Radiation treatment in prostate cancer: balancing between tumor control and toxicity

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Chapter 3

Gastrointestinal Toxicity and its Relation to Dose Distributions in the Anorectal Region of Prostate Cancer Patients treated with Radiotherapy

Wilma D Heemsbergen, Mischa S Hoogeman, Guus AM Hart, Joos V Lebesque, Peter CM Koper

ABSTRACT

**Purpose:** To study the correlations between the dose distributions in the anorectal region and late gastrointestinal (GI) symptoms in patients treated for localized prostate carcinoma.

**Patients and methods:** Data from a randomized study were analyzed. In this trial patients were treated with either rectangular or conformal fields with a dose of 66 Gy. Data concerning GI symptoms were collected from questionnaires of 197 patients. Dose distributions in the anorectal region were projected on maps and dose parameters were calculated. The incidences of complaints were studied as a function of the dose-area parameters and clinical parameters, using a proportional hazard regression model. Finally, we tested a series of dose parameters originating from different parts of the anorectal region.

**Results:** Analyzing the total region, only a significant dose-area effect relation for bleeding was found ($p < 0.01$). Defining subareas, we found effect relations for bleeding, soiling, fecal incontinence and mucus loss. For bleeding and mucus loss the strongest correlation was found with the dose received by the upper 70% - 80% of the anorectal region ($p < 0.01$). For soiling and fecal incontinence we found the strongest association with the dose to the lower 40% - 50% ($p < 0.05$).

**Conclusions:** We found evidence that complaints originate from specific regions of the irradiated lower GI tract. Bleeding and mucus loss are probably related with irradiation of the upper part of the rectum. Soiling and fecal incontinence are more likely related to the dose of the anal canal and the lower part of the rectum.

Introduction

As a consequence of radiation therapy for prostate cancer, patients might suffer from gastrointestinal (GI) complications afterwards. A significant volume of the bowel (i.e. the rectal wall and anal canal) is close to the target volume. Therefore every patient is at risk, even when conformal fields are applied. The side effects occurring after radiation treatment of the rectum and anal canal are different, as can be expected from its function. As described by the Radiation Therapy Oncology Group (RTOG) / European Organization for Research and Treatment of Cancer (EORTC) toxicity
scoring system, late reactions to be expected after irradiation of the lower GI tract include proctitis related symptoms such as bleeding and mucus loss, increased stool frequency, cramping and diarrhea. [1]

A number of studies have investigated the underlying mechanisms of the observed side effects, mainly aiming at the assumed dose-volume effect relationships. Linking the clinical data of rectal toxicity to individual dose-volume data has yielded interesting results, teaching us more about the significance of irradiated rectal volumes. In particular, the relationship between irradiation of the rectum and bleeding has been subject of many studies. [2-9] The relationships between dosimetric parameters and overall RTOG/EORTC scores have been reported in other studies, where significant volume effects were found. [10-11] Boersma et al. did however not find a relationship between overall GI toxicity scores and dose volume parameters. [2] Similar dose volume analyses involving specific GI symptoms other than bleeding as endpoints have not been frequently published.

Apart from dose-volume data, also dose-surface data can be used to study dose-effect relations. [12] At our institution, a method was developed to use dose maps to describe the dose received by the outer area of the rectum. [13] In these dose maps, the dose to the outer rectal wall is projected onto a two-dimensional normalized angular map. In our study, we used this method to analyze the patient data of a clinical trial to study the GI symptoms and their supposed relationship with the dose-area maps. The main goal was to correlate these clinical data to the dose map data to generate hypotheses, which explain the origin of patient symptoms. Our hypothesis was that the dose to the rectum and to the anal canal could cause different complaints, because the anatomy and its function are different.

Patients and methods

Study population
We reviewed data from a Phase III randomized clinical trial performed at the Daniel den Hoed Clinic / Erasmus Medical Center in Rotterdam, The Netherlands. This study had recruited 266 T1-4 N0M0 prostate carcinoma patients between 1994 and 1996. After patients provided informed consent, randomization was performed between conventional and conformal RT fields. Details of this study population have been described elsewhere. [14] Of the 266 patients, 197 patients were eligible for our study. They answered a baseline questionnaire and at least one questionnaire during follow-up concerning GI complaints. Every patient we selected had records with yearly
examinations for a maximal follow-up period of 3 years. The characteristics of the selected group are summarized in Table 1.

