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Profiles and Time Course of Acute Radiation Toxicity Symptoms during Conformal Radiotherapy for Cancer of the Prostate

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Symptoms of gastrointestinal toxicity are dose-limiting for pelvic radiotherapy (RT). Existing toxicity registrations (RTOG/EORTC) are helpful in defining maximal tolerated doses, but tend to underestimate the total toxicity burden by excluding several minor complaints. We have applied a more detailed and quantitative recording of symptoms and related these scores to RT-induced endoscopic and histopathologic changes. Prevalence and severity of specific toxicity symptoms were recorded before, during (weeks 2 and 6) and 2 and 8 weeks after RT in 96 patients undergoing external beam RT for localized prostate cancer. RTOG/EORTC acute toxicity and ad hoc total toxicity scores (TTS) were recorded. TTS scores were calculated by adding scores based on visual analog scale (VAS) grading of individual symptoms. Fifty of the patients also underwent sequential proctoscopy with mucosal biopsy. Individual symptoms increased, but differed in prevalence and intensity during and after RT. TTS increased during the entire treatment course in spite of normalizing histopathologic and endoscopic changes from week 2 onwards. Twenty-seven patients had no RTOG/EORTC toxicity, four had grade 3 and none had grade 4 toxicity. All patients with grade 0 had increased TTS. Thus, TTS appeared more sensitive than RTOG/EORTC scoring. The study demonstrates that multiple toxicity symptoms contribute to total toxicity in response to pelvic RT. TTS is a feasible and sensitive method for detecting and quantifying acute toxicity and unveils morbidity which remains hidden with the RTOG/EORTC score system. The development and timing of symptoms may give clues to pathogenesis, treatment, and prophylaxis.

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Symptoms of acute radiation toxicity occur in the majority of patients during radiotherapy (RT) for malignant pelvic disease. The symptoms vary in intensity and character, and may be sufficiently severe to forestall optimal completion of the planned treatment. Radiation toxicity depends on total irradiation dose, fraction size, fraction interval, treatment time, and treatment volume. The severity of acute radiation toxicity symptoms is one of the main predictors for the development of chronic rectal injury (1, 2) and for tumor response (3, 4). Much effort is therefore applied in individual tailoring of the treatment, and several measures have been developed to minimize extra-tumoral irradiation (positioning of the patient, special treatment boards ('belly board'), surgical abdominopelvic partitioning with omentum or displacement of the gut by intra-abdominal absorbable meshes). Pharmacologic prophylaxis and treatment have so far not been very helpful (5, 6).

Symptoms tend to increase in frequency during RT and decrease after cessation of radiation (7, 8). The mechanisms by which symptoms are elicited are poorly understood, as recently reviewed (9). Apart from acute mucosal inflammation, dysmotility seems to play an important role. Current methods of toxicity recording have low sensitivity. The aim of the present study was to assess the prevalence, severity and time related progression of abdominal symptoms during pelvic RT by accurate recording of individual symptoms and calculation of a score for total toxicity burden. The results are compared to the existing RTOG acute toxicity score and related to RT-induced endoscopic and histopathological changes, and discussed in relation to previously known factors that may be of pathogenic importance.

MATERIAL AND METHODS

Radiotherapy

Patients with organ confined prostate cancer (T1c–T3, N0–X, M0) scheduled to undergo curative pelvic RT were included consecutively. Patients with significant gastrointestinal disease (inflammatory bowel disease, gastrointest-

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inal cancer, coeliac disease) were not included. All patients underwent conformal external beam RT administered as single daily doses of 2 Gy to a total dose of 66–70 Gy over $6\frac{1}{2}$–7 weeks, typically as four fields, given five days a week with weekend breaks. The treatment was planned individually and was given as 6–18 MV photons. T1 and T2 tumors were treated with a margin of 10 mm against the rectum, T3 tumors were initially given whole pelvic field up to 50 Gy, followed by radiation to the prostate only, with 5 mm margin against the rectum. The rectum was shielded by customized blocks or multileave collimators. Calculated doses to the anterior and posterior rectal wall at the level of the mucosal biopsy were 100% and 40–60% of prescribed dose, respectively, and in no case more than one third of the rectal circumference was included in the field.

