Radiation treatment in prostate cancer: balancing between tumor control and toxicity
Heemsbergen, W.D.

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Chapter 2

Impact of Volume and Location of Irradiated Rectum Wall on Rectal Blood Loss after Radiotherapy of Prostate cancer

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ABSTRACT

**Purpose:** To identify dose-volume parameters related to late rectal bleeding after radiotherapy for prostate cancer.

**Patients and methods:** Clinical complication data from a randomized trial were collected and linked to the individual dose volume data. In this trial, patients with prostate cancer were treated with either conventional (with rectangular fields) or three-dimensional conformal radiotherapy to a dose of 66 Gy. Patient complaints, including rectal blood loss were collected for 199 patients, using questionnaires. The outer rectal wall was delineated manually and the inner wall was automatically generated. Absolute and relative Dose Volume Histograms (DVHs) of the rectal wall (with and without the anal region) were calculated with and without rectal filling. A Proportional Hazard Regression (PHR) model was applied to estimate the probability of any rectal blood loss within 3 years, as a function of several DVH parameters. In a multivariable analysis, dose volume parameters were tested together with patient and treatment related parameters (age, smoking, diabetes, cardiovascular disease, tumor stage, neo-adjuvant androgen deprivation, conformal versus conventional, and rectal bleeding during treatment).

**Results:** The estimated incidence of any and moderate/severe rectal bleeding at 3 years was 33 % and 8 %, respectively. Differences between the conventional and conformal technique were small and not significant. The analysis of relative DVHs of the rectal wall (with and without the anal region), showed significant ($p < 0.01$) relations between the irradiated volume and the probability of rectal blood loss within 3 years, for dose levels between 25 Gy and 60 Gy. This relationship was shown in subgroups defined by dose volume cutoff points as well as in the PHR model where a continuously rising risk was seen with increasing volumes. For absolute DVHs and DVHs of the rectum including filling, less or no significant results were observed. The most significant volume-effect relation ($p = 0.002$) was found at 60 Gy for the rectum wall excluding the anal region. The probability of rectal bleeding increased from 10 % to 63 %, when the irradiated rectum volume at 60 Gy increased from 25 % to 100 %. Other factors including age, smoking, diabetes, cardiovascular disease, tumor stage, neo-adjuvant androgen deprivation, conformal versus conventional, rectal bleeding during treatment, rectum length and whole rectum volume did not have a significant effect in the multivariable analysis. When controlling for the volumes at 60 Gy, the volumes at lower dose levels (25 - 55 Gy) were not significant ($p = 0.5$) anymore.
Conclusions: For any rectal bleeding within 3 years, an overall incidence of 33% was observed for patients treated to 66 Gy. For this endpoint, a volume-effect relation was found for DVH parameters of the relative rectal wall volume. This relationship appeared to be most significant for the rectum without the anal region and for the higher dose levels (50 - 60 Gy).

Introduction

In recent years, Intensity Modulation Radiotherapy (IMRT) and dose escalation have been introduced in the treatment of prostate cancer. Retrospective and prospective cohort studies have shown these concepts to be possible. [1-4] With IMRT techniques doses up to 86.4 Gy are proven to be feasible. [3] In a randomized study [5] the tumor control was found to be higher with doses of 78 Gy compared to 68 Gy.

On the basis of literature recommendations [6, 7] and local clinical experience [8-10] dose volume constraints have been used to guide the optimization process of the IMRT planning. In general, these techniques aim to control the volume exposed to high doses in order to limit serious late toxicity. Recent publications indicated, however, that doses in the range of 35 Gy - 57 Gy might be at least equally important. [4,11-13] Therefore, a better understanding of the relationships between complications and dose-volume parameters over the whole dose range, including other prognostic factors, might help us in the optimization of the IMRT techniques.

In most studies, these late complications are being scored using a composite score, such as the Radiation Therapy Oncology Group (RTOG) and Late Effect Normal Tissue / Subjective, Objective, Management, and Analytic (LENT/SOMA) score. In these scoring systems, compliance related symptoms (such as stool frequency) and proctitis related symptoms (such as rectal bleeding) are combined to one overall score. The use of such an overall score might obscure the relation between dose volume parameters and complications. It is probably better to study the sub-items of the composite score, like rectal bleeding in relation to the dose volume parameters. For this analysis, the data on rectal bleeding as reported in a patient questionnaire were used.