Table 1. Patient and treatment data.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total group (n = 197)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (y)</td>
<td>70 (6.2 SD)</td>
</tr>
<tr>
<td>Tumor stage:</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>25 13 %</td>
</tr>
<tr>
<td>T2</td>
<td>98 50 %</td>
</tr>
<tr>
<td>T3</td>
<td>68 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>33 17 %</td>
</tr>
<tr>
<td>no</td>
<td>164 83 %</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>51 26 %</td>
</tr>
<tr>
<td>no</td>
<td>146 74 %</td>
</tr>
<tr>
<td>Radiotherapy technique:</td>
<td></td>
</tr>
<tr>
<td>conventional</td>
<td>98 50 %</td>
</tr>
<tr>
<td>conformal</td>
<td>99 50 %</td>
</tr>
<tr>
<td>Anorectal wall volume (cm³)</td>
<td>32.9 (5.8 SD)</td>
</tr>
<tr>
<td>Length of anorectal structure (cm)</td>
<td>14.7 (1.8 SD)</td>
</tr>
</tbody>
</table>

Endpoints of interest

The patients scored their perceived morbidity at regular intervals during the trial. They completed a patient self-report questionnaire grading their complaints on a four point scale: ‘not at all’, ‘a little’, ‘quite a bit’ and ‘very much’, as described by Tait et al. [15]. Only diarrhea was not scored on a grading scale; the patient had to indicate whether he had watery stools. This questionnaire was developed as a checklist to identify the symptoms mentioned on the RTOG/EORTC GU and GI toxicity scoring system. [1] A similar questionnaire has been published by Goldner et al. [16]

The bowel symptoms evaluated by the patient were: rectal bleeding, mucus loss, increased stool frequency, diarrhea (watery stools), urge without stools, painful abdominal cramps, fecal incontinence, and soiling (spots in underwear). All questions referred to the patients experience with regard to the preceding week. In this study we analyzed whether a complaint was present or not, regardless of the grading reported.
Planning procedure and treatment
The prescribed dose to the Planning Target Volume (PTV) was 66 Gy in 33 daily fractions of 2 Gy. For T1 tumors the Gross Tumor Volume (GTV) was defined as the prostate. For other stages prostate and seminal vesicles was defined as the GTV. The GTV was three-dimensionally expanded with a 15-mm margin to the planning target volume. A three-field technique was used with one anterior and two lateral (oblique) treatment fields. In the conventional RT arm, patients were treated with rectangular fields. Within the conformal arm, patients were treated with conformally shaped treatment fields using a multileaf collimator. Patients were treated supine, without special instructions for bladder or bowel filling.

Contouring and construction of dose maps
The planning CT scan was used to obtain individual three-dimensional dose-volume data of the anorectal wall. The outer wall of the bowel was delineated from the anal region to the level of the inferior border of the sacroiliac joints. The anorectal region was defined cranially as long as it had a close relation to the sacrum. Where the bowel moved ventrally away from the sacrum, it was defined as sigmoid. On average, the delineated anorectal region was 15 cm long (SD 1.8 cm, range 10-20 cm). The inner rectal wall was generated from the outer rectal wall and contours, using the method of Meijer et al. [17]

We used a previously developed method to virtually unfold the delineated rectal wall and project the dose to the outer rectal surface onto a 2D angular map [13]. To make a map, first a central axis was computed through the rectum and this central axis was divided into 0.5-cm segments. Perpendicular to each segment, we constructed a planar cross-section. We assumed that the amount of rectal wall tissue was a constant in all orthogonal cross-sections throughout the entire rectum. [17] The orthogonal cross-sections were unfolded at the dorsal side and the associated dose was projected onto the map. The vertical axis of the maps (i.e. the length of the rectum) was normalized to 100 %.