Symptoms

Symptoms were recorded prior to treatment (referred to as 'week 0'), at 2, 4, and 6 weeks into treatment (referred to as 'week 2', 'week 4', and 'week 6', respectively), and 2 weeks and 8 weeks after end of treatment (referred to as 'week 9' and 'week 15', respectively). The prevalences of abdominal pain, loose stools, macroscopic blood in the stools, tenesmus, bloating, and fecal incontinence were recorded in all patients. The last 47 patients examined also graded the severity of symptoms (pain, loose stools, tenesmus, bloating, and nausea), using a visual analogue scale (VAS). A symptom registration form was filled in at each visit based on the doctor's detailed interview. The VAS scales were marked by the patient supervised by the doctor. An ad hoc global grading based on these symptoms was constructed by adding the VAS scores of each symptom at each timepoint, expressing a 'total symptom score' (TSS). The RTOG/EORTC acute toxicity scale (10), shown in Table 1, was applied in all patients.

Endoscopy

Rigid proctoscopy was performed at week 0, week 2, and week 6. Endoscopic appearance was assessed using a four-point scoring system (11, 12) where 0 = normal mucosa; 1 = edema and/or loss of normal vascular pattern, granularity of the mucosa; 2 = friable mucosa (visible, induced bleeding on examination) or peteciae; and 3 = spontaneous hemorrhage or visible ulcers.

Histology

During proctoscopy, rectal mucosal cup biopsies were obtained from the posterior rectal wall 10 cm above the anal verge. The results from quantitative histology have been reported previously (12).

Ethics

The protocol was approved by the Regional Committee for Medical Research Ethics. Written, informed consent was obtained from all patients before inclusion in the study.

Statistics

Symptom severity, endoscopic scores, and TTS at different timepoints were analyzed with paired t-tests using GraphPad Prism (GraphPad Software Inc., USA). Symptom prevalences were analyzed using McNemar's test. Statistical significance was defined as p-values less than 0.05.

RESULTS

A total of 96 patients were included (mean age: 65.6 ± 6.9 years, range: 49–78 years). Generally, symptoms appeared early and then gradually increased in prevalence (Fig. 1) and severity (Fig. 2) during the rest of the treatment. No patient had to reduce, postpone, or stop RT because of radiation toxicity.

Loose stools

Loose stools were an early and the most common symptom. The prevalence increased significantly up to week 2 and was still present in the majority even 2 months after cessation of treatment. The subjective discomfort occurred early and was considerable as expressed on the VAS scale.

Tenesmus

Tenesmus increased significantly in prevalence during the entire treatment period, occurred in one fifth of the patients, and was still prevalent at week 15 ($p < 0.05$). However, most

Table 1

RTOG/EORTC acute radiation morbidity scoring criteria for pelvic radiation (10)

0	1	2	3	4
No change	Increased frequency or change in quality of bowel habits not requiring medication/rectal discomfort not requiring analgesics	Diarrhoea requiring parasympatholytic drugs/mucous discharge not necessitating sanitary pads/rectal or abdominal pain requiring analgesics	Diarrhoea requiring parenteral support/severe mucous or blood discharge necessitating sanitary pads/abdominal distension (flat radiograph demonstrates distended bowel loops)	Acute or subacute obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion

