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

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Chapter 5

Acute and late gastrointestinal toxicity after radiotherapy in prostate cancer patients: consequential late damage

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ABSTRACT

Background: Late gastrointestinal (GI) toxicity after radiotherapy can be partly explained by late effects of acute toxicity (consequential late damage). We studied whether there is a direct relationship between acute and late GI toxicity.

Patients and methods: A total of 553 evaluable patients from the Dutch dose escalation trial (68 Gy vs. 78 Gy) were included. We defined three outcomes for acute reactions: 1) maximum RTOG (Radiation Therapy Oncology Group) acute toxicity, 2) maximum acute mucous discharge (AMD) and 3) maximum acute proctitis. Within a multivariable model, late endpoints (overall toxicity and five toxicity indicators) were studied as a function of acute toxicity, pretreatment symptoms and relevant dose parameters.

Results: At multivariable analysis, AMD and acute proctitis were strong predictors for overall toxicity, “intermittent bleeding” and “fecal incontinence” ($p \leq 0.01$). For “stools ≥ 6/day” all three were strong predictors. No significant associations were found for “severe bleeding” and “use of steroids”. The predictive power of the dose parameters remained at the same level or became weaker for most late endpoints.

Conclusions*:* Acute GI toxicity is an independent significant predictor of late GI toxicity. This suggests a significant consequential component in the development of late GI toxicity.

Introduction

Acute and late gastrointestinal (GI) toxicity rates after radiotherapy for prostate cancer are considerable and have been the subject of many studies. Dose-volume effect relationships have been described extensively in the past decades. More recently, several authors have mentioned that there might be a direct relationship between acute and late GI toxicity independent of dose. [1,2] This phenomenon, known as consequential late effect (CLE), is defined as a direct consequence of acute radiation response causing tissue damage, which eventually leads to late effects after a latent symptom-free interval. This mechanism is schematically depicted in **Fig. 1**. It has been described for several organs at risk such as skin, mucosa and the GI tract. [1,3]

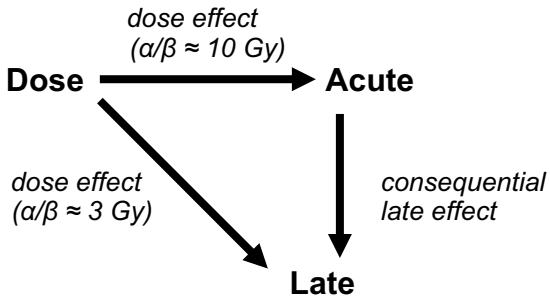

Fig. 1. Scheme presenting the mechanisms that lead to late toxicity:
a direct dose effect and an indirect dose effect ("consequential late effect")

Previous studies with rats described CLE in the GI tract: acute epithelial damage after irradiation of the rectum induced late toxicities after a latent period. [2,4] Dubray and Thames [5] describe late stenosis in rats as a result of both early and late responding rectal wall components after irradiation. In clinical studies concerning prostate cancer patients, little has been published however about CLE. Several authors described the correlation between acute and late toxicity, but in most studies individual dose data were not included in the models. [3,6,7] Dose-volume parameters of the organs at risk are known to be related to acute toxicity as well as late toxicity, so a straightforward comparison of late toxicity risks in patients with and without acute toxicity is not sufficient because the interfering relation with the dose parameters will obscure the measurement of the possible consequential effects (**Fig. 1**). Some authors have reported that acute toxicity scores remain significant in multivariable (MV) models predicting late GI toxicity, even when dose parameters are included. [8,9] These results strongly suggest that acute toxicity plays a role in the development of late GI toxicities after radiotherapy for prostate cancer. Some authors reported however that acute toxicity did not remain significant in MV models. [10]

We have previously reported on acute and late toxicity in a randomized trial (68 Gy vs. 78 Gy) for prostate cancer patients. [11,12] In that earlier study we identified dose parameters that correlated with different late GI complications. We also found relationships between pretreatment complaints and the incidence of several late endpoints. We used this extensive data set from our randomized trial to investigate whether there is a direct link between acute and late effects, which could not be explained by the dose-volume effects or pre-treatment GI symptoms.

