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Brachytherapy for rectal cancer

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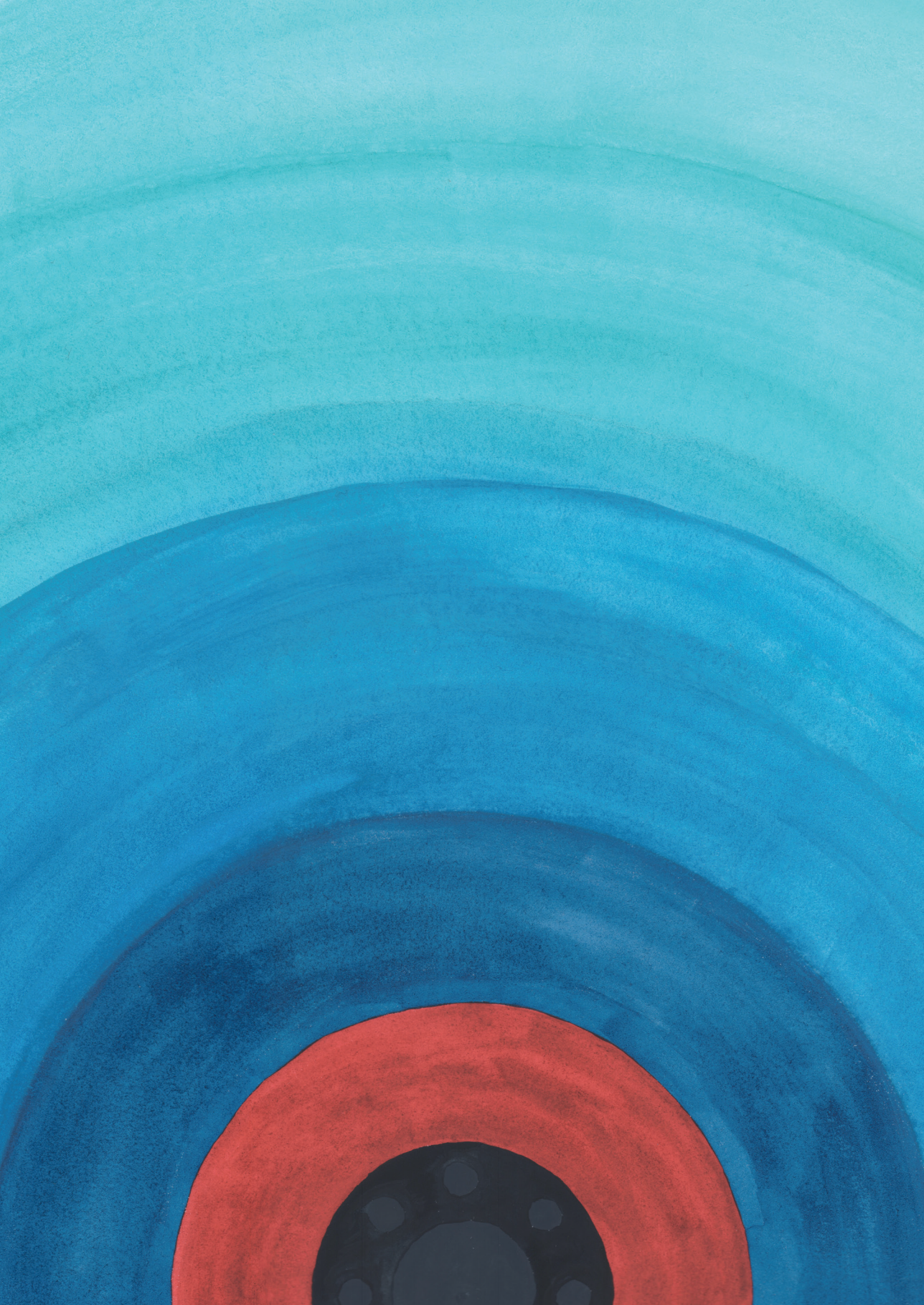

Chapter 6

Benefit of adaptive CT-based treatment planning in high-dose-rate endorectal brachytherapy for rectal cancer

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ABSTRACT

Purpose

In this planning study, we investigated the dosimetric benefit of repeat CT-based treatment planning at each fraction versus the use of a single CT-based treatment plan for all fractions for high-dose rate endorectal brachytherapy (HDREBT) for rectal cancer.