Therefore, the main objective of this study was to evaluate in detail the relation between rectal bleeding and rectal dose-volume parameters together with other possible prognostic factors. Rectal dose-volume parameters will be evaluated, including and excluding bowel content and anal part of the rectum.
Patients and methods

The patients for this study were taken from a phase III randomized toxicity study comparing conventional radiotherapy and conformal radiotherapy. In total 265 T1-4 N0M0 prostate carcinoma patients were included in this trial. There were no significant differences in patient and tumor characteristics (Table I) for both study arms 8. After informed consent, randomization was performed stratifying for Gross Target Volume (GTV) definition and not for tumor grade and PSA (prostate specific antigen) level. For T1 tumors the GTV was defined to be the prostate. For the other tumor stages prostate and seminal vesicles were considered to be the GTV. Patients were treated in supine position, without special instructions for bladder or bowel filling. A conventional dose of 66 Gy was applied in both study arms.

Planning procedure / treatment

All patients were treated to a dose of 66 Gy in the ICRU reference point in 33 daily fractions. [9-11] The GTV was expanded in three dimensions with 5 mm to create a Clinical Target Volume (CTV). The CTV was further expanded with 10 mm to create the Planning Target Volume (PTV) to take positioning errors and GTV mobility into account. The planning, treatment technique, linear accelerator, and portal imaging procedure were identical for both treatment arms of the trial. Patients in the conventional treatment arm were treated with rectangular, open fields. Patients in the conformal treatment arm were treated with conformally shaped treatment fields using a multi leaf collimator.

A three-field technique was used with one anterior and two lateral (oblique) treatment fields. During treatment, regular megavoltage imaging was performed, including a setup verification and correction protocol. [12] Due to this protocol the systematic positioning inaccuracy could be limited to 2 mm (1 standard deviation). The outer wall of the bowel was delineated from (and including) the anal region to the level of the inferior border of the sacroiliac joints. From this delineation, different intestinal structures were extracted, namely rectum, sigmoid and anal region. The anal region was defined, more or less arbitrarily, as the most caudal 3 cm. The rectum that excludes the anal region was defined cranially as long as it had a close relation to the sacrum. The position where the bowel moved ventrally away from the sacrum, it was defined to be the sigmoid. We analyzed rectal bleeding as a function of dose-volume-histogram (DVH) parameters of the rectum (without the anal region), of the rectum including the anal region and of the anal region alone for two reasons. First, because of the arbitrary cut-
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off level of 3 cm and second because it is, a priori, not evident from which region rectal bleeding, as reported by patients, is originating.

The contouring protocol resulted from a study on the delineation accuracy of prostate and organs at risk within the context of a randomized trial. [13] The inner bowel wall was estimated from the delineated outer wall surface, using the methodology of Meijer et al. [14] and taking a rectal wall area in each perpendicular slice of 2.1 cm². Consequently, we were able to calculate DVHs for the rectum and anus with and without filling (walls). The length of the rectum was defined as the length along the central axis of the rectum. It was calculated by summing the lengths of the vectors between the centers of the delineated contours.

Dose volume histograms were calculated for the rectum excluding and including the anal region and for the anal region. For all three structures we calculated DVHs with (if present) and without filling and in relative and absolute volumes. Thus, we obtained in total 12 datasets.

Clinical endpoint

Some aspects of acute and late intestinal toxicity have been reported. Acute intestinal toxicity was reduced in the conformal treatment arm in this trial because of a reduction in anal exposure and, consequently, anal toxicity. [8] For RTOG Grade 2 [15] (scored prospectively defined by the clinician) late intestinal toxicity, a trend for less toxicity was observed in favor of the conformal technique mainly because of a reduction of compliance related symptoms (submitted for publication¹).