Patients and methods

Patient group
We selected prostate cancer patients from the Dutch randomized Phase III trial (68 Gy vs. 78 Gy), known as the CKVO 96-10 study (Commissie Klinisch Vergelijkend Onderzoek / Committee Clinical Comparative Research). These patients were all treated with external radiotherapy for localized prostate carcinoma between June 1997 and February 2003 at the Erasmus Medical Center in Rotterdam and The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital in Amsterdam, the Netherlands. The total study population is described extensively elsewhere. [11,12] We did not select patients from the other two participating hospitals, because their patients did not fill out the self-report checklist on a regular basis. From the selected 575 patients, there were no dose data available for 7 patients. For another 15 patients there were no checklists available during treatment, leaving 553 patients of the 575 with complete data for analysis (96 %).

Treatment
Patients were treated with conformal fields (CTV to PTV margin of 10 mm for the first 68 Gy, margins of 0-5 mm for the last 10 Gy when applicable). Prescription of the dose was according to International Committee on Radiation Units and Measurements (ICRU) criteria, with 2 Gy per fraction. The rectum was delineated from the anal verge until the inferior border of the sacro-iliacal joints or to the point where the rectum was no longer close to the sacrum. Dose constraints for the GI tract were: the percentage of the rectum receiving ≥ 74 Gy should not exceed 40 % and the dose to the small bowel should not be higher than 68 Gy. During treatment patient setup was verified using an offline verification protocol, keeping systematic setup errors within 5 mm. Further details about treatment planning have been described elsewhere. [11,12]

Recording of symptoms
Before and during radiotherapy the patient filled out a self-report symptom checklist (on a weekly or two-weekly basis) as well as prior to each follow-up visit. Goldner *et al.* published a similar checklist. [13] The bowel symptoms on this checklist were: pain with stools, painful abdominal cramps, urgency, rectal bleeding, mucus discharge, stool frequency, fecal consistency, fecal incontinence, and soiling.

Pretreatment symptoms
We assigned each patient to the subgroup “pretreatment GI complaints” or “no pretreatment GI complaints”, based on the presence of any GI symptom at baseline. With regard to fecal consistency, stools without consistency were regarded as a GI symptom. With regard to stool frequency, 4 stools or more/day was scored. Other authors also evaluated the presence of baseline symptoms as a predictor for toxicity. [7,10]

Acute toxicity
We formulated three outcomes for acute toxicity: the maximum score of RTOG (Radiation Therapy Oncology Group) acute toxicity (which was present in the trial database), the maximum score of acute proctitis and the maximum score of acute mucous discharge (AMD). The maximum score of acute proctitis (grade 0-2) was calculated as follows: Grade 0 in case no blood or mucous discharge was reported during radiotherapy; Grade 1 in case any rectal blood loss or mucous discharge was reported; and Grade 2 in case the patient reported rectal blood loss or mucous discharge in combination with at least two moderate to severe complaints (concerning pain, cramps, diarrhea, stool frequency or urge). We additionally assigned ‘Grade 1’ proctitis to 7 patients who had reported a high stool frequency and watery diarrhea but no blood or mucous discharge. The third defined type of acute reactions was the maximum score of acute mucous discharge (AMD) as reported by the patient (Grade 0 in case of ‘none’, Grade 1 in case of ‘mild’, and Grade 2 in case of ‘moderate’ or ‘severe’). Acute toxicity was determined within the period 28-120 days from start of treatment.

Late toxicity
Late toxicity was scored according RTOG/EORTC criteria and determined at regular follow-up intervals: every 3-4 months during the first two years, biannual during years 3-5 and yearly thereafter. Scoring of late toxicity started at 120 days after the first day of radiotherapy. Toxicity was evaluated upon known local or regional progression or metastasis. Late toxicity endpoints in this study were: RTOG/EORTC Grade ≥ 2 late toxicity (‘late R/E ≥ G2’) and four Grade ≥ 2 toxicity indicators, which have been described previously by Peeters *et al.* [11]: 1) severe bleeding requiring laser treatment or transfusion (‘severe bleeding’), 2) late proctitis treated with steroids (‘use of steroids’), 3) stool frequency 6 or more per day (‘stools ≥ 6/day’), 4) pads for incontinence more than 2 days/week in combination with reported loss of blood, mucus, or feces (‘fecal incontinence’). We formulated a fifth late endpoint concerning Grade ≥ 1 late intermittent bleeding more than 2

