(Un-)certainties in radiotherapy of rectal cancer
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3D analysis of recurrence patterns in rectal cancer: the cranial border in hypo-fractionated pre-operative radiotherapy can be lowered

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Abstract

Purpose
The aim of this study was to determine whether and where the radiotherapy (RT) clinical target volume (CTV) could be reduced in short-course preoperative treatment of rectal cancer patients.

Material and methods
Patients treated in the Dutch total mesorectal excision trial with a local recurrence were analyzed. For 94 (25 who underwent radiation therapy 69 who did not) out of the 114 patients with a local recurrence the location of the recurrence was depicted in a three dimensional (3D) model. The data in the 3D model were correlated to the clinical trial data to distinguish a group of patients eligible for CTV reduction. Effects of CTV reduction on dose to the small bowel was tested retrospectively in a dataset of 8 patients with 3-field conformal plans and intensity-modulated RT (IMRT).

Results
The use of preoperative RT mainly reduces anastomotic, lateral and perineal recurrences. In patients without primary nodal involvement no recurrences were found cranially of the S2-S3 interspace, irrespective of the delivery of RT. In patients without primary nodal involvement and a negative circumferential resection margin (CRM) only one recurrence was found cranial of the S2-S3 interspace. With a cranially reduced CTV to the S2-S3 interspace over 60% reduction in absolute small bowel exposure at dose levels from 15 to 35 Gy could be achieved with 3-field conventional RT, increasing to 80% when IMRT is also added.

Conclusions
The cranial border of the CTV can safely be lowered for patients without expected nodal or CRM involvement, yielding a significant reduction of dose to the small bowel. Therefore, a significant reduction of acute and late toxicity can be expected.
Introduction
The standard treatment for patients with rectal cancer has evolved to preoperative (chemo-) radiation followed by a total mesorectal excision (TME) [1–3]. For patients with clinically resectable adenocarcinoma of the rectum, short-course radiation therapy (RT) of 5 x 5 Gy, followed by a TME, can be used to reduce the local recurrence rate to approximately 6% [1–3].

Major disadvantage of using RT is an increase in acute and late toxicity such as faecal incontinence, impaired sexual functioning, and late small bowel obstruction that requires surgery [4–9]. The major cause of toxicity can be found in the dose to the small bowel [7–15]. It is especially the volume of small bowel that receives more than 15 Gy that is predictive of acute complications [10, 11]. For long-term toxicity, only dose effect relationships have been studied for conventional treatment with postoperative RT of 25 x 2Gy [12, 13]. In these studies, especially high-dose levels of 45 to 50 Gy to large bowel volumes were found to be predictive of late toxicity. For short-course RT, with an α/β ratio of 3, correction to 2 Gy per fraction equivalent dose, these high, small bowel doses are hardly reached. Birgisson et al. [9], however, showed that short-course treatment with two-field anterior–posterior beams, and treatment with higher energies increase the risk of small bowel obstruction. This also implies that for late toxicity, the dose to the small bowel has a significant impact. The complexity in establishing dose-effect relationships for late toxicity is shown in the Swedish trial, where a follow-up of 8 years was needed to prove that addition of preoperative RT increases the risk of small bowel obstruction [7].

In the Swedish trial, the upper border of the treatment fields was the mid-L4, while this was at the promontory in later trials [1, 3]. Due to this change, the dose to the small bowel has already significantly decreased. Modern RT techniques, such as intensity-modulated radiotherapy (IMRT), can be used to create conformal dose distributions, reducing the exposure even further [16, 17].

Besides more conformal treatment planning, it might also be possible to revise the currently accepted definition of the clinical target volume (CTV) in certain cases. Roels et al. [18] and the RTOG consensus panel [19] both developed contouring atlases which can be used to guide the delineation of the CTV for IMRT treatment. In general, coverage of the tumor, involved lymph nodes, the mesorectum, and the perirectal, presacral, and internal iliac lymph node regions is advised. Roels et al. [18] developed their atlas based on literature about patterns of local recurrences to come to a general definition of the CTV. In certain subgroups, however, a smaller CTV might also be sufficient [20, 21].