In this study, late (more than 180 days after radiotherapy) rectal bleeding as reported by the patients was the clinical endpoint. The information on this bleeding was taken from patient questionnaires. The patients themselves filled in these questionnaires at regular hospital visits to evaluate their perceived morbidity. The patients scored their complaints in four grades: no, some, moderate and severe. One of these questions “rectal blood loss” was used in this study. For 199 patients (Table 1), patient self-assessment questionnaires up to 3 years of follow-up (range 1-3 years) were available for analysis. For 1 patient, the acute morbidity data were missing.

Table 1. Patient and treatment data.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total group (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 199)</td>
</tr>
<tr>
<td>Age: mean (SD), year</td>
<td>70 (6.2 )</td>
</tr>
<tr>
<td>Tumor stage</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>25 13 %</td>
</tr>
<tr>
<td>T2</td>
<td>99 50 %</td>
</tr>
<tr>
<td>T3</td>
<td>69 35 %</td>
</tr>
<tr>
<td>T4</td>
<td>6 3 %</td>
</tr>
<tr>
<td>Neo-adjuvant hormonal therapy</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>34 17 %</td>
</tr>
<tr>
<td>No</td>
<td>165 83 %</td>
</tr>
<tr>
<td>Radiotherapy technique</td>
<td></td>
</tr>
<tr>
<td>Conventional</td>
<td>99 50 %</td>
</tr>
<tr>
<td>Conformal</td>
<td>100 50 %</td>
</tr>
</tbody>
</table>

Statistics
The Kaplan-Meier method was used to estimate the incidence of reported bleeding (any and moderate/severe) at 1, 2 and 3 years of follow-up for all groups of patients in this study. We calculated average DVHs and the standard deviation at each dose level of different patient groups (i.e. conformal vs. conventional and bleeders vs. nonbleeders). To test if the differences between the average DVHs were significant, we evaluated the area under the DVH curve (AUCs) as parameter, using the unpaired \( t \) test assuming equal variances of the AUCs. This AUC is mathematically equal to the mean dose. [23]

In a number of published studies on rectal bleeding [4, 16-19], significant volume effects were found at various dose levels in the DVH. Therefore, for a number of dose level in the DVH, the rectal volumes were divided into two groups, using different volumes as cutoff level. Only cutoff points were used, which resulted in subgroups of at least 30 patients. For each subgroup the incidence at 3 years was calculated (Kaplan Meier). A series of these cutoff points was tested on their ability to discriminate between high and low risk for developing rectal bleeding, using Log Rank statistics. Each cutoff point with a \( p \) value < 0.01 (Log Rank) was considered significant.

A proportional hazard regression (PHR) model was applied to estimate the probability of rectal blood loss within 3 years as a function of the percentage rectal wall at least irradiated to a certain dose level. Because of the large time intervals between the different moments of follow up, an interval-censoring method was used as described by Collett. [20] We used
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the SAS package [SAS, release 8.1] to fit the complication probability \( C(t, V) \):

\[
C(t, V) = 1 - \exp[-H_0(t) \times \exp(\beta V)], \quad \text{(Eq. 1)}
\]

where \( H_0(t) \) is the cumulative hazard at the time \( t \), \( \beta \) is the regression coefficient, and \( V \) the percentage of rectal wall volume at least irradiated to a certain dose level. In this study we report the results at the time point of 3 years.

To test whether other published patient- or treatment-related factors [4, 16-19] had a significant impact on bleeding, these factors were also tested in a similar univariable PHR model. To investigate the effect of a number of variables in a multivariable analysis, we added additional terms to \( \beta X \) in the argument of the second exponent of Eq. 1.

