Reducing uncertainties in image-guided radiotherapy of rectal cancer

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Chapter 7

General discussion

GENERAL DISCUSSION

The studies described in this thesis focus on the reduction of treatment-related uncertainties in image-guided high-dose-rate endorectal brachytherapy (HDREBT) and external beam radiotherapy (EBRT) for rectal cancer patients. Currently, the standard of care for rectal cancer patients consists of a surgical resection. Depending on disease stage, neoadjuvant (chemo)radiotherapy is given in order to reduce local recurrence rates. After standard chemoradiotherapy, 10-20% of patients develop a complete response. In these patients, a 'watch and wait' approach in which surgery is omitted seems safe. Dose response analyses suggest that escalating the dose to the gross tumor volume (GTV) leads to higher response rates. Various dose escalation techniques have been described in literature, including contact therapy, HDREBT and EBRT. For a dose escalation technique to be successful, it needs to lead to higher complete response rates in combination with limited acute and late toxicity. Therefore, the dose to healthy tissue should be as small as possible. In addition, if a boost dose can be delivered with higher accuracy, the dose to the GTV could be higher with similar dose to healthy tissue. Although the optimal treatment technique for dose escalation has not yet been determined, the work described in this thesis can be used to enhance the accuracy and decrease treatment related uncertainties related to a boost dose.

For HDREBT, most studies focus on oncological outcome and treatment-related toxicity. Although literature describes an adaptive approach using a treatment planning CT at each fraction, the dosimetric benefit of such an approach had not been investigated. Furthermore, the preferred image modality for target volume definition and treatment planning is MRI due to its superior soft tissue contrast. To realize a HDREBT workflow including MRI, a MRI-compatible fiducial marker was required that is visible on MRI imaging. Therefore, we have evaluated the visibility of four types of gold fiducial markers on MRI. Finally, the individual channels of the applicator are not visible on currently used anatomical MRI sequences. To be able to perform treatment planning on MRI, a method was needed to visualize the individual channels of the applicator on MRI. We have proposed a MRI sequence utilizing ultrashort echo times for visualization of the individual channels within the applicator.

With increased interest for organ preservation, improvements aimed at EBRT boost delivery are timely. Although some studies have evaluated the displacement of the GTV with respect to bony anatomy, most of them were based on CT and/or CBCT with inherent limited soft tissue contrast for GTV visualization. As a result, a wide range of PTV margins of 7-30 mm is described in literature. In addition, fiducial markers could be used as a surrogate for the GTV in order to perform setup correction based on fiducials instead of bony anatomy. However, data on the stability of fiducials relative to the GTV was lacking. Therefore, we have derived GTV displacement relative to bony anatomy using fiducials and provided data on the uncertainty of the GTV-fiducial spatial relationship. Together with the evaluation of the MRI visibility of four fiducial types, this thesis provides a basis for further research and subsequent clinical implementation of an EBRT GTV boost strategy using fiducial markers.

To facilitate organ preservation and avoid TME surgery in early stage rectal cancer patients, (chemo)-radiotherapy has to be given to control the tumor. The risk of pelvic lymph node involvement or distal mesorectal nodal involvement is low in this group of patients. Therefore, the typically large target volume may not be needed in this group of patients, and restricting the target volume to the peritumoral region of the primary tumor and mesorectum seems reasonable. In the STAR-TReC trial, a novel target volume is used which includes only the mesorectum [1]. Mesorectum only planning is intended for early stage rectal cancer with the aim of reducing the clinical target volume (CTV) and thereby reducing dose to the healthy tissue while maintaining local control. By showing the impact of a national study group meeting on the variability and quality of treatment plans for a novel target volume, we provide a basis for the realization of a more homogeneous treatment, potentially improving the quality of clinical trials on treatment outcome and toxicity.