days/week ('intermittent bleeding'). All patients who had reported 'bleeding > 2 days/week' on the questionnaire and patients who were treated for blood loss, were scored for this endpoint. Scoring of intermittent bleeding is in concordance with other studies where intermittent bleeding is scored as Grade 2 toxicity. [8,14]

Selection of relevant dose parameters

Previously, an extensive analysis was performed to study all Grade ≥ 2 late toxicity endpoints to determine which relative dose-volume parameters from the rectum or anal canal were most predictive for late damage. [11] For this purpose, the anal canal was defined as the most caudal 3 cm of the delineated anorectal tract. A summary of the results with regard to the most significant dose parameters is presented here: the dose parameter 'mean dose to the anal canal' (anal D_{mean}) was strongly associated with the endpoint 'late R/E ≥ G2' (p = 0.009) and with the indicators 'fecal incontinence' (p = 0.002), and 'use of steroids' (p = 0.03). For the indicator 'severe bleeding', the anorectal volume receiving ≥ 65 Gy was found to be a strong predictor (p = 0.004) and for 'stools ≥ 6/day', the mean dose to the anorectum (D_{mean}) (p = 0.01). These results were obtained from Cox proportional hazard regression analyses including dosimetric variables and adjusted for hospital.

Statistical analysis

We calculated the correlations (Pearson correlation coefficients) between the pretreatment symptoms and the three outcomes for acute toxicity (maximum score of acute RTOG, AMD, acute proctitis). A proportional hazard model (Cox regression) was used to estimate the effect of acute reactions for each evaluated late endpoint, taking into account relevant dose parameters and the presence of pretreatment GI symptoms as well. Hazard ratios and their p values were calculated. Acute toxicity scores as well as volumetric and dosimetric parameters were tested as continuous variables. The hazard ratio (HR) indicates the relative increase in the hazard rate for an increase of 1 unity of the acute toxicity score (1 grade), the volumetric (1 %) or the dosimetric variable (1 Gy), respectively. Because of the multiple testing, results with a p value of 0.01 or below were considered statistically significant. We also included the variable 'hospital' if it was associated with the tested endpoint (when $p < 0.05$). SPSS for Windows software (release 10.0; SPSS Inc., Chicago, IL, USA) was used for calculation of Kaplan-Meier curves. The SAS software package for Windows (release 8.02) was used for fitting the proportional hazard regression models (SAS Institute Inc., Cary, NC, USA).

Results

General statistics

Characteristics of the analyzed patient group are summarized in **Table 1**. Median follow-up time was 44 months. The mean age was 69 years (6.4 1SD). The mean volume of the delineated anorectal wall was 34.3 cm³ and the mean length was 16.8 cm. Pretreatment symptoms were present in 19 % of the patient population. Most frequently reported was 'urgency' (8 %) and 'abdominal cramps' (7 %). The distributions of the maximum acute proctitis score, the maximum acute RTOG score and the maximum AMD score are shown in **Table 2**. Maximum score of acute proctitis, AMD, and the acute RTOG score were mutually correlated (Pearson correlation coefficients in the range of 0.6-0.8, $p < 0.001$).

The incidences of late toxicity are shown in **Table 2**. The cumulative incidence at 4 years of 'late R/E ≥ G2' was 28 %. The indicators with the highest cumulative incidence at 4 years were 'stools ≥ 6/day' (10 %) and 'intermittent bleeding' (20 %).

Table 1: Characteristics of the study population.