Results

Intestinal complications
For the 199 patients in this study, intestinal toxicity Grade 2, according to the RTOG scoring system, occurred for 6 %, 12 % and 10 % of the patients at 1, 2, and 3 years of follow-up, respectively. For the cumulative incidences these figures were 6 %, 13 % and 16 %, respectively. During the follow up period of the study, no laser treatments or blood transfusions were given for the treatment of rectal blood loss. In the patient self-assessment questionnaires, no patients reported blood loss before the start of radiotherapy, whereas 34 % of the patients mentioned blood loss during radiotherapy. At 1, 2 and 3 years of follow-up, the (any) blood loss incidences were 16 %, 19 % and 19 %, respectively. The cumulative incidences were 16 %, 26 % and 33 % at 1, 2 and 3 years of follow-up, respectively. For moderate/severe blood loss these figures were much lower (Fig. 1). For the conventionally and conformally treated patients, the incidences were not different \((p = 0.5)\) at all follow-up periods. The cumulative incidences at 1, 2 and 3 years were 17 %, 29 % and 32 %, respectively for the conventional group and 12 %, 23 %, 34 % for the conformal group.

Dose and volume parameters
The distribution of the wall volumes and volumes including filling of the rectum without the anal region, showed a wide variation (Fig. 2). The wall volume varied between 12.6 and 44 cm³ with an average of 27.1 cm³. This
volume was strongly correlated ($r = 0.81$) with the length of the defined rectum (Fig. 2A). The volume including filling varied between 18.1 and 273 cm$^3$. Because of the variation in filling, the correlation between this rectum volume and length was poor ($r = 0.30$, Fig. 2B). Similar correlations were found for the rectum including the anal region.

The average relative DVHs of the rectum wall including the anal region for the conventionally and conformally treated patients showed lower volumes at each dose level for the conformally treated patients (Fig. 3A). The difference of the average DVHs was evaluated by the area under the curve (AUC), which area is equal to the mean dose. Using this AUC, the difference (4.1 Gy) with a standard error (SE) of 0.8 Gy was statistically highly significant ($p < 0.001$). In accordance with earlier results for all randomized patients [8] this difference was mainly caused by differences (14.9 Gy, SE: 1.2 Gy) of the DVHs in the anal region ($p < 0.001$, Fig. 3C); the DVHs of the rectum excluding the anal region (Fig. 3B) were not significantly ($p = 0.09$) different (1.6 Gy, SE: 0.9 Gy).

**PHR analysis: patient and treatment related factors**

First, we tested in a univariable PHR analysis the association of age, diabetes, cardiovascular disease and tumor stage with the studied clinical outcome (any bleeding). No association was found ($p \geq 0.1$). Treatment-related items (neo-adjuvant androgen deprivation, conformal versus conventional, length of rectal canal, rectal wall volume and rectum volume including filling -all with and without the anal region- ) were also tested and no associations were found. Only for the presence of rectal bleeding during treatment ($p = 0.06$) and smoking ($p = 0.08$) some suggestion was found for an association with rectal blood loss, indicating less rectal bleeding for patients without rectal bleeding during treatment and for smokers. Of the nonsmokers ($n = 145$) 37 % reported rectal blood loss, whereas only 14 % of the smokers ($n = 51$) mentioned blood loss at 3 years of follow-up (cumulative incidences as estimated with the Kaplan-Meier method). Of the patients without bleeding during treatment ($n = 131$) 32 % reported rectal blood loss during follow-up against 36 % for patients with bleeding during treatment ($n = 67$). The small difference of 4 % between these subgroups at 3 years was more evident at 1 and 2 years where the cumulative incidences of late rectal bleeding was 10 % against 22 % (1 year) and 21 % against 36 % (2 years), respectively.
**PHR analysis: dose volume parameters**

To investigate the relation between dose-volume parameters and rectal bleeding, we first compared average relative DVHs of bleeders and nonbleeders (Fig. 3). We chose here to look at relative DVHs, because the relative DVHs correlated better with rectal bleeding than absolute DVHs (see the following section). The average DVH of the wall structures of the bleeders was compared to the average DVH of the nonbleeders (Fig. 3). For the rectum with and without the anal region, the average DVH of bleeders (Fig. 3D and 3E) was significantly higher (2.9 Gy, SE: 1.0 Gy and 2.9 Gy, SE: 1.1 Gy, respectively) compared to the average DVH of the nonbleeders ($p = 0.004$ and 0.006, respectively). For the anal region, (Fig. 3F) this difference (2.3 Gy, SE: 1.8 Gy) was not significant ($p = 0.2$).