High-dose-rate endorectal brachytherapy

Repeat imaging

The HDREBT procedure as described in literature uses a planning CT scan at each fraction and endoluminal clips to indicate the tumor position. Position verification prior to irradiation is performed with an X-ray, using the endoluminal clips and radiopaque markers inserted in the channels of the applicator. Although literature describes a transition from using a single-planning CT for all fractions to using a planning CT at each fraction, the difference in terms of target coverage and dose to organs at risk had not been evaluated [2–5]. In **Chapter 2**, we have shown that use of a single planning CT for all fractions can result in insufficient target coverage. The most important cause of limited target coverage was the presence of air and/or faeces between the applicator and the target volume. Air and/or faeces cannot be accurately assessed on the X-ray images used for position verification. Therefore, CT imaging at each fraction should be the minimal standard in HDREBT for rectal cancer.

Fiducial markers

Because of the limited soft tissue contrast of CT imaging, ideally a MRI should be used to define the target volume. However, the endoluminal clips create large artifacts on MRI, which limits target volume visibility. Therefore, an alternative marker allowing target volume visibility on MRI was needed. In addition, the alternative marker should be visible on MRI to determine the spatial relationship between the target volume and the fiducial marker. To determine a suitable alternative fiducial marker, we have evaluated the MRI visibility of four different MR-compatible gold fiducials in **Chapter 3**. The results of the study show that the Visicoil 0.75 and the Gold Anchor were the best visible fiducials on MRI and that a corresponding (CB)CT scan is required to provide an estimation of the fiducial localization on MRI. Although those fiducials were the best visible in the study, it can be argued whether the use of fiducials is clinically feasible, given the limited retention and visibility rate observed in **Chapter 3**. For future use of fiducial markers in the rectum, it is expected that the fiducial retention rate and visibility will improve for several reasons. First, the retention rate of fiducials in this study was better for fiducials that were inserted in the mesorectum, compared to fiducials inserted in the tumor, as shown by Rigter *et al.* [6].

Second, the use of a T1 3D sequence with prolonged echo time will increase the size of the artifacts that the fiducials create on MRI, which may enhance the fiducial visibility. We therefore recommend to insert fiducials in the mesorectum, in proximity of the tumor and to include a T1 3D sequence with prolonged echo time of at least 5 ms. Third, in brachytherapy, the planning CT and MRI are acquired with applicator in situ. This leads to a more similar anatomy between the CT and MRI, thereby increasing the accuracy of initial localization of fiducial markers on MRI.

Although the visibility of fiducials is expected to increase with a T1 3D sequence with prolonged echo time, manual fiducial identification on MRI remains a challenging and time-consuming procedure. In addition, fiducial marker appearance on MRI depends on sequence parameters and fiducial orientation with respect to the magnetic field [7]. Automatic fiducial detection could aid in the identification of fiducials and possibly eliminate the need for a corresponding (CB)CT. Multiple studies report on automatic fiducial detection on MRI in the prostate, with fiducial detection rates of 94-96% [8–10]. Since none report a marker detection rate of 100%, implementation of such a method would have to be in a semi-automatic workflow with an initial automatic fiducial detection on MRI with possible manual corrections. In addition, the proposed automatic fiducial detection methods would first have to be validated for the application in rectal cancer patients.

Given the increased interest in organ preservation strategies for rectal cancer patients, MRI will be increasingly used to determine whether a complete response has been reached. Among other sequences, a DWI sequence is used to assess tumor response. Since this sequence is sensitive to distortions in the magnetic field, fiducial markers that are placed (too) close to the tumor may hamper response assessment. As an alternative, a liquid marker that forms a semisolid gel after injection may be used [11,12]. These liquid markers are visible on MRI as a signal void due to the absence of water protons. This is different compared to gold fiducial markers, which cause signal voids due to absence of water protons *and* due to their alteration of the static magnetic field. Currently, only one study has evaluated the use of these liquid markers in rectal cancer [13], with positional stability as primary outcome. Preliminary results have been published in an abstract, in which the authors report that after 5 weeks of chemoradiotherapy, 96% of 74 liquid markers were still in situ and available for analysis. Marker pair distances, as a measure for marker stability, showed stable or negative slope of fits during chemoradiation. It was concluded that the liquid marker was feasible to act as a tumor location surrogate. However, stability with respect to the GTV was not reported in the abstract.