To fully explore the possibilities for CTV reduction, the patient data from the Dutch TME trial [1] were used to perform a three-dimensional analysis of patterns of local recurrence. Also, the potential benefit in terms of small bowel dose was determined by a planning study of reduction of the CTV.
Material and methods

Patients
Patients were derived from the Dutch TME trial, a randomized multicenter study analyzing the effect of 5 x 5 Gy RT in patients who had undergone TME (RT+ patients), compared to patients who had undergone TME alone (RT- patients). Inclusion criteria for the study were primary adenocarcinoma of the rectum, with the tumor within 15 cm from the anal verge, without evidence of metastatic disease or fixation of the tumor.

For RT treatment, the CTV included the primary tumor and the mesorectum with vascular supply containing the perirectal, presacral, and internal iliac nodes. The recommended upper border was at the level of the promontory. The perineum was included if a abdominoperineal resection (APR) was planned, whereas the lower border was 3 cm above the anal verge if the planned operation was an low anterior resection (LAR). Three- or four-field conformal treatment techniques were used.

For the current study, only Dutch patients were selected. The following patient groups were excluded from the analysis: ineligible patients (n = 50), those who had no resection (n = 37), and those who had no tumor at operation (n = 26), leaving 1,417 patients for analysis, with a total of 114 local recurrences (78 RT- and 36 RT+ patients). Local recurrence was defined as rectal cancer recurrence within the small pelvis which was or would have been covered by the RT treatment. Recurrences were clinically, radiologically, or histologically diagnosed and reviewed by a team of two radiologists, one radiation oncologist, and one surgeon.

Recurrence modeling
For all recurrences, the trial data were reviewed to verify the exact location of the recurrence. The locations were retrieved from CT scans, magnetic resonance (MR) scans, or diagnostic reports of the recurrences (e.g. sigmoidoscopy for anastomotic recurrences). Each recurrence was subsequently manually placed in a reference CT scan of a typical rectal cancer patient, using in-house-developed software. Placement of the recurrences was based on bony landmarks and soft tissue landmarks such as the prostate, uterus, or bladder. The center of recurrences was used as location in the model, assuming that recurrences grow radially. All recurrences were linked to the trial database, providing the ability to query the trial database and visualize the locations of the recurrences.

Recurrence analysis
In the recurrence analysis, the original tumor distance from the anal verge, tumor stage, nodal stage, number of examined lymph nodes, type of surgery, circumferential resection margin (CRM), gender, and distal margin were measured. These variables were used to identify a possible group of patients for which the CTV could be reduced.
CTV reduction analysis
The effect of CTV reduction on the dose to the small bowel was determined by means of a planning study. Eight patients, scanned in the supine position with small bowel contrast and a full bladder protocol, were selected. Patients were selected to have at least 15 Gy exposure to the small bowel with a conventional three-field conformal treatment plan. For all patients, two CTVs were delineated: one according to the recommendations of Roels et al. [18] (CTV_conv), and a reduced CTV based on the findings of this study (CTV_small). Both CTVs were expanded by a uniform 10-mm PTV margin to create a PTV_conv and a PTV_small. Both a three-field conformal plan and a seven-field IMRT plan were calculated using these PTVs for treatment with 5 x 5 Gy.

For comparison between the different treatment plans, each loop of small bowel was delineated, and the biological equivalent dose (α/β ratio of 3) to the absolute volume was calculated in steps of 5 Gy [10, 11]. The achieved reduction of dose to the small bowel for both IMRT plans and the PTV_small plan compared to the three-field PTV_conv plan were tested for significance using a two-tailed paired Student’s t test (p<0.05).