For the same datasets, a series of dose-volume cutoff points was tested (Fig. 4) for significance of discriminating between bleeders and nonbleeders. Each cutoff point with $p < 0.01$ was considered to be significant. For the anal region, no significant cutoff points could be found. For the rectum wall including the anal region, significant volume cutoff points were found for all dose levels between 30 Gy and 60 Gy, with the most significant ($p = 0.0002$) cutoff point at 60 Gy and 70 % volume (Fig. 4A). Patients with DVHs below this point had an incidence 21 % of rectal bleeding compared to a 52 % incidence above this cutoff point.

For the rectum without the anal region, significant cutoff points were found for 30 Gy and between 45 Gy and 60 Gy (Fig. 4B). Again, the most significant cutoff point ($p = 0.0005$) was at 60 Gy and 70 % volume. Rectal bleeding incidence was 20 % below and 52 % above this cutoff point. For the patients with moderate/severe late rectal bleeding no significant cutoff points could be determined because of a low number of cases. The average incidence of bleeding above all significant cutoff points was 45 - 69 %, whereas 19 - 25 % below these points.

For the dose levels between 25 Gy and 60 Gy, we further analyzed the relation between the volume parameters and the incidence of rectal bleeding, using the univariable PHR model. For this analysis, we studied all 12 datasets: rectum, anus and rectum including the anal region, for absolute and relative volumes, both with and without filling. For the four anal data sets, no associations were found. For the other eight datasets including the rectum significant correlations were found. The relation for the absolute volumes was weaker compared to the relative volumes. Including filling weakened the relation between bleeding and relative volume. For the relative rectum wall DVHs, at all dose levels a significant relation was found, with a $p$ value varying between $0.03 - 0.04$ for 25 Gy to $0.002 - 0.004$ for 60 Gy (Table 2). The most significant volume relation ($p = 0.002$) was found at
60 Gy for the relative rectal wall excluding the anal region. Therefore, we will restrict ourselves to this anatomical entity for the further results in this section.

In Fig. 5, the estimated volume-effect relations for the cumulative incidence of rectal bleeding after 3 years (with its 95 % confidence intervals) are shown for 30, 45 and 60 Gy. These volume-effect relations compared well with the underlying data, presented by the estimated cumulative incidences in quartiles, each with approximately 50 patients. For the 30 Gy level (Fig. 5A), the probability rose from 10 % to 43 % when the rectal wall volume increased from 40 % to 100 %. For 60 Gy, the volume-effect relation was steeper. The rectal bleeding probability increased from 10 % at a relative rectal wall volume of 25 % to 63 % for a relative rectal volume of 100 % (Fig. 5C). This volume-effect relation with the full range of incidence levels was more descriptive for the data than the earlier found significant cutoff level of 70 % (see arrow in Fig. 5C) with only two incidence levels (20 % and 52 % below and above this cutoff point, respectively).

Prognostic factors for late rectal blood loss: multivariable analysis
In the subsequent multivariable PHR analysis, other variables were tested in combination with the relative rectal wall volume at 60 Gy. Age, tumor stage, conformal versus conventional, neo-adjuvant androgen deprivation, smoking, diabetes and cardiovascular disease were tested. Furthermore, other volume parameters were tested like length of rectal canal, rectal wall volume and rectum volume including filling. No significant parameters were found. For acute rectal bleeding and for smoking the $p$ values increased ($p = 0.10$ and $p = 0.09$, respectively). When we included the volumes at an intermediate dose of 30 Gy together with the volumes at 60 Gy in the PHR analysis, the volumes at 30 Gy became completely insignificant ($p = 0.5$), while the volumes at 60 Gy remained significant ($p = 0.03$).
Fig. 1. The cumulative incidence of any and moderate/severe rectal bleeding at 1, 2, and 3 years of follow-up.

