinical target volumes plus an arbitrary uniform 1 cm PTV margin. We also showed a significant potential benefit from adaptive radiotherapy to reduce shape variation errors, using repeat CT scans take on the first 4 treatment days. For patients with early-stage rectal cancer with node negative disease and a negative circumferential resection margin we have shown that the clinical target volume can be reduced substantially on the cranial side, further reducing the treated volume. With the obtained results either side-effects of radiotherapy can be reduced by reducing the dose to the organs at risk, or dose escalation can be applied to increasing local control.

The ultimate goal is of course to find the optimal balance between disease free and overall survival and morbidity. To my opinion, genetics and functional imaging will provide better patient tailored treatment, resulting in an increase in minimal invasive surgery with an important role for RT, leaving the more advanced cases for neo-adjuvant treatment in combination with a TME.
References


General discussion


Chapter 10