HDREBT MRI-only workflow

As the individual channels within the applicator are not visible on the currently used MRI sequences, delineation of the target volume and organs at risk, applicator reconstruction and treatment planning are still performed on CT. Image registration of the CT and MRI with applicator in situ is performed to aid in the target volume definition. A further improvement in HDREBT treatment planning would be a MRI-only workflow, in which the delineation of the target volume and organs at risk, applicator reconstruction

and treatment planning are all performed on MRI. This would eliminate any image registration errors between MRI and CT due to possible changes in applicator position. In addition, it would save time and increase patient comfort as the patient does not have to be transferred between CT and MRI. A MRI-only workflow can be realized if the fiducials can be identified on MRI without corresponding (CB)CT and if the individual channels within the applicator can be visualized. In the previous paragraph, improvements have been suggested to facilitate MRI fiducial identification without corresponding (CB)CT, including a T1 3D sequence with prolonged echo time and the use of automatic fiducial detection methods. In **Chapter 4**, we have proposed a MRI sequence utilizing an ultrashort echo time to visualize the applicator and the individual channels within it. We have shown that the applicator and the individual channels can be visualized, both in a phantom and in patients. By performing a rigid registration with an anatomical sequence, geometric fidelity was within acceptable range. Therefore, applicator reconstruction, delineation of target volume and organs at risk, and treatment planning can all be performed on MRI. However, before clinical implementation of such a workflow, the geometrical fidelity of all MRI sequences that are going to be used for treatment planning should be verified.

A next step in the HDREBT workflow would be to irradiate the patient while the patient is lying on the MRI scan table. This would eliminate the transfer of the patient between the MRI table and the treatment table, thereby reducing the chance of changes in applicator position between the planning MRI and the time of irradiation. In addition, fiducial markers would no longer be needed as both the target volume and the applicator can be visualized using MRI. Irradiation of the patient while the patient is lying in the MR bore would however require a MRI-compatible afterloader. The feasibility of such a procedure has been demonstrated using a prototype MRI-compatible afterloader [14]. However, the MRI-compatible afterloader is not clinically available yet.

Applicator design

The current most used applicator for HDREBT consists of eight catheters circumferentially placed near the edge of the applicator which allows selective use of channels for a more conformal treatment compared to one central channel. In addition, a shielding lead or tungsten insert can be placed in the central channel of the applicator to spare the contralateral healthy rectal wall. While EBRT techniques have evolved to become increasingly conformal using intensity modulated and dynamic arc radiotherapy, the applicator is limited in shielding options and is therefore far from conformal, which leaves substantial room for improvement. Several studies have proposed alternative applicator designs, aimed at increasing the conformality of the dose distribution. Webster *et al.* report on simulated dosimetric properties of several alternative applicator designs, mostly incorporating additional shielding [15]. In another paper, the same group describes dynamic modulated brachytherapy for rectal cancer [16]. The authors propose a design containing a long cylindrical tungsten alloy shield with a small window in which a ^{192}Ir can be encapsulated, resulting in a highly directional beam profile. The shield should then be rotated and translated within the applicator by a robot arm in order to irradiate a target volume. So far, the dosimetric properties of these alternative applicator designs have only been produced using in silico simulations and

are not currently clinically used, possibly because of the complexity. Belezzo *et al.* describe an alternative applicator design that can be used for contact radiotherapy using a ^{192}Ir source [17]. It contains multiple channels which allows planning optimization and tailoring of the dose distribution to the target volume. In addition, lateral shielding is incorporated, resulting in a uniform circular treatment surface with a 22 mm diameter. This applicator could result in more conformal treatments of small tumors. However, the applicator is not clinically used yet.

Future use of HDREBT

Altough literature reports promising results on the use of HDREBT as a neoadjuvant treatment, no randomized trials have yet been performed comparing neoadjuvant HDREBT to neoadjuvant EBRT [18–20]. The currently ongoing CORRECT trial will show us whether the promising results presented so far can be reproduced in a randomized trial. In the CORRECT trial, patients with resectable rectal cancer are randomized between neoadjuvant chemoradiotherapy or neoadjuvant 4x 6.5 Gy HDREBT [21]. The primary endpoint is pathological complete response rate. However, time to surgery is not reported.