Fig. 2. Relation between rectal length (without anal region), and rectal wall volume (a), and rectum including filling (b).
Fig. 3. Average relative DVHs of rectum including anal region, rectum without anal region and anus, for conventional and conformal patients and for bleeders and non-bleeders. The error bars represent the standard deviations at each dose level.
Irradiated rectal wall volume and rectal bleeding

**Fig. 4.** Cutoff points for the DVHs of rectum including the anal region (a) and rectum without the anal region (b); +: p ≥ 0.01, ▲: p < 0.01.

**Table 2.** *p* values of the Proportional Hazard Regression model for the relative rectal wall volumes with and without the anal region at different dose levels.

<table>
<thead>
<tr>
<th>Dose level (Gy)</th>
<th>Relative rectal wall including anal region</th>
<th>Relative rectal wall excluding anal region</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>0.03</td>
<td>0.04</td>
</tr>
<tr>
<td>30</td>
<td>0.02</td>
<td>0.03</td>
</tr>
<tr>
<td>35</td>
<td>0.01</td>
<td>0.02</td>
</tr>
<tr>
<td>40</td>
<td>0.01</td>
<td>0.02</td>
</tr>
<tr>
<td>45</td>
<td>0.009</td>
<td>0.01</td>
</tr>
<tr>
<td>50</td>
<td>0.006</td>
<td>0.006</td>
</tr>
<tr>
<td>55</td>
<td>0.004</td>
<td>0.003</td>
</tr>
<tr>
<td>60</td>
<td>0.004</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Fig. 5. The probability of rectal bleeding as a function of the relative rectal wall volume (without anal region) at three dose levels. The four bars in Panels a, b and c represent the cumulative incidences in four volume bins with about 50 patients each. The drawn lines represent the fits to Eq. 1 of the proportional hazard regression model together with the 95 % confidence intervals. (c): The arrow indicates the most significant cutoff level at 70 %.
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Fig. 6. The probability of rectal bleeding as a function of the relative rectal wall volume (without anal region) at 60 Gy. The solid lines represent the fit to Eq. 1 of the Proportional Hazard Regression model; the dashed lines represent the 95% confidence interval of this fit. + and ▲ (at 65, 70 and 75%) indicate non-significant and significant cutoff levels (Fig. 4b). The four bars in (a) indicate the cumulative incidences in four quartiles. The use of cutoff points based on these quartiles at 59, 67 and 78% is illustrated in b, c and d, respectively.

Discussion

Patients reported any bleeding in 33% and moderate to severe bleeding in 8% at 3-year follow up in the patient self-assessment questionnaire. The significant difference of the DVHs of the rectum including the anal region between conformal and conventional treated patients (Fig. 3A) did not result in a significant difference in rectal bleeding. The reason for this finding was that the difference of the DVHs of the rectum including the anal region was mainly caused by a difference of DVHs of the anal region (Fig. 3C) and not
by a difference of the DVHs of the rectum without the anal region (Fig. 3B). For the anal region alone, no relation was found between the average DVHs and rectal bleeding (Fig. 3F). Also in the proportional hazard model, no relation between anal DVH parameters and rectal bleeding was found.

For the rectum wall with and without the anal region, a number of DVH parameters were significantly related to rectal bleeding (Fig. 3D, 3E and 4). Including filling gave less or no significant relations. Although the filling will not contribute to toxicity by itself, filling might be important, because changes in filling will displace the rectum in or out of the treatment fields. When the rectum filling in the planning CT scan is larger than the rectal filling during treatment, the anterior rectal wall will be displaced dorsally during treatment. With an empty rectum in the planning scan, the anterior rectal wall can be displaced ventrally. [21]