Variable		Total group (*n* = 553)	
		n	%
Tumor stage	T1	102	18 %
	T2	244	44 %
	T3	199	36 %
	T4	7	1 %
Randomization arm	68 Gy	275	50 %
	78 Gy	278	50 %
Anorectal wall volume (cm^3)	Mean (range)	34.3	(23.0 - 54.3)
Anorectal length (cm)	Mean (range)	16.8	(11.7 - 25.8)

Dose parameters

For all endpoints, the dose parameter found in a previous analysis was included in our MV models (see also the summary in the methods section). For the formulated indicator 'intermittent bleeding', we tested in the current dataset which dose parameter was most relevant. We found the anorectal and rectal wall volume receiving ≥ 70 Gy to be the only relevant (significant) dose parameters in our dataset (p = 0.02). The anorectal wall volume receiving ≥ 70 Gy was therefore included in our MV models.

Table 2. Incidences of GI symptoms (pretreatment, acute and late).

Gastrointestinal symptom		%
Pretreatment symptoms present		19 %
Acute toxicity		
Acute R/E score	G0/G1/G2/G3	10/38/46/5 %
Acute mucous discharge	G0/G1/G2	34/50/16 %
Acute proctitis	G0/G1/G2	30/41/29 %
*Late toxicity**		
Late R/E ≥ Grade 2		28 %
Indicators		
Severe bleeding		6 %
Use of steroids		7 %
Fecal incontinence		9 %
Stools ≥ 6/day		10 %
Intermittent bleeding		20 %

Abbreviations: G = Grade

* Cumulative incidence at 4 years, estimated by Kaplan-Meier method

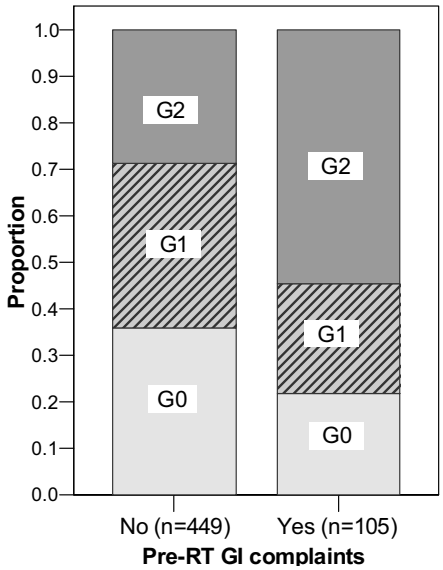

Fig. 2. The distribution of proctitis Grade 0-2 for patients with and without pretreatment GI symptoms (Chi-square test: $p < 0.001$).

Pre-RT symptoms and toxicity

The relationship between pretreatment complaints and the incidence of acute proctitis is depicted in **Fig. 2**. It shows that patients with pretreatment symptoms have on average more serious acute proctitis (chi-squared test for difference in distribution: $p < 0.001$). The other two outcomes for acute reactions show similar associations (AMD: $p = 0.02$, acute RTOG score: $p = 0.002$) With regard to late complications there is also a significant association with pretreatment complaints: the cumulative incidence of 'late R/E ≥ G2' at 4 years is about 45 % (1 SE 7 %) for the subgroup with pretreatment GI symptoms versus 24 % (1 SE 3 %) for the group without (Log Rank $p = 0.003$).

Relationship between acute and late toxicity

We tested whether acute toxicity was significantly associated with late toxicity endpoints at MV testing. In these tests, the covariables 'presence of pretreatment symptoms' and the most relevant dose parameter were added to the model if they appeared relevant for that particular endpoint at UV testing (significance level chosen of 0.1). The variable 'hospital' appeared to be a significant factor for 'blood loss > 2 days/week' only, and was therefore always included in the model for that outcome. We tested three outcomes of acute toxicity as well as six defined late endpoints, adding up to a total of 18 tests.

The results of the UV and MV proportional hazard regression are summarized in **Tables 3** and **4**. For the endpoint 'late R/E ≥ G2' (**Table 3**), pretreatment complaints as well as the three acute toxicity outcomes are significant predictors at UV analysis; the association with the dose parameter 'mean dose to the anal canal' is weaker ($p = 0.04$). At MV analysis, AMD and acute proctitis remain significant within the MV model; corresponding HRs are 1.8 and 1.7, respectively (which indicates the relative increase in hazard rates for each increase of 1 grade). The p value of the dose parameter and pretreatment symptoms slightly increases and the dose parameter loses significance at MV analysis ($p > 0.05$). In **Fig. 3** the incidence of 'late R/E ≥ G2' is shown for 3 subgroups based on acute toxicity (grade 0-2 proctitis).