Given the increased interest in organ preservation, HDREBT may play a role in delivering a boost dose to the GTV to enhance the complete response rates. There has only been one randomized trial on the use of a HDREBT boost, in which patients were randomized between chemoradiation with or without a HDREBT boost of 2x 5 Gy, prescribed at 10 mm from the applicator surface [22]. No difference in pathological complete response was reported. However, the major response rate (defined as Mandard tumor regression grade 1 and 2) was significantly higher in the HDREBT group (44% vs 28%) for patients with a T3 tumor with no increase in toxicity. No effect on the major response rate was observed in T4 tumors [23]. An explanation could be that larger tumors that extend widely into the mesorectum are inaccessible to brachytherapy and/or the dose prescription at 10 mm from the applicator surface did not allow full coverage of the tumor.

The potential use of HDREBT in an organ preservation setting will depend on the ability to limit long-term toxicity, since the rectum will not be removed. In the HERBERT trial, acute grade 2 and 3 proctitis was observed in 68.4% and 13.2% of patients respectively, while late grade 2 and grade ≥3 proctitis occurred in 48% and 40% of patients. The most severe toxicity was observed 12-18 months after treatment [24]. An analysis on the predictive factors for toxicity in this group of patients showed that brachytherapy CTV size and high doses at the mucosa of the CTV was correlated to endoscopic toxicity at the tumor site [25]. Due to the steep dose gradient and the aim to enclose the CTV with the 100% isodose, the dose at the mucosa can reach 400%. The dose to the contralateral wall was not correlated to endoscopic toxicity, which suggests that the dose was reduced sufficiently using the balloon that was placed between the applicator and the contralateral healthy rectal wall. The HERBERT trial was a dose escalation study, which partly explains the observed toxicity. In addition, no shielding was used and most patients in this study were treated with a single planning CT for all fractions, leading to uncertainties in the delivered dose to the CTV and surrounding healthy tissue. The added value of a HDREBT boost

after EBRT in elderly, frail patients will be further assessed in the HERBERT 2 trial. In this phase III trial, patients will be randomized between 13 x 3 Gy EBRT with or without a HDREBT boost of three weekly fractions of 7 Gy, at least 10 weeks after the end of EBRT. The primary endpoint is clinical complete response at 6 months after brachytherapy.

So far, the trials that have reported on the clinical outcome after HDREBT for rectal cancer vary in dose prescription methods, fractionation schemes, study endpoints and toxicity reporting [26,27]. In order to determine the added value of HDREBT in different clinical scenarios and to be able to compare different trials, consensus on the mentioned variables is urgently needed.

External beam radiotherapy

Higher doses to the tumor are suggested to result in higher complete response rates, which is interesting in the light of increased interest for organ preservation [28]. Due to the limited soft tissue contrast of imaging used for setup correction, such as CBCT, setup correction based on the GTV itself is not possible. Since fiducial markers are visible on (CB)CT imaging, they could be used as a surrogate for the GTV for setup correction in a GTV boost setting. Such an approach requires that the fiducials are representative of the GTV, and therefore stable with respect to the GTV. In addition, the spatial relationship between the fiducials and the GTV has to be determined, preferably on MRI, which means that they have to be visible on MRI. The visibility of fiducials on MRI as evaluated in **Chapter 3** has already been discussed in the previous paragraph.

Stability of fiducials relative to the GTV and inter- and intrafraction displacement

In **Chapter 5**, we have determined the stability of fiducials relative to the GTV and the inter- and intrafraction displacement of fiducials relative to bony anatomy. Subsequently, we have derived required margins in different setup correction scenarios in a GTV boost setting. The use of setup correction based on fiducials results in a substantial margin reduction compared to setup correction based on bony anatomy. The findings of this study were based on imaging that was mostly acquired in the first week of radiotherapy. While that makes it applicable for a boost during or directly after a short course radiotherapy schedule, it may not apply for a boost applied during or after a long-course chemoradiotherapy schedule. In a recent study it has been shown that tumor regression during LC-CRT occurred mostly during the first half of treatment [29]. The displacement of the fiducials relative to the GTV and the inter- and intrafraction displacement relative to bony anatomy may be different at the end of a LC-CRT schedule, after most GTV regression has taken place.