**Applied methodology to study dose volume effects**

The volume effect relationship was studied in different ways. First, the area under the curve (AUC) of the DVH (or mean dose) showed a significant difference between bleeders and non-bleeders (Fig. 3D and 3E). Secondly, in the approach with cutoff points, significant volume cutoff points at p < 0.01 were observed for dose points between 30 and 60 Gy (Fig. 4A and 4B). The strongest predictor was the cutoff point at 60 Gy for 70 % of the rectal wall volume with 52 % and 20 % of rectal bleeding above and below this cutoff point, respectively. The third analysis was based on the Proportional Hazard Regression (PHR) model (Eq. 1), because this allows the incidence of rectal bleeding to continuously rise as the irradiated volume increases (see Fig. 5). This is illustrated in Fig. 6 at a dose level of 60 Gy. The observed incidence of rectal bleeding was presented in quartiles (Fig. 6A) as in Fig. 5A, 5B and 5C. Fiorino *et al.* [16] also used quartiles to define cutoff levels, which they subsequently tested for significance. This method is illustrated for our patient group in Fig. 6B, 6C, and 6D. We selected cutoff points simply by testing with volume intervals of 5 %. The loss of information using cutoff points instead of using the incidences in quartiles, or even the full information of each individual patient with the PHR model, is illustrated by comparing the two bars in Fig. 6B, 6C and 6D with the four bars in Fig. 6A, and the solid lines in these figures, respectively. Furthermore, the PHR model should be preferred above a threshold model, because it seems rather unlikely that the cumulative incidence of rectal bleeding should rise steeply around some threshold and be relatively constant below and above that point. Indeed, we found some evidence against this steep rise. In Eq. 1, only a linear component of volume was used. In a preliminary analysis, we tested whether this model was contradicted by the data, by comparing its fit with a
more complex model based on restricted splines. [22] At no dose level the fit was significantly better in the non-linear model, as one would have expected in the presence of an irradiated volume threshold above which the incidence of rectal bleeding sharply increases. This finding was in favor of a more gradual increase over the volume range.

As described in the previous sections, we analyzed the relation between DVH parameters and rectal blood loss in a number of ways. When doing multiple comparisons, it could be that one is likely to find a significant effect for a specific parameter, even if in fact no such relation exists. Still, we consider our results to be proof of a DVH-effect relationship. This conclusion is based on the following considerations. First, the analysis based on average DVHs was considered by us to be the primary analysis and this gave a highly significant $p$ value (< 0.006). Second, all DVH parameters tested were highly correlated ($r > 0.86$). Hence, the effective number of independent tests, on which, for instance a Bonferroni correction should be based, is much smaller than the number of tests actually performed (around 200). Third, in most analyses, small $p$ values (< 0.01) were found, which one would not expect when no relation exists. Finally, the smallest $p$ value found (0.0002 for a cutoff point of 70 % volume at 60 Gy) would still be significant, even when the highly conservative Bonferroni correction of a multiplication by 200 was applied.

Our conclusion that the high-dose volumes at 60 Gy are most predictive for rectal blood loss, is of a more speculative nature. However, it seems supported by the fact that it was found in both types of analysis - volume cutoff point as well as PHR analysis – and by the fact that in the PHR analysis including volumes at both the 30 and 60 Gy levels, only the latter retained a $p$ value < 0.05.

Dose-volume effect data
The comparison of the data from the Fiorino study [16] and this study was hampered by a number of differences. They published the results of a retrospective multi-center study. Confounding factors were the large number of patients treated postoperatively, different treatment procedures and doses, creating a somewhat inhomogeneous population. The definition of the rectum included the anal canal (personal communication) and rectal filling. They excluded 18 % of their patients having more than 100 cm$^3$ of rectal volume in the planning CT scan. In our study, this criterion would have excluded 40 % of the patient population. Probably an even more important difference was the range of tumor doses between 70 and 76 Gy in their study, whereas in our study all patients had a tumor dose of 66 Gy. In Fiorino’s study, the volumes at 50 Gy and 55 Gy (V50 and V55) were found
to be the two most important prognostic factors, with volume cutoff points of 58 % and 50 %, respectively. These cutoff points are lower compared to the cutoff points found in our study (Fig. 4B). These differences can be explained by a number of factors. Fiorino et al. reported on Grade 2 and 3 rectal bleeding, whereas we analyzed any bleeding. We were not able to find a clear relationship for moderate/severe toxicity due to the small number of events. Another explanation might be the higher tumor dose (70-76 Gy) in their study compared to the tumor dose in our study (66 Gy).