Table 3. Results of univariable (UV) and multivariable (MV) analysis for late endpoints related to mean dose (anal canal or anorectum).

Endpoint:	Late R/E ≥ G2		Use of steroids		Fecal incontinence		Stools ≥ 6/day	
Models	**HR**	***p***	**HR**	***p***	**HR**	***p***	**HR**	***p***
UV model								
(Anal) D_{mean} #	1.02	*0.04*	1.03	*0.05*	1.04	***0.007***	1.06	*0.03*
Pre-RT complaints	1.8	***0.003***	0.9	0.8	2.2	*0.03*	2.3	*0.03*
Acute R/E score	1.6	***0.01***	1.4	0.4	1.6	0.2	2.6	***<0.0001***
AMD	1.9	***<0.0001***	2.0	*0.02*	2.4	***0.0002***	2.4	***0.0001***
Acute proctitis	1.8	***<0.0001***	1.4	0.2	2.2	***0.0009***	3.3	***<0.0001***
MV model								
Acute R/E score	1.5	*0.02*	-		1.5	0.3	2.5	***0.0002***
(Anal) D_{mean}	1.01	*0.08*	-		1.04	***0.01***	1.05	*0.03*
Pre-RT complaints	1.7	***0.008***	-		2.0	0.05	1.9	*0.05*
AMD	1.8	***<0.0001***	1.9	*0.03*	2.3	***0.001***	2.1	***0.001***
(Anal) D_{mean}	1.01	0.1	1.03	*0.07*	1.03	*0.02*	1.05	*0.07*
Pre-RT complaints	1.5	*0.05*	-		1.6	*0.2*	1.8	*0.07*
Acute proctitis	1.7	***<0.0001***	-		2.0	***0.004***	2.9	***<0.0001***
(Anal) D_{mean}	1.01	0.1	-		1.03	***0.01***	1.04	0.1
Pre-RT complaints	1.5	*0.08*	-		1.6	*0.02*	1.6	0.2

Abbreviations: AMD = acute mucous discharge; D_{mean} = mean dose; pre-RT = pretreatment. Hazard ratio's (HR) and corresponding *p* value are shown. Significant results (*p* values 0.01 or below) in italics and bold, trends (0.01< p <0.1) in italics. All UV parameters with *p* value <0.1 are included in MV models.
D_{mean} of anal canal tested, except for 'stools ≥ 6 / day' where D_{mean} of anorectum is tested.

For the endpoints 'fecal incontinence' and 'stools ≥ 6 / day' (**Table 3**), AMD as well as acute proctitis were very strong predictors at UV and MV analysis (all *p* values 0.001 or below). For 'stools ≥ 6 / day' the acute RTOG score was also a strong predictor. For the endpoint 'use of steroids' only a trend was found for AMD ($p = 0.03$). With regard to the included dose parameters, we found that the chosen dose parameter was only a strong predictive factor (at UV analysis) for the endpoint 'fecal incontinence' in our study population, where it remains also a relevant factor at the MV analyses.

Table 4 shows the results of UV and MV analyses for the late endpoints 'intermittent bleeding' and 'severe bleeding'. No association was found between severe bleeding and acute toxicity at UV analysis. The relationship with the dose parameter (V65 of anorectum) is relatively weak in this data set. There was a strong association ($p = 0.005$) between intermittent bleeding and AMD and proctitis, respectively (UV and MV).

Table 4. Results of univariable (UV) and multivariable (MV) PHR model for both indicators concerning 'bleeding'. Hazard ratio's and corresponding *p* value are shown. Significant results (*p* values 0.01 or below) are in italics and bold, trends (0.01< *p* <0.1) are in italics.