Materials and methods

We included eleven patients that received a CT scan with applicator in situ for all three fractions. The treatment plan of the first fraction was projected on the repeat CT scans to simulate the use of a single treatment plan. Additionally, replanning was performed on the repeat CT scans and these were compared to the corresponding projected treatment plans.

Results

Repeat CT-based treatment planning resulted on average in a 21% higher ($p=0.01$) conformity index compared to single CT-based treatment planning. Projecting the initial treatment plan to the repeat CT scans of fraction two and three, 12/22 fractions reached a CTV D98 of 85% of the prescribed dose of 7 Gy, which increased to 14/22 using replanning. For the remaining fractions, median CTV D98 was 4.2 Gy and an intervention would be necessary to correct applicator balloon setup or to remove remaining air and/or feces between the CTV and the applicator.

Conclusions

Using a single CT-based treatment plan for all fractions may result in a suboptimal treatment at later fractions. Therefore, repeat CT imaging should be the minimal standard practice in HDREBT for rectal cancer to determine whether an intervention would be necessary. Replanning based on repeat CT imaging resulted in more conformal treatment plans and is therefore recommended.

INTRODUCTION

Total mesorectal excision is the mainstay in the treatment of rectal cancer. For more advanced cases, the addition of neoadjuvant (chemo)radiotherapy has resulted in lower local recurrence rates, but none of the recent trials has demonstrated a benefit in overall survival.[1-4] Unfortunately, (chemo)radiotherapy is associated with an increased risk of side effects such as bowel and sexual dysfunction.[5] Vuong et al. introduced high-dose rate endorectal brachytherapy (HDREBT) as a replacement of neoadjuvant external beam radiation therapy (EBRT) with promising results in local control.[6,7] For patients unfit or unwilling to undergo surgery, definitive or palliative radiotherapy are alternatives. Rijkmans et al. demonstrated the feasibility of a HDREBT boost after EBRT in inoperable patients.[8] Compared to EBRT, HDREBT can deliver high doses to the tumour while sparing surrounding organs due to a steeper dose gradient.[7] As a consequence, HDREBT has the potential to decrease morbidity and reduce the risk of side effects.[9] However, the steeper dose gradient means that an anatomical inter-fraction variation of millimetres can have a high impact on the delivered dose to the target volume or surrounding organs. Therefore, high precision is required in imaging, contouring and treatment planning.

For HDREBT treatment planning, the conventional approach is to use the treatment plan generated at the first fraction, for all later fractions.[10,11] Alternatively, an adaptive approach could be used by creating a new treatment plan based on new imaging acquired at each fraction, taking into account inter-fraction anatomical variation.[12,13] For cervical cancer, several studies on image-guided brachytherapy compared the use of one treatment plan for all fractions to an adaptive approach using a newly generated treatment plan at each fraction.[14,15] The treatment plan for the first fraction was simulated on the imaging of the later fractions. The results showed that the treatment plan based on imaging of the first fraction did not lead to comparable target volume coverage and dose to organs at risk at later fractions.[14,15] Nowadays, repeat MR imaging is therefore recommended in brachytherapy for cervical cancer.[16]

Most studies on the use of HDREBT for rectal cancer focus on oncological outcome and treatment related toxicity in the pre-operative setting, with limited detail on treatment planning. They do not address the question of using a non-adaptive or adaptive approach.[9,17-19] Vuong *et al.* initially reported a non-adaptive approach using one planning CT scan with applicator in situ on which a treatment plan is generated and used for all later fractions.[10,11] Recent publications by the same group describe an adaptive approach generating a new treatment plan based on a new CT scan for each fraction.[12,13] A recent abstract concludes that an adaptive approach resulted in a more conformal dose distribution.[20]

In our study, we further investigated the comparison between a non-adaptive and an adaptive approach and added a quantification of conformity. Additionally, we analysed the repeat CT scans and reported causes of insufficient target volume coverage. The aim of this study was to determine the differences regarding treatment plan conformity, target volume coverage and dose to organs at risk between using a single treatment plan for all fractions versus a new treatment plan at each fraction in HDREBT for rectal cancer.