Descriptive statistics
The Life-table method was used to estimate the overall cumulative incidences of complaints at 3 years. For these estimates, complaints were only scored as present when the symptom was reported as worse with regard to baseline. The tetrachoric correlation coefficient was calculated to test whether associations existed between the reported symptoms. The life table method was also used to estimate the cumulative incidence at 3 year
for each complaint within defined dose bins, each bin containing about 25 %
of the population.

_Statistical modeling of dose-effect relationships_
Relative areas receiving a certain dose or more were calculated, with the
dose varying between 20 Gy and 60 Gy (dose steps of 10 Gy). A
proportional hazard regression (PHR) model was applied to estimate the
probability of a complaint within 3 years, as a function of the calculated dose
map parameters. These dose map parameters were extracted from different
regions of the total dose map. An interval-censoring method was used, as
described by Collett [18], to correct for the large time intervals between the
different times of follow up. In this study we calculated and reported
cumulative risks at three years. The SAS package was used for fitting the
PHR model (SAS Institute, Cary, NC).

The patient and treatment characteristics were also tested in a
similar way (univariable) to study whether these factors had a significant
impact on the complaints. The effect of univariably significant variables was
also tested in multivariable analysis.

_Mean dose maps_
For each symptom, two average dose maps were constructed: an average
absolute dose map of the patients with the symptom and an average
absolute dose map for the patient subgroup without the symptom. Thus,
differences in dose distributions were visualized. In these mean dose maps,
the variation in follow-up between patients could not be taken into account.
Therefore, the results of the PHR model are more valid in this study.

Results

_Selected population_
The study group consisted of 98 patients treated with rectangular fields and
99 patients treated with conformal fields. The variables GTV definition, age,
hormonal therapy, anorectal wall volume and length of anorectal structure,
were well balanced. With regard to tumor stage and smoking habits, a slight
unbalance was present between the two groups. The conventional group
contained more patients with T2 tumors \( n = 54 \) against \( n = 44 \) whereas the
conformal group contained more patients with T3 tumors \( n = 39 \) against \( n =
29 \). The conformal group also contained more smokers \( n = 29 \) than the
conventional group \( n = 22 \).
**Incidence of complaints**
The incidences of complaints at baseline are shown in **Table 2**. The most frequent symptoms reported were: painful cramps (16 %) and urge (12 %). The cumulative incidences of baseline-corrected GI complaints at 3 years of follow-up (life table method) are shown in **Table 2**. It shows cumulative incidences in the range of 5 % (diarrhea) up to 58 % (increased stool frequency and soiling). Diarrhea appeared to be a rare late complaint and was therefore not analyzed further.

The prevalence throughout the follow-up period was much lower than the cumulative incidence at 3 years. At 2 years, the prevalence of complaints was 19 % for rectal bleeding, 31 % for increased stool frequency, 34 % for soiling, 26 % for fecal incontinence, 15 % for painful cramps, 23 % for mucus loss and 16 % for urge. Much less moderate and severe complaints were reported. At 2 years, the prevalence of moderate/severe complaints was: 5 % for cramps, 5 % for fecal incontinence, 5 % for soiling, 5 % for rectal bleeding, 4 % for mucus loss, 2 % for urge and 5 % for stool frequency of at least five times daily.

Most clinical endpoints investigated showed mutual positive associations. All endpoints were positively associated with each other (statistically significant), except for bleeding with cramps and bleeding with increased frequency. The closest association was observed between fecal incontinence and soiling: 80 % of the patients reported both symptoms either absent or present (tetrachoric correlation coefficient = 0.80, \( p < 0.001 \)).

**Proportional hazard model**
Within the PHR model, clinical characteristics and dose parameters were included as independent variables. The results are summarized in **Table 3** and **Table 4** (univariable analysis). The presence of the corresponding symptom during the acute phase of radiotherapy appears to be the most outspoken clinical factor, which is significant \( p < 0.05 \) for every endpoint except for abdominal cramping and bleeding \( (p = 0.06) \). In view of the number of tests performed, we found no strong evidence for an association between any of the other clinical characteristics and the endpoints.