| Table 5.1: Clinical and pathological characteristics |
|-------------------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                          | All patients     | Modeled local recurrences |
|                                          | RT- N = 704      | RT+ N = 713      | RT- N = 69      | RT+ N = 25      |
| Age (yrs)                                | 66 (23-92)       | 64 (26-88)       | 66 (43-83)      | 62 (26-82)      |
| Median (range)                           |                  |                  |                  |                  |
| Sex (%)                                  |                  |                  |                  |                  |
| Male                                     | 445 (63)         | 461 (65)         | 39 (57)         | 20 (80)         |
| Female                                   | 259 (37)         | 252 (35)         | 30 (43)         | 5 (20)          |
| Distance from anus (%)                   |                  |                  |                  |                  |
| < 5 cm                                   | 228 (32)         | 207 (29)         | 25 (36)         | 15 (60)         |
| 5 – 10 cm                                | 275 (39)         | 301 (42)         | 32 (46)         | 6 (24)          |
| > 10 cm                                  | 201 (29)         | 205 (29)         | 12 (18)         | 4 (16)          |
| Resection type (%)                       |                  |                  |                  |                  |
| LAR                                      | 453 (64)         | 451 (63)         | 39 (56)         | 11 (44)         |
| APR                                      | 218 (31)         | 218 (31)         | 26 (38)         | 13 (52)         |
| Hartmann                                 | 33 ( 5)          | 44 ( 6)          | 4 ( 6)          | 1 ( 4)          |
| T-stage (%)                              |                  |                  |                  |                  |
| T1                                       | 35 ( 5)          | 44 ( 6)          | 0 ( 0)          | 0 ( 0)          |
| T2                                       | 218 (31)         | 244 (34)         | 7 (10)          | 3 (12)          |
| T3                                       | 419 (60)         | 406 (57)         | 58 (84)         | 19 (76)         |
| T4                                       | 32 ( 4)          | 19 ( 3)          | 4 ( 6)          | 3 (12)          |
| N-stage (%)                              |                  |                  |                  |                  |
| N0                                       | 401 (57)         | 428 (60)         | 18 (26)         | 8 (32)          |
| N1                                       | 161 (23)         | 161 (23)         | 27 (39)         | 6 (24)          |
| N2                                       | 142 (20)         | 124 (17)         | 24 (35)         | 11 (44)         |
| CRM (%)                                  |                  |                  |                  |                  |
| Negative                                 | 563 (80)         | 587 (82)         | 47 (68)         | 13 (52)         |
| Positive                                 | 141 (20)         | 126 (18)         | 22 (32)         | 12 (48)         |
Chapter 5

Results

Patients

For 94 (69 RT- and 25 RT+ patients) of 114 patients, it was possible to determine the location of the recurrence with certainty (Table 5.1). Primary nodal stage was classified into node negative (N0), up to four positive nodes (N1), and four or more positive nodes (N2). Primary tumor location was classified into low (≤5 cm from the anal verge), mid (5–10 cm from the anal verge), and high (>10 cm from the anal verge) tumors.

Of the 20 missing recurrences in the model, 11 recurrences were from the RT+ group, of which 2, 6, and 3 patients had nodal stage N0, N1, and N2, respectively. Five, 4, and 2 of them had a low-, mid-, and high-rectum tumor, respectively. For the 9 patients in the RT- group, nodal stage was divided into 1, 7, and 1 for N0, N1, and N2, respectively. Primary tumor locations were 3 low-, 5 mid-, and 1 high-rectum.

Recurrences

In Fig. 5.1, the recurrence locations are colored according to the primary tumor distance from the anal verge for CRM+ and CRM- patients. As can be appreciated in Fig. 5.1, the addition of RT reduces the amount of anastomotic, lateral, and perineal recurrences. Interestingly, a CRM+ does not necessarily mean that the recurrence appears at the same level as the primary tumor. The most cranial recurrences were presacral, with the highest recurrence halfway to the level of S1, which was easily covered by the RT fields used.Interestingly, the most cranial recurrences originated from tumors less than 5 cm from the anal verge. In addition, these cranial recurrences originated from patients with primary nodal involvement (Fig. 5.2) and a positive CRM. The most cranial recurrence for N0 and CRM- patients was found at the junction between S2 and S3 in the RT+ group and at the level of S3 in the RT- group.