Endpoint:	**Intermittent bleeding**		**Severe bleeding**	
Models	**HR**	***p* value**	**HR**	***p* value**
UV model				
Anorectal vol ≥65 Gy (%)	-		1.04	*0.06*
Anorectal vol ≥70 Gy (%)	1.02	*0.02*	-	
Pretreatment complaints	0.6	0.2	0.5	0.4
Acute R/E score	1.1	0.4	0.9	0.9
AMD	1.6	***0.003***	1.1	0.7
Acute proctitis	1.5	***0.01***	1.0	1.0
MV models				
AMD	1.6	***0.005***	-	
Volume ≥70 Gy (%)	1.02	*0.04*		
Acute proctitis	1.5	***0.01***		
Volume ≥70 Gy (%)	1.02	*0.03*	-	

Abbreviations: vol = volume; AMD = acute mucous discharge; HR = hazard ratio.

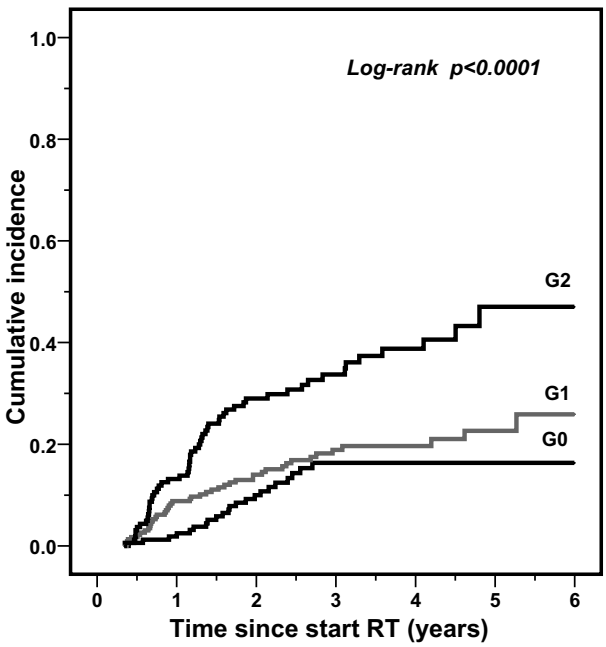

Fig. 3. Kaplan-Meier curves of 'late R/E ≥ G2' toxicity for 3 subgroups based on acute toxicity (proctitis Grade 0, 1 and 2).

Fig. 4 shows the cumulative incidences at 4 years (with 1SE) for the late endpoint 'intermittent bleeding' (4A) and 'fecal incontinence' (**4B**), as a function of both acute toxicity (AMD grade 0-2) and dose (below or above median). The relevant dose-volume parameters were: for intermittent bleeding the relative volume of anorectal wall receiving 70 Gy or more, and for incontinence the mean dose to the anal canal. Note that the standard error of several subgroups is relatively large (6-8 %), probably because the available follow-up within some small subgroups was limited. **Fig. 4** illustrates both the dose effect (incidence in subgroup above median is always higher compared to below median) and the acute toxicity effect (incidence in subgroups grade 2 is always higher compared to corresponding grade 1 subgroups which are higher compared to grade 0 subgroups, except for one case).

Pretreatment symptoms subgroups

We tested whether there was an interaction between the effects of acute toxicity and pretreatment symptoms or between dose parameters and pretreatment symptoms. We found no significant interactions ($p \leq 0.01$). Most HRs of acute toxicity and the dose were, however, estimated to be smaller within the subgroup with pretreatment symptoms. For example, the HR for acute proctitis as a predictor for stools ≥ 6/day was estimated 3.8 in the subgroup without pretreatment symptoms against 1.5 for the patients with symptoms (interaction test $p = 0.10$); for the total population the HR was 2.9 **(Table 3**). Another example regarding the dose effect was that for the endpoint 'late R/E ≥ G2' the HR of 'mean dose to the anal canal' was 1.02 ($p = 0.01$) in the subgroup without pretreatment symptoms and 0.99 ($p = 0.5$) in the subgroup with pretreatment symptoms (interaction test $p = 0.04$).