Univariable (UV) testing of areas receiving at least a certain dose was performed for dose levels between 20 Gy and 60 Gy, with dose steps of 10 Gy. These dose parameters correlated highly (Pearson correlations between 0.70-0.97, all \( p < 0.001 \)). In **Table 4**, the results of a low dose (30 Gy), high dose (60 Gy), and mean dose are presented. These results show that testing the total anorectal area map, only significant results for bleeding are found (UV \( p \) values in the range of 0.008 – 0.01).
Table 2. Prevalence (%) of reported complaints at baseline and the cumulative incidence of each complaint at 3 years corrected for baseline, with its standard error (Life table estimates).

<table>
<thead>
<tr>
<th>Complaint#</th>
<th>Baseline (n = 192)</th>
<th>Year 3* (n = 197)</th>
<th>Standard Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal bleeding</td>
<td>1 %</td>
<td>43 %</td>
<td>6 %</td>
</tr>
<tr>
<td>Frequency ≥ 3</td>
<td>8 %</td>
<td>58 %</td>
<td>6 %</td>
</tr>
<tr>
<td>Soiling</td>
<td>8 %</td>
<td>58 %</td>
<td>6 %</td>
</tr>
<tr>
<td>Fecal incontinence</td>
<td>4 %</td>
<td>57 %</td>
<td>6 %</td>
</tr>
<tr>
<td>Painful cramps</td>
<td>16 %</td>
<td>28 %</td>
<td>6 %</td>
</tr>
<tr>
<td>Mucus loss</td>
<td>4 %</td>
<td>55 %</td>
<td>6 %</td>
</tr>
<tr>
<td>Urge</td>
<td>12 %</td>
<td>35 %</td>
<td>6 %</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 %</td>
<td>5 %</td>
<td>4 %</td>
</tr>
</tbody>
</table>

#These cumulative estimates also include mild complaints. Incidences of moderate/severe complaints only were much lower (range of 1 - 6 %).
* Cumulative at 3 years.

Table 3. Results (p values) of univariable testing for clinical characteristics within the PHR model.

<table>
<thead>
<tr>
<th>Dependent outcome variable</th>
<th>Urge</th>
<th>Cramp</th>
<th>Blood</th>
<th>Mucus Incontinence</th>
<th>Soil</th>
<th>Freq 3+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.37</td>
<td>0.8</td>
<td>0.7</td>
<td>0.5</td>
<td>0.2</td>
<td>0.8</td>
</tr>
<tr>
<td>Acute compl#</td>
<td>0.007*</td>
<td>0.06</td>
<td>0.06</td>
<td>&lt;0.001*</td>
<td>0.02</td>
<td>0.001*</td>
</tr>
<tr>
<td>HT pre-RT#</td>
<td>0.3</td>
<td>0.7</td>
<td>0.2</td>
<td>0.8</td>
<td>0.6</td>
<td>0.3</td>
</tr>
<tr>
<td>Treatment</td>
<td>0.3</td>
<td>0.4</td>
<td>0.5</td>
<td>0.4</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>Smoking#</td>
<td>0.3</td>
<td>0.3</td>
<td>0.07</td>
<td>0.3</td>
<td>0.1</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Abbreviations: PHR=proportional hazard regression; RT=radiotherapy; HT = hormonal therapy; compl = complaints; freq = frequency. * p ≤0.01 ; #yes vs. no

Table 4. Results (p values) of univariable testing for general dose parameters within the PHR model (calculated area for the total anorectal region).