Dose escalation to the GTV can be achieved by using a simultaneous integrated boost (SIB) or a sequential boost. Boosting using a SIB with setup correction based on fiducials would require daily plan re-optimization to take into account the GTV position of that day. Alternatively, the boost dose could be given after the elective dose of each fraction. This would require setup correction twice for each fraction: once based on bony anatomy for the elective irradiation of the CTV and once for the GTV boost.

A sequential GTV boost could be given after all fractions of the elective CTV irradiation have been given. Given the GTV shrinkage during the treatment, a sequential boost would be applied on a smaller residual GTV, thereby minimizing the additional dose to the organs at risk. In addition, it would allow for selection of patients that could possibly benefit from a GTV boost.

A sub analysis in **Chapter 5** suggests a difference in GTV displacement between tumors located in the lower rectum and tumors located in the mid- and upper rectum. As a result, the potential margin reduction by performing setup correction based on fiducials is smaller for low-lying tumors, compared to higher tumors. This raises the question whether the use of fiducials is justified for lower tumors. However, the difference in inter- and intra-fraction displacement between tumors located in the lower rectum and tumors located in the mid- or upper rectum should be verified in a larger patient cohort. Finally, the introduction and clinical implementation of MRI systems with integrated linear accelerators will obviate the need for fiducial markers. With such systems, the GTV can be imaged (real time) with the superior soft tissue contrast of MRI. However, MRI systems with integrated linear accelerators are not widely available yet. Until such systems are widely available, a GTV boost should be given using setup correction based on fiducials in order to reduce margins, and therefore dose to healthy tissue.

STAR-TReC planning study

In the STAR-TReC trial, a novel target volume is used which only includes the mesorectum. There is lack of data on the association of dose to bowel, bladder and femoral heads and the risk of late complications for dose levels up to 50 Gy. In addition, there is no data regarding OAR constraints using this novel target volume. Therefore, there were no mandated OAR constraints but optimization objectives were specified for the dose to the OAR for dose levels of 20-45 Gy. As a result, there was substantial variation in the dose to organs at risk between centers after treatment planning for 5 cases, while all cases fulfilled target volume constraints. Furthermore, we demonstrated that a study group meeting with subsequent replanning led to better treatment plans, with decreased dose to the organs at risk and decreased variability between centers.

These observations show the added value of performing QA for a clinical study. The question remains whether the study group meeting itself led to higher quality treatment plans, or that only the distribution of initial planning results among centers could potentially lead to the same result. By comparing initial planning results, centers were able to determine whether a treatment plan could be further optimized. This illustrates the inherent limitations of manual optimization of the treatment plan. Although the experience of the planner certainly influences the plan quality, determining whether a plan can be further optimized can be even difficult for experienced planners. Automated treatment planning techniques, such as knowledge-based treatment planning, protocol-based automatic iterative optimization or multicriteria optimization can aid in the decision whether a plan can be further optimized [30]. The added value of automated treatment planning is also observed in the differences in dose to organs at risk between cases. While in some cases the objectives might be easily reached, in other cases the objectives

might be hard to satisfy, depending on patient anatomy. This shows the limitation of imposing fixed constraints/objectives for treatment planning. Nonetheless, automated treatment planning can aid in the decision whether a plan can be further optimized, but will still lead to a broad range of acceptable plans if there is a lack of evidence on dose volume constraints. Therefore, automated treatment planning is not expected to lead to a substantial decrease in variability. The lack of evidence also contributes to the observed variability in dose to the organs at risk. In order to develop dose volume constraints and optimization objectives for an organ preservation setting, toxicity and clinical outcome data has to be carefully collected.

The treatment plan quality achieved in **Chapter 6** may be higher compared to treatment plans produced in clinical practice, as in clinical practice less extensive discussion and time is spent on the treatment plan. In order to monitor treatment plan quality in a clinical trial, it can be beneficial to require regular QA of treatment plans. As an educational process, a similar QA as presented in **Chapter 6** can be performed, identifying differences between centers and followed by a discussion how to handle them.

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