![Fig. 5.2: Overview of the recurrence locations for the RT+ (left) and the RT patients (right) stratified for nodal stage, N0 (lime), and N+ (red) in an anterior-left view. The red plane indicates the cranial border of the treatment fields used in the trial.](image-url)
For tumor stage, gender, and distal margin, no obvious classification for RT target volume reduction was found (not shown). Recurrences in patients operated with a LAR procedure were found mainly in the presacral and anastomotic regions, while in patients with an APR of Hartmann resection, recurrences were found in all regions (Fig. 5.3).

Since for patients in the RT- group recurrences were found more caudally in the perineal region compared to the RT+ group, caudal CTV reduction was not investigated.

**Fig. 5.1:** Overview of the recurrence locations for the RT+ (left) and the RT- patients (right), with a negative CRM (top) and a positive CRM (bottom) stratified for primary tumor distance from the anal verge of <5 cm (aqua), 5–10 cm (lime), and >10 cm (red) in an anterior-left view. The red plane indicates the cranial border of the treatment fields used in the trial. The purple plane indicates the level of the S2–S3 interspace.
Fig. 5.3: Overview of the recurrence locations for the RT+ (left) and the RT patients (right) stratified for type of surgery, LAR (aqua), APR (lime), and Hartmann (red) in an anterior-left view.

Fig. 5.4: Sagittal view of the CTV_conv and PTV_conv (black) and the reduced CTV_small and PTV_small (white) of one exemplary patient. The dotted line denotes the S2–S3 interspace.
3D analysis of recurrence patterns in rectal cancer

**CTV reduction analysis**

Based on the recurrence patterns of both irradiated and nonirradiated patients, a reduction of the cranial border in a subgroup of patients seemed justified. Therefore, the effect of a CTV reduction cranially to the level of the S2/S3 junction was analyzed. This proposed CTV reduction resulted in a 4.0-cm-lower location of the cranial border of the CTV. In Fig. 5.4, a sagittal view of the delineated CTV_conv and PTV_conv in black and CTV_small and PTV_small in white are shown for one patient.

The average, minimum, and maximum absolute volume of small bowel exposed in the conformal three-field plans on the PTV_conv are shown in Table 5.2. The average relative volume reduction of exposed small bowel with the use of the three-field PTV_small plan and both IMRT plans is shown in Fig. 5.5. Lowering the upper border of the CTV for the conformal treatment plan reduced the V15 with 65%, which is significantly more than changing from conformal plans to IMRT plans (31%, p = 0.02). Combining IMRT with the CTV reduction gave the largest relative reduction in V15 with an average of 78% (range, 40–100).

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<th>Table 5.2: Absolute volume of small bowel exposed in the conformal 3-field plan on the PTV_conv after correction with α/β = 3</th>
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<td>Average (cc)</td>
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**Discussion**

This is the first study to evaluate local recurrences in rectal cancer patients fully in three dimensions, comparing preoperative short-term RT plus TME with TME treatment alone. The aim of the study was, based on the shown recurrence patterns, to identify if and for which patients the clinical target volume could be reduced. We have shown that the most cranial recurrences were located a few centimeters caudal of the promontory, irrespective of RT or not. For patients without primary nodal and CRM involvement the most cranial recurrences were located at the level of the S2–S3 interspace. We therefore suggest that the cranial CTV border can be lowered in early rectal cancers.

**Recurrences and field reduction**

In our series, the majority of local recurrences were located at the lower two-thirds of the pelvis. No clear correlation could be found between the level of the local recurrence and the location of the primary tumor (Fig. 5.1). For patients with a positive CRM, the location of the recurrence did not correlate with the primary tumor location. In addition, tumor stage, gender, and distal margin also did not show any clear correlations. In patients
with an LAR, however, most recurrences were located centrally and presacrally, whereas after APR and Hartmann resections, widespread recurrences developed throughout the pelvis (Fig. 5.3).