<table>
<thead>
<tr>
<th>Dependent outcome variable</th>
<th>Urge</th>
<th>Cramp</th>
<th>Blood</th>
<th>Mucus Incontinence</th>
<th>Soil</th>
<th>Freq 3+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area &gt; 60 Gy</td>
<td>0.2</td>
<td>0.9</td>
<td>0.008*</td>
<td>0.1</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>Area &gt; 30 Gy</td>
<td>0.3</td>
<td>0.9</td>
<td>0.01*</td>
<td>0.2</td>
<td>0.3</td>
<td>0.1</td>
</tr>
<tr>
<td>Mean dose</td>
<td>0.2</td>
<td>1.0</td>
<td>0.01*</td>
<td>0.1</td>
<td>0.2</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 3.
* p ≤ 0.01
Multivariable (MV) testing was performed for all endpoints with two or more covariables with a univariate p value of < 0.1. MV testing with bleeding as endpoint was performed for smoking, acute bleeding complaints and the area receiving a dose ≥ 60 Gy. Only the latter covariable was statistically significant (MV \( p = 0.02 \)); for smoking and acute complaints, the \( p \) value was 0.1 and 0.2, respectively. MV testing with soiling as endpoint was performed with smoking and acute soiling complaints as covariables. In this analysis the acute complaints remained significant (MV \( p = 0.003 \)) and smoking became statistically significant (UV \( p = 0.08 \), MV \( p = 0.01 \)), indicating a lower risk for soiling complaints in the smoking group. Acute complaints and age were tested MV with increased stool frequency (three or more time daily) as the endpoint. The MV \( p \) values were < 0.0001 for acute complaints (UV < 0.0001) and 0.05 for age (UV \( p = 0.03 \)). A greater age was associated with a greater incidence of increased stool frequency.

Mean dose maps
For “bleeding and no bleeding”, “soiling and no soiling”, the average dose maps are shown in Fig. 1. These maps show a difference in the superior area for bleeding vs. no bleeding, and in the inferior area for soiling vs. no soiling. The dose map patterns for mucus loss were similar to the maps of the bleeders and the maps for fecal incontinence showed similar patterns as for soiling. The dose maps have to be interpreted with caution, because it is not possible to correct for the variation in follow-up between patients (variation between 1 and 3 years) within these dose maps.

Testing of subareas in the PHR model
Using the information of the dose maps, we defined a series of subareas, for which the area receiving a dose ≥ 60 Gy was tested (univariable) in the PHR model. A series starting from superiorly and another from inferiorly were defined: 10 % of the total dose map, 20 %, 30 % and so forth, until 100 % was included (total map). They were tested for all symptoms separately as endpoints. For every combination of endpoint and subarea, the natural logarithm (ln) of the hazard ratio (HR) was calculated for the % of the area irradiated to ≥ 60 Gy. The ln HRs plotted in Fig. 2 are the ratios for each 10 % of the area irradiated to ≥ 60 Gy. The HR expresses the increase in the complication rate for each increase of 10 % area receiving the defined dose.

The results for bleeding, soiling, fecal incontinence, urge and mucus loss are shown in Fig. 2. Together with the ln HRs, its standard error is plotted in each graph. In each graph, the series starting from inferiorly and superiorly, both started at the left side of the graph until they contain 100 % of the dose-area map; at that point, the two series are identical.
Fig. 1. Absolute dose maps of the total anorectal outer wall for different patient groups. The horizontal axis indicates the position along the circumference of the rectum: P = posterior, A = anterior, L = left and R = right. At the vertical axis, the relative position to the anal region (at the bottom: 0 %) and the most cranial part of the rectum (at the top: 100 %) is plotted. Upper maps represent patients reporting bleeding during follow-up (right) and patients without bleeding (left). Lower maps represent patients reporting soiling (right) and patients not reporting soiling (left).
For bleeding (Fig. 2A), the series starting from inferiorly show low HRs that were not statistically significant, until the inferior 70% - 100% is included in the dose-area tested; from 70% to 100% superiorly the results are significant ($p < 0.05$). The other way around starting from superiorly, the tested dose-areas remained significant all the way through to the final point of 100%. The graph for bleeding clearly showed a maximum in the ln hazard ratio at the superior 80% of the map, indicated with an arrow ($p = 0.0012$). Including another 10% (to a total of 90%) after this point causes a clear decrease in the HR.