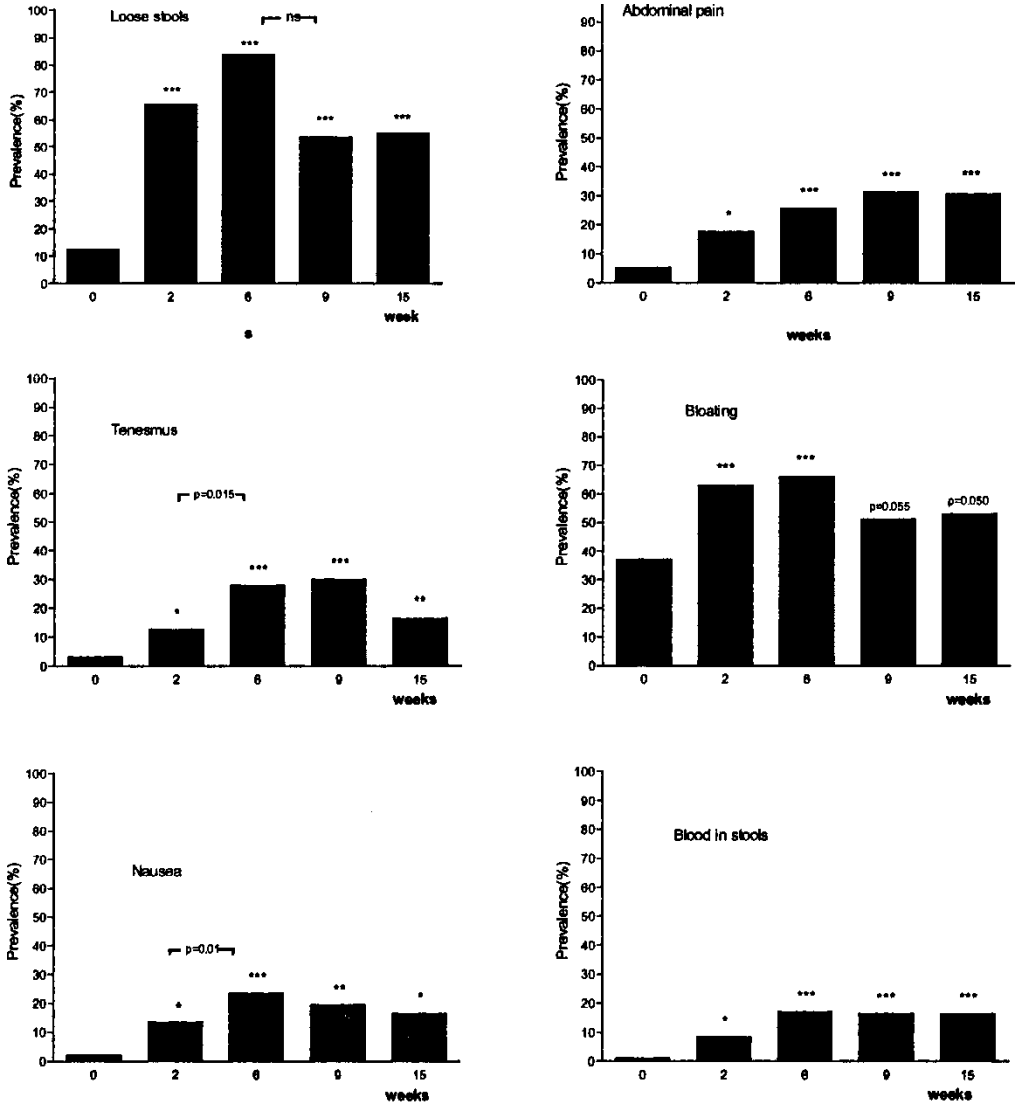

Fig. 1. Prevalence of toxicity symptoms (mean) before, during (weeks 2 and 6), and after (weeks 9 and 15) radiotherapy. The p-values refer to pretreatment. *** = $p < 0.001$, ** = $p < 0.01$, * = $p < 0.05$.

of the patients scored low on tenesmus intensity on the VAS scale.

Nausea

The prevalence of nausea increased significantly early and tended to increase further during treatment ($p = 0.09$), persisting unchanged at week 15. However, this appeared to be a troublesome symptom only for a few patients, the majority scoring low on the VAS scale.

Abdominal pain

The prevalence of abdominal pain increased significantly from week 0 to week 2 and week 4, but did not change significantly thereafter. Pain intensity as recorded on the VAS scales was generally low, but increased significantly during the later part of the treatment, reaching its maximum 2 weeks after end of RT (week 9), but was not significantly increased at week 15 compared to pre-treatment.

Bloating

Bloating is a common symptom in the general population and occurred in over 30% of patients before treatment. However, compared to week 0 a significantly increased prevalence was observed during the entire treatment and post-treatment period, although the subjective discomfort as expressed by the VAS recordings was not increased at any time.

