(Un-)certainties in radiotherapy of rectal cancer
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Citation for published version (APA):
Summary

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Introduction
In the Netherlands approximately 3500 patients are diagnosed with rectal cancer each year. Every year about 900 patients die of rectal cancer, and 5-year survival rate after diagnosis is approximately 65%. The general treatment of rectal cancer is centered around extensive surgery using total a mesorectal excision (TME) technique. During surgery the rectum with its surrounding soft-tissue and lymphatic system is removed as an intact unit covered by the mesorectal envelope. To increase local control, patients with early-stage rectal cancer are first treated with short-course radiotherapy (SCRT) of 5 fractions of 5 Gy each in one week, followed by a TME within one week. In advanced staged rectal cancer patients first fluorouracil based (FU) chemotherapy is given in combination with long-course RT of 25 fractions of 2 Gy in 5 weeks (LCCRT) to improve operability, followed by a TME after 3-10 weeks. The clinical target volume (CTV) for RT generally consists of the mesorectum, the pre-sacral lymph node region and the lateral internal iliac lymph node regions.

The addition of RT is, however, associated with an increase in acute- and late-toxicity, such as diarrhea, fecal incontinence, increased bowel frequency, and sexual dysfunctions. The challenge in RT is to minimize the dose to the surrounding organs at risk (OAR), while maintaining good coverage of the target volume. To assure coverage, geometric uncertainties, i.e. discrepancies between planning and execution of the treatment, should be taken into account by adding a planning target volume (PTV) margin to the CTV. In rectal cancer RT, these uncertainties consist mainly of target volume delineation errors, patient setup errors with respect to the treatment machine, and shape variation of the target volume. When uncertainties can be decreased, margins can be reduced leading to a decrease in toxicity. Other measures are a full bladder protocol, using a belly board and by using modern dose planning and delivery such as intensity-modulated RT (IMRT). The bladder protocol and belly board are used to push small bowel, which is the main OAR, away from the target volume. Finally, the definition of the CTV itself is generally only tailored to the location of the tumor within the rectum, while local control is also dependent on other clinical factors.

The work provided in this thesis aimed to estimate, reduce and compensate for geometric uncertainties in pre-operative RT of rectal cancer. Furthermore, an estimate of the necessity of all OAR dose limiting measures was provided. Finally, local control data of a randomized trial comparing RT + TME with TME alone was used to further tailor the target volume definition to clinical factors.

Patient orientation
A planning study was conducted to assess the additional benefit of using a belly board in the setting of a full bladder protocol and IMRT (chapter 2). For 11 volunteers, 4 MR scans were acquired, on a flat table in prone position, on a flat table in supine position, and on 2 different belly boards. On each scan a standardized CTV was delineated and a 7-field IMRT plan was created after adding a 1 cm PTV margin. The bowel area was also
delineated on each scan, and dose-volume parameters for this region were compared between patient setups. In this study we have shown that the least comfortable belly board with the most compression of the lower abdomen also resulted in the least dose to the bowel area. Simultaneously, setup of the volunteers on this belly board also had to be repeated for the majority of volunteers to achieve proper placement. Although bowel exposure was higher on the prone and supine scans, unacceptable values predicting acute and late toxicity were on average not reached. Therefore, usage of the belly board was questioned in the setting of a full bladder and IMRT, and application was recommended in patients with unfavourable anatomy only. Based on the lack of difference between prone and supine setup on a flat table our clinical practice was changed to supine positioning.

**Clinical target volume delineation**

For target volume delineation two guidelines are available in the literature defining which pelvic regions need to be included in the CTV. In 2006, Roels and colleagues published an evidence based guideline, selecting pelvic regions based on local recurrence risk. In 2009 the Radiation Therapy Oncology Group (RTOG) published consensus guidelines, derived from delineations of 9 expert radiation oncologists on one example patient.