For soiling (Fig. 2B) the series starting from superiorly show low levels of the ln HR that were not statistically significant. Starting from inferiorly, the first five tested dose-areas (inferior 10% - inferior 50%) were statistically significant models ($p < 0.05$). Passing the point of the inferior 40% (indicated with an arrow), the tested dose-areas became less significant and passing the inferior 50% the tested areas becomes not significant ($p > 0.05$), although the estimated HR is still at the same level. In Fig. 2B, the results for fecal incontinence are also plotted with two thin dotted lines. The ln HRs and corresponding $p$ values found for this endpoint are close to the results of the endpoint “soiling”.

For the endpoint “urge” (Fig. 2C), almost every tested dose-area was not significant, except the most superior 10% and 20% ($p < 0.05$). For mucus loss (Fig. 2D), a similar pattern as for “bleeding” was found. For this endpoint the results show a maximum of the HR at 70% (corresponding $p = 0.007$). For increased stool frequency, a weak association was found (ln HR of 0.09) with the inferior 60% of the anorectal map ($p = 0.16$).

For the optimal subarea related with bleeding (superior 80%), soiling (inferior 40%) and mucus loss (superior 70%), graphs were constructed showing the volume effect of RT on the probability of developing the complaint at risk within 3 years. In Fig. 3, the estimated incidence at 3 years of a complaint as a function of the area receiving a dose > 60 Gy is shown. The actual cumulative incidence at 3 years is also shown for four fixed bins (quartiles). If we repeat this for other dose levels (e.g. area irradiated to at least 40 Gy, 50 Gy and 65 Gy), similar probability lines are found, which are shifted to the left (lower dose levels) or to the right (higher dose levels).
Fig. 2. Results of Proportional Hazard Regression (PHR) analyses concerning endpoints (A) bleeding, (B) soiling (solid lines) and fecal incontinence (dotted lines), (C) urge and (D) mucus loss. Rectal map analyzed in different pieces: a series of 10 relative cutoff points were tested, starting from inferiorly (10% of map to 100%) and another, similar, series starting from superiorly. Tested covariate was in all cases: % of area receiving $\geq$ 60 Gy. The In hazard ratios of the corresponding tested PHR models are plotted on the y axis together with its standard error (plotted for one direction). Arrows indicate cutoff values taken for the depicted graphs in Fig. 3.

**Analyses of isolated subareas**

Besides the division into superior and inferior parts, we also cut the anorectal map into isolated subareas. Each dose map (similar to Fig. 1) was cut into 4 regions from superior to inferior, and four regions from posterior to anterior (left, anterior, right, posterior). The 16 created isolated pieces of rectum or anal canal were tested in explorative analyses. These analyses revealed no new information on local dose-effect relations (results not shown).
Fig. 3. The estimated incidences within 3 years (fitted lines) of soiling, bleeding and mucus loss as a function of the area receiving a dose $\geq 60$ Gy. For soiling, inferior 40 %, for bleeding, superior 80 %, and for mucus loss, superior 70 % of the dose maps is taken for the fit. Confidence intervals (95 %) and Life table estimates at 3 years (quartiles) are shown for each fit.
In this study we found evidence that specific symptoms were related with dose-area parameters of different regions of the lower GI tract. Analyzing rectal bleeding revealed that the best prediction was found from the dose in the superior 80% of the anorectal map ($p = 0.001$). Similar results were found for mucus loss ($p = 0.007$ for the upper 70%). These results have to be interpreted with caution with regard to its explorative nature and the large standard errors found (Fig. 2).

A visual inspection of the mean dose maps confirms the results found in statistical analysis for bleeders: in the region of the anal canal no clear differences in the dose pattern were found between the patient group ‘bleeding’ and the patient group ‘not bleeding’ while there clearly was a difference in the dose pattern at the superior side of the map (Fig. 1).

Some evidence for a dose-effect relation for soiling and fecal incontinence was found within the inferior 40% - 50% of the dose map, situated in the anal region and the lower part of the rectum ($p = 0.03$ for both endpoints). The width of the confidence intervals, however, indicated that these relationships were not accurately obtained. Although less significant, this observation is relevant as the majority of the patients is bothered with compliance-related symptoms. Looking at the mean dose maps of the patient group reporting soiling vs. the group not reporting soiling (Fig. 1), a difference was present at the average dose received by the most inferior part of the dose map (i.e. the anal canal), confirming the results of the PHR analysis. For the more high-dose regions (> 60 Gy), however, the difference between the areas for the group reporting soiling vs. the group not reporting soiling was less clear.