MATERIAL AND METHODS

Patient selection

For the current study, we selected eleven patients from the HERBERT trial in whom repeat CT scans with applicator in situ were available at each fraction (the HERBERT trial, registered with the Dutch Central Committee on Research Involving Human Subjects; registration no. NL17037.031.07).[8,21]

Treatment

All patients were treated with 13×3 Gy EBRT at four fractions per week, followed by three weekly fractions of HDREBT using a prescription dose of 5-8 Gy starting six weeks after conclusion of EBRT. We adapted the brachytherapy equipment, application and positioning procedures from Devic *et al*. as described in Rijkmans *et al.*[8,11] Patients received an enema prior to the CT scan with applicator in situ at each fraction.

We acquired a planning CT scan with applicator in situ prior to the first fraction. An inflatable balloon around the applicator on the opposite side of the clinical target volume (CTV) was used to fixate the applicator and to decrease the dose to the normal rectal wall. Treatment planning was performed using Oncentra Brachy (Elekta, Veenendaal, The Netherlands). The aim for treatment planning was to cover the CTV with the 100% isodose while containing the 400% isodose within the applicator. Repeat CT scans with applicator in situ were acquired for research purposes. In case of obvious differences compared to the CT scan of the first fraction, the treatment plan was adapted accordingly. These adapted treatment plans were not used in this study.

Delineation

The CTV was defined as residual macroscopic tumour and scarring after EBRT. CTV, anus, mesorectum and healthy rectal wall were delineated by two observers with help of diagnostic MRI, rectoscopy images and inserted endoluminal clips at the proximal and distal border of the tumour. The rectoscopy images were acquired before EBRT and before the first brachytherapy fraction. Comparing CTV delineations between fractions of the same patient was allowed to check for consistency. In case of discrepancy between delineations, consensus was sought.

Projection and replanning

To determine the differences in conformity, CTV coverage and dose to organs at risk between the use of a single treatment plan for all fractions and a new treatment plan at each fraction, the treatment plan of the first fraction and the new treatment plan were compared for each repeat CT scan. In order to obtain the dose distribution of the initial treatment plan on the repeat CT scans, the treatment plan of the first fraction was projected on the repeat CT scans. For this

purpose, the most cranial activated dwell position was identified on the repeat CT scans in the same location with respect to the most cranial slice of the CTV delineation as on the CT scan of the first fraction. Subsequently, the dwell position pattern and dwell times were copied.
An experienced radiation treatment technologist created new treatment plans based on the repeat CT scans. As a result, for each repeat CT scan we thus obtained both a projected treatment plan of the first fraction and a new treatment plan.

Analysis

To quantify dose conformity, the COnformal INdex (COIN) parameter was used, as defined by Baltas *et al.* in the following equation:[22]

$$COIN = \frac{TV_{RI}}{TV} \times \frac{TV_{RI}}{V_{RI}} \times \prod_{i=1}^{N_{CO}} \left[1 - \frac{V_{COref,i}}{V_{CO,i}}\right]$$

With TV_{RI} the tumour volume covered by the reference isodose, TV the tumour volume, V_{RI} the reference isodose volume, N_{CO} the number of critical organs, $V_{COref,i}$ the volume of the critical organ with index i covered by the reference isodose and $V_{CO,i}$ the volume of the critical organ with index i (Figure 1). The healthy rectal wall, mesorectum and anus were considered critical organs. The COIN parameter ranges from 0-1, with 0 representing no conformity and 1 representing full conformity.