Correlations between dose parameters and acute reactions

In a previous analysis, we found that the maximum acute RTOG score (grade ≥ 2) was associated with the relative volume of the anorectal tract, receiving ≥ 50 Gy, ≥ 60 Gy and ≥ 65 Gy, respectively. [12] In the current dataset both the proctitis score and maximum AMD score appeared to be related to similar dose parameters; the strongest correlations were found with the relative volume of the anorectal wall receiving 50 Gy or more and 60 Gy or more, as well as with the mean dose to the anorectal wall.

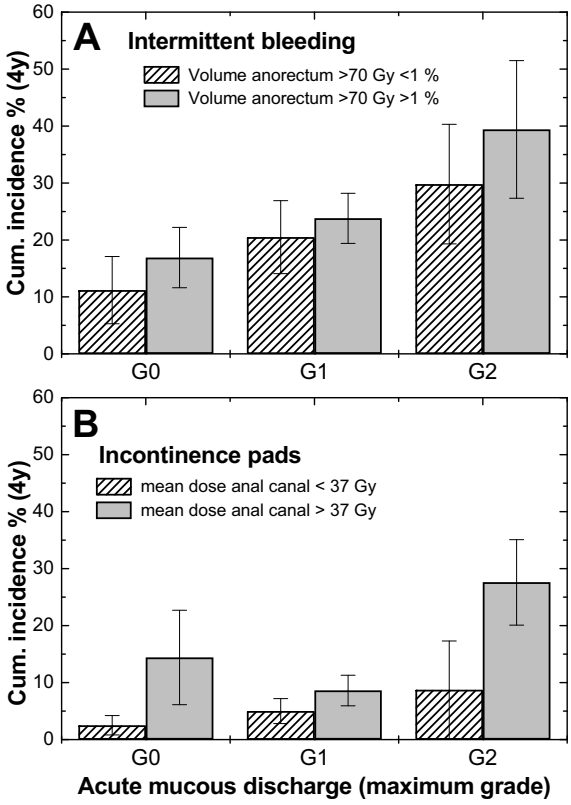

Fig. 4: Cumulative incidences at 4 years (1 SE) for the endpoints 'intermittent bleeding' (A) and 'fecal incontinence' for subgroups (B). The plotted subgroups in each graph are based on the maximum grade of AMD (G0-G2) and on the relevant dose parameter: (A) relative volume of anorectal wall receiving 70 Gy or more, below and above median (1%) and (B) the mean dose to the anal canal, below and above median (37 Gy).

Discussion

The presented analyses strongly suggest that acute tissue reactions have a major impact on the development of late GI toxicity, apart from dose-volume effects. The acute 'maximum score of acute proctitis' and 'maximum score of acute mucous discharge' were strongly related with the majority of the investigated late gastrointestinal (GI) toxicity endpoints. The acute RTOG score showed much weaker associations with the late endpoints. Patients who reported strong acute reactions (acute proctitis) had a higher risk for developing moderate to severe late toxicity (late R/E ≥ G2), up to 40 % (1SE 5 %) cumulative incidence at 4 years against 16 % (1SE 3 %) for the group with no acute reactions.

A second result of this study was that the factor 'pretreatment GI symptoms' remained a significant factor (or borderline) for most endpoints, suggesting that this is an independent predictor for both acute and late GI toxicity. Furthermore, the predictive power of the dose parameters remained at the same level or became weaker (lower HR) for most endpoints at MV analysis. In conclusion, the dose-volume models as described previously by our group (11) can be extended by adding a second relationship between acute and late toxicity and probably with a third relationship between pretreatment symptoms and toxicity. Another significant relationship we reported in this previous analysis was that a history of abdominal surgery was an independent predictor for 'late R/E ≥ G2', 'severe bleeding' and 'fecal incontinence'. This factor remained also significant in the current analyses (results not shown).