For the observed increase in the incidence of urge and stool frequency no explanatory dose-area effect relation could be described within the studied lower GI tract. For urge we did find a significant association with the most upper part of the delineated rectum, close to the colon and the sacrum ($p = 0.02$ for the superior 10% of dose map), indicating a greater risk for larger areas. However, we could not explain this. Given the number of tests we performed, it might have been due to chance.

Dale et al. [19] investigated the correlation between dose-volume data of the rectum and several complaints scored on patient questionnaires in a small group of 52 prostate cancer patients. They found that the high-dose levels were best correlated with the late side effects studied (i.e. diarrhea, cramps, gas, blood, mucus, pain). The correlation coefficients they found were, however, small and only significant for cramps ($p < 0.01$).
Yeoh et al. [20] investigated the anorectal functioning after radiotherapy (motility and sensory function) and found an association of radiotherapy with objective changes of the rectal sensitivity. However, an analysis including dose-volume data was not reported. Other studies concerning the anorectal function after radiotherapy also found affected functioning of rectum and anus even when conformal techniques were applied. [21-22] Hayne et al. [23] published a review of the literature concerning anorectal injury after pelvic radiotherapy. This concerned prostate patients, as well as patients treated for cancer of the rectum or cervix. The maximum tolerated rectal volume was decreased in all studies investigating this endpoint, indicating that the rectal capacity was affected.

Vordermark et al. [24] studied fecal incontinence in relation to dose-volume histogram data and reported no significant correlations. They did find, however, greater minimum doses to the anal canal for patients with severe complaints. They also compared the complaints of 44 patients treated 0.6 - 4.5 years previously for prostate cancer with the complaints in a control group of 30 untreated prostate cancer patients and found significantly worse scores in the treated group. In their study, fecal incontinence, increased bowel movements, urge, and soiling, were included in the continence score. In our study, we also did not find a very strong relationship between continence problems and dose data.

The separation into superior and inferior parts corresponds with the anatomical and functional region of the rectum and the anal canal. This is in agreement with the results indicating that bleeding and mucus loss originates from the rectum and complaints concerning soiling and fecal incontinence are a consequence of irradiating the anal region and probably the lower rectal region. However, fecal incontinence is likely to be a result of a number of underlying factors like soft stools, increased stool frequency, cramps, capacity of the rectum and sphincter function. These factors are obviously not exclusively related to the anal canal, which makes it more complicated.

A number of the analyses reported in this study, would have been possible with dose-volume data instead of dose-area data. For every projection of dose distributions on the outer rectal wall it is possible to obtain the corresponding dose-volume data. We chose to use the dose-area data because we already obtained the dose-area data to construct the dose maps. With regard to dose-volume data, the correlations between the dose-area data and the dose-volume data were high in this dataset, with a Pearson correlation coefficient of 0.94 - 0.96 for dose levels of 20-60 Gy. The number of reported moderate to severe symptoms was low. In these small subgroups, no indications for a dose-effect relation were found.
However, in this study, 66 Gy was prescribed to the tumor. With regard to the current developments of describing a higher dose to a tighter planning target volume, it would be very interesting to repeat these analyses in a large patient group. Therefore, we plan to do additional investigations in our trial randomizing between 68 Gy and 78 Gy, with conformal fields and more extensive follow up.

**Conclusions**

Irradiation of the anorectal region is associated with several side effects, showing a continuously rising risk with an increasing irradiated volume. Incorporating the spatial information of the dose distribution in our analyses indicated that different complaints origin from different regions. Rectal bleeding and mucus loss were related with irradiation of the more upper part, i.e. the rectal region. Fecal incontinence and soiling showed both a stronger association with the lower part of the GI tract, i.e. the lower part of the rectum and the anal canal.
References