In chapter 3 a pilot study on the potential benefit of using the RTOG guidelines in a multi-center randomized trial is described. Fourteen radiation oncologists involved in a South-West Oncology Group (SWOG) trial were asked to delineate a single T3N0M0 case based on a trial protocol. Immediately after submission of the delineations half of the observers were asked to re-delineate using the, then unpublished, RTOG atlas and the other half re-delineated using the original instructions. In this study we have shown that using the trial protocol resulted in delineation variation up to 1.5 cm SD for the sphincter regions and upper-anterior region of the CTV. The group that re-delineated using the RTOG atlas showed significantly less delineation variation, but residual variation was still in the order of 0.8-0.9 cm SD.

In chapter 4 results of a Dutch delineation study are described. In this study 11 radiation oncologists were provided with a dataset of 8 patients with early-stage rectal cancer. First, each observer delineated the CTV for each patient based on local hospital policy. Subsequently, a consensus meeting was planned in which the delineations were discussed, and delineation guidelines were established based on the recommendations of Roels and colleagues. The guidelines were translated to a digital delineation atlas by 3 expert observers which were not part of the delineation group. Seven months after the consensus meeting radiation oncologists re-delineated the dataset, now using the new guidelines and atlas. The average delineated CTV volume decreased from 620 cc to 460 cc (p<0.001). The local surface distance variation (cm SD) reduced from 1.02 to 0.74 for anterior, 0.63 to 0.54 for lateral, 0.33 to 0.25 for posterior and 1.22 to 0.46 for the sphincter region, respectively. The delineation guidelines are therefore considered to be an essential first step in reduction of delineation variation.
Summary

Tailoring the clinical target volume definition
In chapter 5 the locations of local relapse were studied for patients treated in the randomized Dutch TME trial, comparing SCRT + TME with TME alone. By comparing the trial arms, the effect of SCRT on patterns of local recurrence for different clinical factors could be estimated. In the trial the cranial border of the CTV was located at the promontory. For patients who at pathology showed a tumor free circumferential resection margin (CRM) and no nodal involvement, few recurrences were found and these were all located below the S2-S3 inter-space, independent of irradiation. The few recurrences confirmed the good prognostic value for these factors. The fact that all recurrences were located below the S2-S3 inter-space resulted in the recommendation of lowering the cranial border for patients with a predicted negative CRM and NO disease to the S2-S3 level. With this reduction of approximately 4 cm a significant reduction of over 50% in small bowel volume exposed to dose levels of 15-35 Gy could be achieved.

Clinical target volume shape variation and patient setup errors
Chapters 6, 7 and 8 focus on the day-to-day shape variation of the CTV. In chapter 6 a retrospective study on daily cone-beam CT (CBCT) data acquired for 27 early-stage rectal cancer patients is described. All patients were treated with SCRT in prone position on a flat table. On each scan the mesorectal part of the CTV was delineated, and shape variation was calculated. The systematic shape variation was found to be heterogeneous, ranging from 0.1 cm close to bony anatomy to 0.7 cm at the upper-anterior side of the mesorectum. Systematic shape variation errors were slightly larger for female patients, compared to male.

In chapter 7, a similar study was conducted, but then for 28 patients treated in supine position on a flat table. Systematic errors were ranging from 0.1 cm to 0.8 cm SD and were similar to the results of chapter 6. There were no significant differences between shape variation in prone and supine orientation. Differences between male and female patients were consistent with chapter 6.