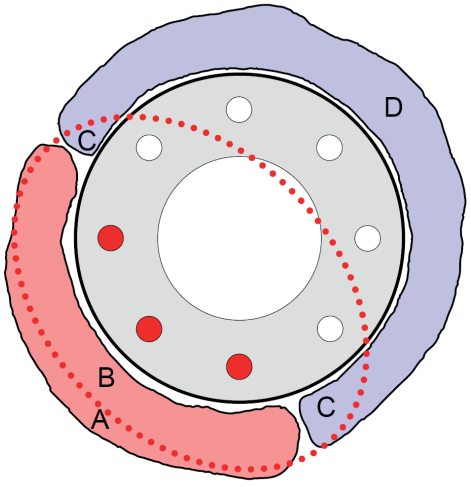

Figure 1. Schematic representation of the parameters of the COIN equation: tumour volume $(TV, A + B)$, tumour volume covered by the 100% isodose (TV_{RI}, B), healthy rectal wall $(V_{CO}, C + D)$, and healthy rectal wall covered by the 100% isodose (V_{COref}, C). VRI is the volume encompassed by the 100% reference isodose, represented by the dotted line. The three filled dots on the lower left side of the applicator represent activated dwell positions.

The HERBERT trial was a dose escalation study and patients were treated with a prescription dose of 5-8 Gy.[8] Therefore, for reporting of dose parameters, we chose to scale the dose distributions to a prescription dose of 7 Gy. To quantify CTV coverage, the CTV D98 parameter (i.e. the minimal dose to 98% of the CTV volume) was collected for each treatment plan. For the dose to organs at risk, the D2cc (i.e. the minimal dose to the 2 cc of the organ at risk that receives the highest dose) for mesorectum and anus were collected. Additionally, a point dose on the healthy rectal wall directly opposing the delineated CTV within the center slice of the CTV was chosen to quantify dose to the healthy rectal wall.
We visually analysed all CT scans and if a suboptimal applicator balloon orientation or air and/or feces between the CTV and the applicator were observed, an intervention would be required to correct applicator balloon orientation or to remove air and/or feces.

Statistics
We used SPSS Statistics 23 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) for statistical analysis. The Friedman test was used to test for volume differences of the CTV delineations between the three CT scans. A univariate analysis of variance was performed for each dependent variable (COIN, CTV D98, healthy rectal wall dose and D2cc of the mesorectum and anus). Included independent variables were *plan type* (projection or replanning), *intervention required* (yes or no), *timepoint* (fraction two or three) and *patient* (one through eleven). All tests were two-sided and the significance threshold was set at 0.05.

RESULTS

CTV delineation
The average delineated CTV volume for all CT scans was 6.8 cc (range 2.4-13.0). Delineated CTV volumes did not differ significantly between the three CT scans for each patient (p=0.31).

Initial treatment planning
Table 1 shows the results for COIN and CTV D98 for the treatment plan of the first fraction, all projections and all new treatment plans. Results are presented as median (range).
The median COIN for treatment plans of the first fraction was 0.14 (0.04-0.20) and the median CTV D98 was 5.8 Gy (3.6-7.3). On four of the eleven CT scans, air and/or feces was seen between the CTV and the applicator. As a result of this, combined with the constraint of the 400% isodose within the applicator, the CTV coverage and conformity were lower in the corresponding four treatment plans (Figure 2). The median COIN and CTV D98 were 0.09 (0.04-0.13) and 5.6 Gy (3.6-5.8), respectively. An intervention would be necessary to remove air and/or feces before creating a more conformal treatment plan with higher CTV coverage. The median COIN and CTV D98 for the seven remaining treatment plans was 0.15 (0.13-0.20) and 6.3 Gy (4.6-7.3), respectively.

Table 1. Conformity (COIN) and target volume coverage (CTV D98) for the initial treatment plan of the first CT scan and the projection and replanning for the repeat CT scans of all patients