The recent results from the Memorial Sloan Kettering Cancer Center [4, 23] indicated a number of significant factors for rectal bleeders. Patient related factors were age, diabetes and rectal wall volume and acute toxicity. We tested these factors as well, but we found them not to be significant in the multivariable analysis. Acute toxicity was only of borderline significance ($p = 0.06$) in the univariable analysis. For the dose volume parameters, they found the volume at high doses (102 % of prescription dose, which was closely related to the maximum dose) and the volume at intermediate doses (62 % of prescription dose), which was closely correlated to enclosure of the outer rectal contour by the 50 % isodose. In the multivariable analysis of our study, the volumes at intermediate doses became insignificant if we controlled for the volumes at 60 Gy. This was, as mentioned before, due to the high correlation between the irradiated rectum wall volumes at different dose levels.

The analysis of the data from the M.D. Anderson group [5, 17, 24] indicated that volumes at relative high dose levels were of major importance. The percentage Grade 2/3 toxicity (modified RTOG/LENT) at 3 year follow up decreased from 28 % to 12 % if less than 25 % of rectum volume was exposed to 70 Gy 24. Huang [17] added volume cutoff points at other dose levels (60 Gy: 41 %, 75.6 Gy: 16 % and 78 Gy: 5 %). Unfortunately, they did not test in a multivariable analysis if these cutoff levels at different dose levels were independently associated with the observed toxicity. Of the clinical factors tested, only hemorrhoids had an additional effect on the incidence of late rectal bleeding.

In the study published by Boersma et al. [19], the data indicated that severe rectal bleeding was related to both radiation dose and volume; patients with a rectal wall volume receiving at least 65 Gy for more than 40 %, 70 Gy for more than 30 % and 75 Gy for more than 5 % of the rectal wall were at a higher risk of developing severe rectal bleeding than patients in whom these volumes were smaller. In this study tumor doses were applied between 70 Gy and 78 Gy, which might explain the different percentages of bleeders above and below the cutoff points.
A major drawback of our study is the relative conservative tumor dose applied. Two other studies [18, 25, 26] have reported the volume effect for tumor doses similar to ours. Fenwick et al. evaluated the results of the Royal Marsden randomized study at a dose level of 60 - 64 Gy [18]. The rate of bleeding fell significantly as the fraction of the rectal wall irradiated to a dose of 57 Gy or more was reduced. In the study of Wachter et al. [25, 26] (with a tumor dose of 66 Gy) a significant cutoff point was found at 57 % of the rectal volume exposed to 60 Gy. It is not clear if the contouring (outer contour limited by the field edges), the use of an inflatable rectal balloon or the more generous margins used (1.5 - 2.0 cm) in their study were responsible for a different cutoff point compared to our study. The mean V60 (110 ± 50 cm³ in the Wachter study compared to 93 ± 48 cm³ in our study) might partly explain the observed difference.

**Future studies**

The data, as presented in this article, may be useful as a starting point to set the dose volume constraints for the optimization process of IMRT planning. However, the most relevant DVH parameter is still not determined and we could only include data with a moderate tumor dose of 66 Gy. Therefore, we will validate the observations in this study and expand them to higher dose ranges with the data from the Dutch randomized dose escalation study (68 Gy vs. 78 Gy), which has accrued more than 650 patients up till now. In this future analysis, we will try to find the most relevant DVH parameter(s) to describe the volume effect, using more elaborate statistical methods, like m-fold cross validation, permutation testing and bootstrapping.

Because we found that not only the irradiated volume, but also the location of the irradiated volume was important (the anal region did not contribute to rectal blood loss), we will also present the results of an analysis using rectal dose map. This method [27-29] fuses spatial and dosimetrical information that is lost in the DVH. Using this method, the dose to the posterior part of the rectum and the influence of exposure of different parts of the rectum and anus will be related to the different aspects of the intestinal toxicity as reported in the patient questionnaires.

**Conclusions**

A significant relationship between relative rectal wall volume (with and without the anal region) and late rectal bleeding was found. The anal region did not contribute to rectal bleeding in this study. The most significant relation seemed to be present for the higher dose levels. Absolute volumes, rectum including filling, rectum length, rectum wall volumes, radiotherapy technique, and acute rectal bleeding seem to have less predictive power.
References