In the datasets of chapters 6 and 7 it was impossible to reliably delineate the entire CTV, due to limited image quality. Therefore, a prospective repeat CT study was initiated (chapter 8). In this study, 33 SCRT (20 male, 13 female) and 30 LCCRT (20 male, 10 female) patients treated in prone position were included. For SCRT patients daily repeat CT scans were acquired, while for LCCRT patients daily scans were taken during the first week, followed by weekly scans. On a total of 482 CT scans the CTV was delineated and shape variation was calculated. Systematic CTV shape variation was ranging from 0.2 cm SD close to bony anatomy to 1.0 cm SD at the upper-anterior edge of the mesorectum. Male patients in the SCRT group exhibited a significantly larger systematic error compared to male patients in the LCCRT group. In the LCCRT group a negative time-trend in rectal volume and CTV volume was present starting halfway treatment, resulting in a group mean shrinkage of the CTV of about 0.5 cm at the upper-anterior side. Differences between male and female patients were not significant. For the lateral lymph node regions smaller, but substantial systematic shape variations of approximately 0.5 cm SD were found at the anterior edge.
The CBCT scans used in chapters 6 and 7 were clinically used to correct the patient setup just prior to treatment, minimizing setup errors. To estimate the patient stability during irradiation, CBCT scans were also acquired just after irradiation. The intra-fraction setup errors in prone position was shown to be significantly larger compared to supine positioning, but with maximal systematic variations in left-right direction of 0.24 cm SD, these errors were small compared to CTV shape variation.

Planning target volume safety margin for shape variation
To assure coverage of the CTV in the presence of geometric uncertainties a PTV margin needs to be added. General margin recipes for calculation of the margin size are only applicable for rigid geometric uncertainties, such as positional variation of the CTV or the patient, thus not for shape variation, which are intrinsically non-rigid. In chapter 8, the repeat CT delineations were used to develop an adapted van Herk margin recipe for rigid errors, \( m_{PTV}=\alpha \times \Sigma + \beta \times \sqrt{\sigma^2 + \sigma_p^2} \) (\( \Sigma \)=systematic error, \( \sigma \)=random error, \( \sigma_p \)=penumbra width), to accommodate the shape variation errors. To assure 95% of the prescribed dose as minimum dose to the CTV for 90% of the patients in a rigid setting, \( \alpha \) is 2.5. To estimate \( \alpha \) for shape variation, the minimum dose to the CTV was estimated for varying values of \( \alpha \) (Chapter 8). We showed that locally defined shape variation errors should be multiplied by \( \alpha = 3.2 \) to assure similar CTV coverage. The locally defined margins were translated to clinically applicable orthogonal margins for sub-volumes of the CTV for SCRT and LCCRT separately. The resulting PTVs, based on strict CTV delineation and proposed margins (which were up to 3.2 and 2.4 cm at the anterior at the upper half of the mesorectum for SCRT and CRT, respectively) were approximately 20% smaller in volume compared to the “classical” generously delineated clinical CTVs plus a uniform 1 cm margin.

Adaptive radiotherapy
Adaptive radiotherapy (ART) is used to estimate patient specific systematic errors based on repeat imaging before or at the beginning of the treatment, and adapt treatment accordingly. With substantial systematic shape variation errors ranging up to 1.0 cm SD, there is large potential for margin reduction using ART. In chapter 9 the possible margin reduction using single plan adaption in LCCRT is described, based on the repeat CT data. The tested adaptations consisted of generating an average CTV shape based on the delineation of the planning CT and the delineations of the first repeat CT scans, ranging from 1 to 5. The remainder of the repeat CT delineation was used to calculate the residual systematic and random errors, and corresponding margins. The optimal strategy involved averaging the CTV over the planning CT and the first 4 repeat CT scans and resulted in a maximum margin reduction at the upper-anterior side of the CTV from 2.4 cm to 1.7 cm. With this ART strategy the bowel area volume receiving 45 and 50 Gy was significantly reduced from 111 and 49 cc to 81 and 29 cc \((p<0.001)\).
Summary

Conclusions
We conclude that CTV delineation variation and shape variation are the major uncertainties influencing the accuracy of radiotherapy for rectal cancer. Delineation variation can be reduced significantly using strict guidelines and a delineation atlas, although substantial residual variation demands for further measures. We have shown several measures to significantly reduce the dose to the small bowel, including a full bladder protocol, intensity-modulated RT, a belly board, a reduced CTV for patients with good prognostic clinical parameters and finally adaptive radiotherapy. With the provided results, radiotherapy of rectal cancer can be given more accurately and ultimately individualized resulting in less toxicity.