Parameter	Initial treatment plan	Projections	Replanning	Mean difference projections and replanning (mean (range))	Effect of plan type (p-value)	Mean ratio (projection vs. re-planning)
Number of CT scans						
All	11	22	22			
Only interventions	4	8	8			
Excl. interventions	7	14	14			
COIN (-)						
All	0.14 (0.04 - 0.20)	0.13 (0.01 - 0.18)	0.15 (0.02 - 0.19)	0.02 (-0.02 - 0.08)	0.01	1.21
Only interventions	0.09 (0.04 - 0.13)	0.08 (0.01 - 0.15)	0.11 (0.02 - 0.16)	0.02 (-0.02 - 0.08)	0.17	1.31
Excl. interventions	0.15 (0.13 - 0.20)	0.14 (0.07 - 0.18)	0.15 (0.11 - 0.19)	0.02 (-0.01 - 0.04)	< 0.001	1.15
CTV D98 (Gy)						
All	5.8 (3.6 - 7.3)	6.4 (3.3 - 7.8)	6.6 (2.8 - 7.6)	0.3 (-1.0 - 2.4)	0.11	1.07
Only interventions	5.6 (3.6 - 5.8)	4.2 (3.3 - 6.9)	5.0 (2.8 - 5.9)	0.1 (-1.0 - 1.7)	0.89	1.03
Excl. interventions	6.3 (4.6 - 7.3)	6.9 (3.7 - 7.8)	7.0 (6.1 - 7.6)	0.5 (-0.8 - 2.4)	0.06	1.10

Result are presented as median (range) unless indicated differently.

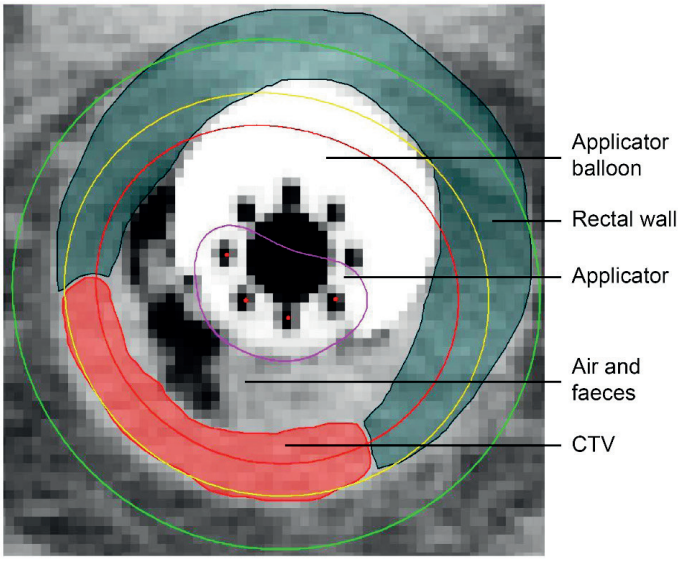

Figure 2. Example of a CT scan in which full coverage of the CTV was not possible considering the constraint of the 400% isodose within the applicator. Air and faeces are seen between the CTV and the applicator. The 400%, 100%, 75% and 50% isodoses are shown. CTV, clinical target volume.

Projection

The treatment plan of the first fraction was projected on the repeat CT scans of the second and third fraction for each patient, resulting in 22 projections. The median COIN and CTV D98 of all projections were 0.13 (0.01-0.18) and 6.4 Gy (3.3-7.8), respectively. In some of the 22 repeat CT scans, air and/or feces was seen between the CTV and the applicator (5/22), a suboptimal orientation of the applicator balloon was observed (2/22) or the applicator balloon was not inflated (1/22). For the projections on these eight repeat CT scans (from six patients), the median COIN and CTV D98 were 0.08 (0.01-0.15) and 4.2 Gy (3.3-6.9), respectively. An intervention would be necessary to remove air and/or feces or to correct applicator balloon orientation before creating a more conformal treatment plan with higher CTV coverage. For the remaining 14 projections (from nine patients), the median COIN and CTV D98 were 0.14 (0.07-0.18) and 6.9 Gy (3.7-7.8), respectively. Figure 3 shows an example of a patient in which the projections lead to similar conformity and CTV coverage as the initial treatment plan and a patient in which air and feces is seen on the CT scan of the third fraction leading to lower conformity and CTV coverage.