Associations between acute and late toxicity in literature

Other studies have also reported data suggesting that consequential late effects play a role in the development of late rectal toxicity. Wang *et al.* [5] used the presence of diarrhea and its severity as an indicator for acute reactions and a predictor for late effects (i.e. proctitis) in patients treated for cervical carcinoma (dose in the range of 40-60 Gy). They tested the relationship between acute and late toxicity in a multivariable analysis, taking into account the prescribed biologically effective dose to the rectal orthogonal maximal point and several clinical factors. They found that the presence of acute diarrhea and its severity was a significant predictive factor for radiation proctitis. They concluded that early damage of acute-responding rectal wall components may contribute to the initiation of late rectal damage. In our dataset, acute diarrhea (and pre-existing diarrhea) was also a strong predictor for late proctitis, but not for other late endpoints.

Denham *et al.* [3] evaluated the peak of acute proctitis as a predictor of late toxicity in prostate cancer patients. In their study, patients were treated with tumor doses between 32 Gy and 70 Gy (median 65 Gy). They found highly significant relationships between acute proctitis and late R/E scores, urgency, diarrhea and frequency. However, they did not include the dose in their models. More recently, O'Brien *et al*. [6] described the relationship between acute and late toxicity, but also in this study dose-volume parameters were not included in the analysis.

Vargas *et al.* [9] reported a dose-volume analysis of predictors for late rectal toxicity and concluded that patients with acute rectal toxicity are more likely to experience late toxicity. They treated 331 prostate cancer patients to a median dose of 75.6 Gy and found that acute toxicity remained a significant factor at multivariable analysis for the endpoint late toxicity grade ≥ 2. They tested the significance of acute toxicity in a MV model with relative dose parameters of the rectal wall in the dose range of 50–72 Gy. Acute rectal toxicity was defined here as grade ≥ 2 (maximum score) according the National Cancer Institute Common Toxicity Criteria.

Our group has previously reported on GI toxicity and its relationships with dose distributions in the anorectal region. [16] These analyses were performed in another clinical dataset, and they showed that the presence of GI symptoms during the acute phase of radiotherapy appeared to be a significant factor predicting late GI symptoms at UV analysis. A similar MV analysis as in the current data set was also performed in this data set (but not published). Several acute symptoms appeared to be predictive for late symptoms at MV analyses: acute mucous discharge, urge and soiling remained predictive factors (p values varying from < 0.001 to 0.1) for the corresponding late symptoms in an MV model with relevant dose parameters found in the study. These previous findings support our present results.

Consequential damage and modeling of late complications

Our data and data from other studies suggest that late toxicity is the result of two different mechanisms, a consequential late effect (CLE) and a direct dose effect, as schematically depicted in **Fig. 1**. In the currently linear-quadratic bio-effect model for predicting late toxicity, this mechanism for CLE is not included. [17] If it is true that late effects are partly a direct result of acute effects, it should be possible to limit late toxicity by limiting acute toxicity. For instance, a hypofractionated radiation scheme with two or three fractions per week instead of five would not only limit acute toxicity but late toxicity as well.

Pretreatment complaints

The predictive value of pretreatment (baseline) GI symptoms that we described for our study population has also been reported by others. Koper *et al.* found that the pretreatment complaint 'higher stool frequency' and also 'overall intestinal symptoms at baseline' were significant factors at UV and MV analyses for late grade ≥ 1 rectal toxicity. [10] Recently, Christie *et al.* published results on late toxicity in prostate cancer patients. They included baseline symptoms in their MV analyses and found baseline proctopathy to be a strong predictor ($p < 0.01$) for the prevalence of Grade 2 or higher proctopathy after 2 to 5 years. [7]

Bleeding

Severe late rectal bleeding is a limiting factor for radiotherapy in prostate cancer. We found no evidence of CLE for this endpoint, whereas we did find a relationship between acute toxicity and late intermittent bleeding. The incidence of severe late bleeding, however, was low and therefore the statistical power to find a significant relationship was limited in our dataset. Furthermore, it is likely that doses of 70 Gy and above are most relevant for bleeding (both intermittent and severe) as described in literature. [18,19] In our study population, only half of the patients were treated to 70 Gy or higher. Possibly our data are not optimal to estimate the relationships between acute reactions, dose parameters, and late bleeding.

Conclusions

Acute tissue damage plays a significant role in the development of late GI toxicity, apart from dose-volume effects and the impact of pretreatment symptoms. This suggests the presence of a consequential component in the development of late GI toxicity.

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