As shown in Fig. 5.2, local recurrences in patients with N0 primary disease all recurred below the level of S2, except for 1 patient in the RT+ group. For this patient, only two lymph nodes were examined after the TME, making the N0 status debatable. After CRM in both groups, only one local recurrence occurred above the S2–S3 interspace level. These results might be influenced by the recurrences missing in our analyses. However, only one of the missing patients in the RT- group was diagnosed with N0 primary disease and a negative CRM. All other missing patients had CRM+, N+, or both. The missing patients would therefore be of minor influence in the model.

The recurrence patterns found are in accordance with the data of Syk et al. [20], in which 75% of the recurrences were located in the lower two-thirds of the pelvis. In their study, the cranial border of the RT fields could be lowered from 1.5 cm above the promontory to 3.5 cm below the promontory while still covering all local recurrences, which is similar to the proposed reduction in this study. These comparable findings underline the fact that the cranial CTV border of node- and CRM-negative patients does not have to be at the level of the promontory. Obviously, this CTV reduction should be carefully applied in very high tumors, where lowering the upper border would exclude the gross tumor volume from the target volume.

Obviously, we can only make such recommendations if identification of nodal involvement and CRM can be done reliably before treatment. Several studies have demonstrated that with the use of MR for staging of lymph node involvement, a specificity of about 80% can be reached, especially in combination with ultrasound and if heterogeneity of intensity and the aspect of the border are taken into account [22–24]. It is, however, often debated that most of these studies have been performed by expert radiologists and that population-based outcomes may be worse. As a consequence, some of the presumably node-negative patients may demonstrate nodal involvement after treatment. Prediction of a positive CRM based on high-resolution MRI is more accurate, with a specificity of about 90% [25–27].

If N+ patients are falsely selected for CTV reduction, the effect is still minor in terms of the recurrence rate. For N+ patients, five recurrences were located at or above the S2/S3 junction (2 RT+ and 3 RT patients). In addition, 4 of these 5 patients had a positive CRM, suggesting locally advanced disease. It will be clear that lowering the upper border in these patients is not a safe option. However, if we consider N+ patients with a negative CRM, only one recurrence was located above the level of S2. Moreover, in the nonirradiated node-positive group, 8 patients were missing, of whom 5 had a positive CRM. So, for patients without signs of CRM involvement on the MRI, a maximum of three extra recurrences could be expected when reducing the CTV, assuming that all these recurrences were located above the S2–S3 interspace. Therefore, even if some of the node-negative patients are misclassified before treatment, the risk of an increased number of local recurrences due to CTV reduction for patients with presumably node-negative disease without CRM involvement is very small.
Since MRI is accurate in diagnosing a close or involved CRM [25–27], we conclude that combining nodal and CRM status for the selection of patients in whom the CTV can be reduced will hardly lead to an increase in the number of local recurrences.

Field reduction effect

Given the fact that 37% of the patients in the trial were diagnosed with N0 and CRM disease and a tumor within 10 cm from the anal verge, CTV reduction for patients without expected nodal and CRM involvement will have a significant effect on potential side-effects in the treatment of rectal cancer.

In the TME trial for the RT+ group, significantly increased rates of fecal incontinence, pad wearing as a result of incontinence, anal blood loss, and mucus loss were reported [6]. Satisfaction with bowel function was also significantly lower, and the impact of bowel dysfunction on daily activities was greater [6].

Several studies have shown that the dose to the small bowel is the main cause of acute and late toxicity [4–15]. Clear correlations between dose reduction and a decline in acute and late toxicity are not found. However, for acute toxicity, Robertson et al. [11] demonstrated that patients with more than 120 cc of small bowel exposed to 15 Gy had a 38% chance of developing grade 3 diarrhea, while 9% of the patients did with lower exposure. For late toxicity such a dose-effect relationship has not been established with modern radiotherapy techniques. Gallagher et al. [12] found in 1986 a critical level of 45 Gy to 78 cc and 50 Gy to 17 cc of the small bowel were predictive for late effects in postoperative RT treatment. Letschert [13] showed afterwards, at the same dose levels, that a small bowel volume increase by a factor of 2, demands a total dose reduction of

Fig. 5.5: Average relative volume reduction of exposed small bowel relative to the conformal three-field treatment plan on the PTV_conv. The error bars denote the range of volume reduction found in the dataset of 8 patients.
17% for the same complication rate. For short-course radiotherapy, Birgisson et al. [9] showed that treatment with two anterior–posterior beams or higher energies increases the risk of small bowel toxicity. Consequently, it seems logical to assume that reduced dose and volume to the small bowel will lead to reduced late toxicity.