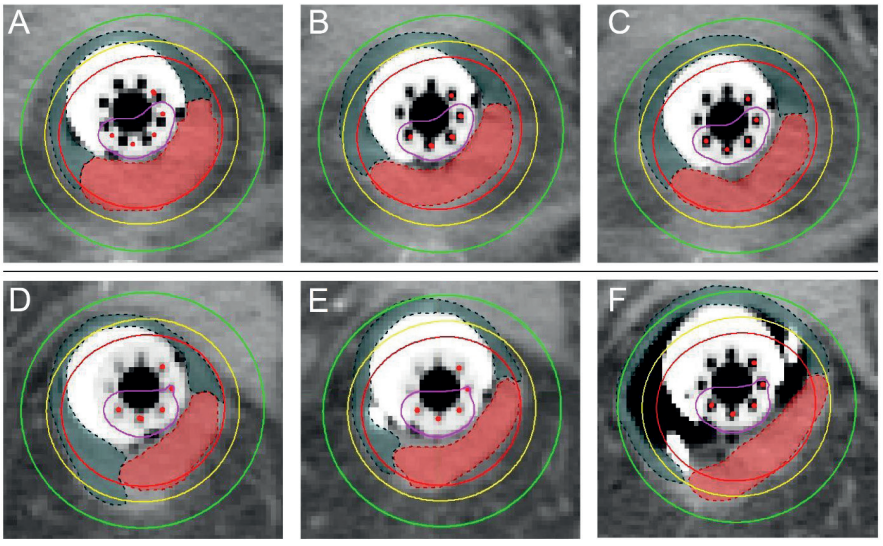

Figure 3. An example of a patient in which the projections (B+C) lead to similar conformity and CTV coverage as the initial treatment plan (A), and a patient in which the projections lead to similar conformity and CTV coverage (E) and lower conformity and CTV coverage (F, due to air and faeces) compared to the initial treatment plan (D). The 400%, 100%, 75% and 50% isodoses are shown. CTV, clinical target volume.

Replanning

New treatment plans were generated based on the repeat CT scans for each patient, resulting in 22 new treatment plans. The median COIN and CTV D98 were 0.15 (0.02-0.19) and 6.6 Gy (2.8-7.6), respectively. For the new treatment plans based on the eight repeat CT scans that required an intervention, the median COIN and CTV D98 were 0.11 (0.02-0.16) and 5.0 Gy (2.8-5.9), respectively. For the remaining 14 new treatment plans, the median COIN and CTV D98 were 0.15 (0.11-0.19) and 7.0 Gy (6.1-7.6), respectively.

Projection versus replanning

There was a statistically significant effect of *plan type* (p=0.01) and *intervention required* (p=0.002) on the COIN parameter considering all cases. The COIN was on average 21% higher after replanning compared to the projected treatment plans. Considering the cases that did not require an intervention, COIN was on average 15% higher after replanning (Table 1).

There was a statistically significant effect of *intervention required* (p=0.001) on CTV D98, considering all cases. Only borderline significance was reached on the effect of *plan type* in the subgroup of cases that did not require an intervention (p=0.06). In those cases, CTV D98 was on average 10% higher after replanning. One case showed an increase of CTV D98 of 2.4 Gy (66%, from 3.7 Gy to 6.1 Gy) after replanning and another case showed an increase of CTV D98 of 1.7 Gy (42%, from 4.0 Gy to 5.7 Gy). In one case, replanning resulted in a CTV D98 decrease of 1.0 Gy (-15%, from 6.9 to 5.9 Gy). All other differences in CTV D98 were smaller than 1.0 Gy.

When considering a plan acceptable when the CTV D98 is at least 85% of the prescribed dose and at least 90% of the initial treatment plan at the first fraction, 12/22 projections were considered acceptable versus 14/22 new treatment plans. In the eight remaining unacceptable treatment plans, an intervention would have been necessary to achieve an acceptable treatment plan.

Dose to organs at risk

The dose to organs at risk is presented in Table 2. There was a statistically significant effect of *intervention required* on D2cc of the mesorectum considering all cases (p<0.001). No other significant effects were observed. In one case, after replanning, a reduction of the rectal wall point dose larger than 1 Gy (3.1 Gy) was observed. In another case, a decrease of mesorectum D2cc of more than 1 Gy (1.3 Gy) was observed. In another patient with a very distal tumour, an increase of the anus D2cc of 2.3 Gy and 2.1 Gy for fraction two and three was observed. All other differences in anus D2cc were smaller than 1 Gy.

Table 2. Dose to organs at risk (rectal wall point dose and D2cc of mesorectum and anus) for the initial treatment plan of the first CT scan and the projection and replanning for the repeat CT scans of all patients

Parameter	Initial treatment plan	Projection	Replanning	Mean difference projection and replanning (mean (range))	Effect of plan type (p-value)	Mean ratio (projection vs. replanning)
Number of CT scans						
All	11	22	22			
Only interventions	4	8	8			
Excl. interventions	7	14	14			
Rectal wall point dose (Gy)						
All	5.2 (2.7 - 6.9)	4.8 (2.8 - 10.6)	5.1 (3.0 - 7.5)	-0.2 (-3.1 - 0.9)	0.28	0.98
Only interventions	5.0 (3.6 - 6.4)	5.1 (4.5 - 10.6)	5.2 (4.0 - 7.5)	-0.5 (-3.1 - 0.8)	0.24	0.95
Excl. interventions	5.3 (2.7 - 6.9)	4.5 (2.8 - 6.5)	4.9 (3.0 - 6.2)	-0.1 (-0.8 - 0.9)	0.66	1.00
Mesorectum D2cc (Gy)						
All	6.1 (4.8 - 7.2)	6.1 (4.0 - 8.0)	5.8 (3.9 - 7.7)	-0.2 (-1.3 - 0.7)	0.15	0.98
Only interventions	5.2 (4.8 - 7.2)	5.5 (4.0 - 8.0)	5.2 (3.9 - 7.7)	-0.4 (-1.3 - 0.6)	0.08	0.94
Excl. interventions	6.4 (5.8 - 6.8)	6.2 (4.4 - 7.5)	5.9 (4.4 - 7.2)	-0.1 (-0.8 - 0.7)	0.65	1.00
Anus D2cc (Gy)						
All	1.7 (0.5 - 3.6)	2.7 (0.4 - 4.5)	3.0 (0.4 - 6.1)	0.2 (-0.8 - 2.3)	0.34	1.07
Only interventions	2.1 (0.9 - 2.6)	3.2 (0.9 - 4.3)	3.1 (0.9 - 6.1)	0.2 (-0.8 - 2.3)	0.66	1.05
Excl. interventions	0.9 (0.5 - 2.6)	2.3 (0.4 - 4.5)	2.7 (0.4 - 4.7)	0.2 (-0.6 - 2.1)	0.37	1.08

Results are presented as median (range) unless indicated differently.

DISCUSSION

The aim of this study was to determine the differences regarding treatment plan conformity, target volume coverage and dose to organs at risk between using a single treatment plan for all fractions versus a new treatment plan at each fraction in HDREBT for rectal cancer. In this study of eleven patients, replanning for each fraction resulted in a significantly more conformal treatment plan and in some cases a substantially higher CTV D98 (Table 1). This study shows that for 12/22 repeat CT scans, the projected treatment plans met the coverage criteria of CTV D98 being at least 85% of the prescribed dose and at least 90% of the CTV D98 of the first fraction. This improved to 14/22 after replanning. An important value of repeat CT at each fraction lies in verifying applicator balloon setup and absence of air and/or feces in the rectum. This is underlined by the significant effect of *intervention required* on COIN and CTV D98. Although replanning resulted on average in a 31% increase in COIN in the cases that needed an intervention, COIN and CTV D98 remain low and demonstrate the limited value of replanning in these cases (Table 1). If interventions would have been performed where needed, we expect that treatment plan conformity and target volume coverage would have been similar to those cases that did not need an intervention. After an intervention, a new repeat CT scan should always be acquired to verify its effect.

Adding repeat CT planning before each fraction adds approximately one hour per fraction. This includes acquiring the CT scan, delineation of target volume and organs at risk and treatment planning. We realise that this adaptive approach is labour intensive and may therefore be difficult to implement. Therefore, we report on the benefit of an adaptive approach in terms of treatment plan quality to aid in the decision whether to implement it or not. Even without replanning, acquiring a repeat CT scan is valuable to verify applicator balloon setup and absence of air and/or feces.