Reduction of dose to the small bowel has already been accomplished in several ways. Patients can be treated in the prone position, with or without the use of a belly board, to reduce the amount of small bowel in the high-dose region [28–30]. Patients are also given drinking instructions to increase bladder filling, thus pushing the small bowel away from the high-dose region [30]. Combining these measures with the use of IMRT reduces exposure to the organ at risk even further [16, 17]. The 8 patients used in the dose reduction study were scanned in the supine position with a full bladder protocol. Patients in our study were selected retrospectively based on the assumption that they would receive at least 15 Gy to the small bowel with a three-field conformal plan. However, the volumes receiving this dose level were on average smaller than the 150 or 120 cc risk volume as stated by Baglan et al. [10] and Robertson et al. [11]. This was mainly due to good compliance with the full bladder protocol, with an average bladder volume of 426 cc. Somewhat lower exposed small bowel volumes could be expected if patients would have been scanned in the prone position, but this effect would be minor in comparison with the reduced CTV and/or the use of IMRT. The reducing effect of IMRT on small bowel exposure is shown in Fig. 5.5, where at the 15 Gy dose level, an average 31% reduction was shown compared to conformal three-field treatment plans. The reduction of the CTV was, however, significantly more effective, with an average reduction of 65%. As with all measures to reduce small bowel exposure, the combination of measures led to the most relative volume reduction of 78%. Therefore, both measures can be expected to give a significant reduction in small bowel toxicity, both acute and late. However, prospective studies are needed to confirm this statement, especially for late toxicity. Based on the results of the Swedish studies, a follow-up of at least 8 years is necessary for reliable conclusions.

Limitations of the study
In this study, 96 of the 114 recurrence locations were modeled. As shown in the discussion, the missing recurrences in the model would probably only have small influences on the established results, especially for patients without nodal involvement. Therefore, we can assume that CTV reduction for patients without nodal or CRM involvement is feasible.

Recurrence locations were modeled according to bony anatomic landmarks and soft tissue landmarks, such as the prostate, uterus, or bladder, from CT scans, MR scans, or diagnostic reports of the recurrences. The center of the recurrence was assumed to be the origin of the recurrence. Based on these methods, the accuracy of recurrence placement in the model can be expected to be on the order of 1 to 2 cm, rather than on the order of millimeters. The results of this study would, however, not be significantly influenced by misplacement of the recurrences due to the fact that the majority of recurrences were located in the lower two-thirds of the pelvis.
The 8 patients selected for demonstration of the dose reduction effect were selected to receive at least 15-Gy exposure to the small bowel. Already within the 8 patients, a lot of variation in exposed small bowel volume was found. In clinical practice, there are also patients who receive no dose to the small bowel with a conventional treatment plan. For these patients, no dose reduction can be achieved. Therefore, the dose reduction effect to the total population of rectal cancer patients is expected to be smaller than the demonstrated 60 to 80%. It is, however, always true that a reduction in irradiated volume will lead to a reduction in exposed healthy tissue.

Conclusions
The addition of hypo-fractionated preoperative RT to the TME treatment of rectal cancer patients reduces anastomotic, lateral, and perineal recurrences. In patients with a positive CRM, the tumor location is not necessarily indicative of the location of the local recurrence. For patients without expected lymph nodes or CRM involvement, the conventional clinical target volume can probably be reduced on the cranial side to the S2–S3 interspace without significantly increasing the local recurrence rate. This reduction of the target volume will have a significant impact on the volume of small bowel exposed to high doses. A further, small reduction of this exposed volume can be achieved by applying IMRT in these patients.
References


3D analysis of recurrence patterns in rectal cancer