As reported, two cases show an increase of CTV D98 of 2.4 Gy and 1.7 Gy after replanning. In the first case, this was due to a different insertion angle of the applicator, which led to a different orientation of the CTV. In the second case, this was due to a suboptimal balloon orientation and a different insertion angle of the applicator, which led to a different orientation of the CTV on the repeat CT scan. Therefore, in these two cases, the projected treatment plan partly missed the CTV. Consequently, after replanning, the new treatment plan was adapted to the CTV on the repeat CT scan and this resulted in a higher CTV D98. One case showed a decrease of CTV D98 of 1.0 Gy and a reduction of the rectal wall point dose of 3.1 Gy because the applicator balloon was not inflated on the repeat CT scan, which resulted in a more conservative treatment planning for the new treatment plan. In another case, after replanning, a decrease of mesorectum D2cc of 1.3 Gy was observed because the CTV orientation was slightly different on the repeat CT scan. This resulted in the projected treatment plan partly missing the CTV and covering a part of the mesorectum instead. After replanning, the new treatment plan was adapted to the CTV on the repeat CT scan, resulting in a lower mesorectum D2cc. An increase of the anus D2cc of 2.3 Gy and 2.1 Gy for fraction two and three was observed in a patient with a distal tumour. For this specific patient, the most caudal slice of the CTV was larger on the repeat CT scans compared to the CTV on the CT scan of the first fraction, resulting in lower CTV coverage of the projected treatment plan. Consequently, after replanning, the new treatment plan was adapted to the larger CTV and this resulted in a higher anus D2cc.

Our conclusions are consistent with a congress abstract of Nout *et al.* on a cohort of 16 patients.[20] Additionally, we report on treatment plan conformity and causes of decreased target volume coverage. Similar studies have been performed for image-guided brachytherapy for cervical cancer, which conclude that an adaptive approach is necessary to correct for possible changes in applicator and anatomy geometry.[14,15]

One paper by Devic *et al.* describes the distribution of the corrections in craniocaudal direction for a cohort of 62 patients and shows for one patient what effect it would have on the CTV dose if these corrections were not applied [11]. Our study did not evaluate variations in dose as a result of uncertainties in applicator positioning correction using X-rays.

Baltas *et al.* describe the COIN parameter for evaluation of implant quality and dose specification in brachytherapy.[22] With HDREBT using an endorectal applicator no implants are involved. As the radiation source is brought next to the tumour instead of into the tumour, the reference isodose volume (V_{RI}) will always be substantially larger than the volume of the CTV that is covered by

the reference isodose (TV_{RI}). The (TV_{RI}/V_{RI}) component of the COIN equation is therefore very low, resulting in low COIN values. This explains the low COIN values reported in this study, compared to the values mentioned in Baltas *et al*.[22] In our opinion, rather than the absolute value, the ratio of the COIN between projection and replanning is informative and a good measure for treatment plan conformity.

Two factors of the COIN equation are dependent on the absolute delineated volume of the tumour (TV) and organs at risk $(V_{CO,i})$. However, as comparisons are made between the projection and the replanning on the same CT scan, the delineated volumes of the tumour and organs at risk are the same for projection and replanning.

There are some limitations in this study. First, the number of patients was small. Secondly, the delineations of the CTV are difficult to perform on CT, even with the provided diagnostic MRI scan, rectoscopy images, digital rectal examination and inserted endoluminal clips at the proximal and distal border of the tumour. No MRI with applicator in situ was available because the endoluminal clips cause large artefacts on MRI. Consequently, there may be delineation variation among the CT scans of the three fractions. Third, we did not report cumulative dose in this study because only four patients did not require an intervention at all three fractions, on which no reliable conclusions can be drawn. Finally, it would be difficult to show the clinical benefit for patients in terms of local control or reduction in toxicity. However, our results show that without additional imaging, patients would have received a suboptimal treatment with substantial underdosage.

CONCLUSION

The results of this study show that using a single CT-based treatment plan for all fractions in HDREBT for rectal cancer may result in a suboptimal treatment at later fractions. Therefore, repeat CT imaging should be the minimal standard practice in HDREBT for rectal cancer to determine whether an intervention would be necessary. Replanning based on repeat CT imaging resulted in more conformal treatment plans and is therefore recommended.

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