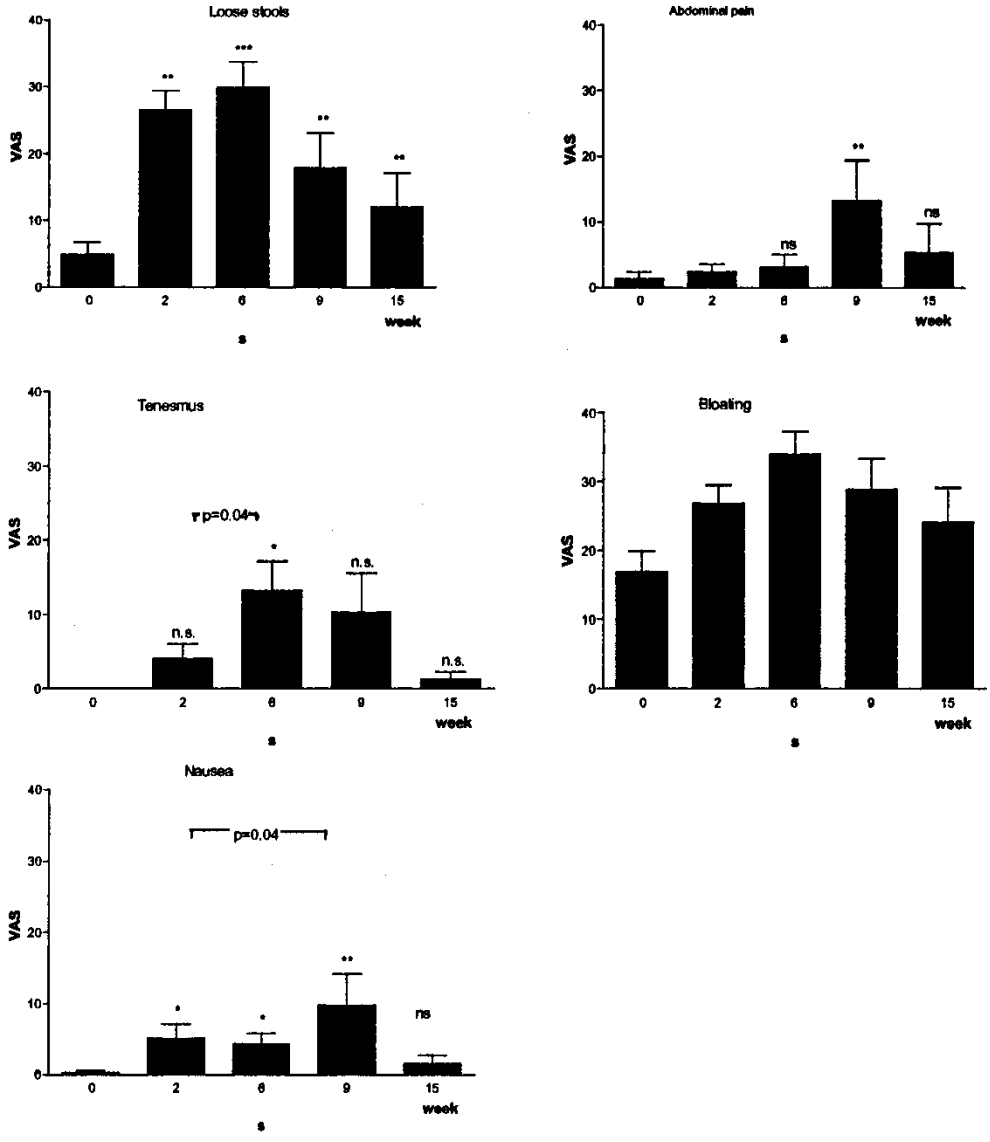

Fig. 2. Symptom severity expressed as VAS-scores (mean) before, during (weeks 2 and 6), and after (weeks 9 and 15) radiotherapy. *** = $p < 0.001$, ** = $p < 0.01$, * = $p < 0.05$.

Blood in the stools

Blood in the stools was seldom recorded. However, a significantly increased prevalence occurred early during the treatment period and was maintained at week 15.

Fecal incontinence

Fecal incontinence (Fig. 3) was recorded in a few patients at week 2, without any further increase thereafter. No data from week 9 and week 15 were recorded.

The TSS score (Fig. 4) increased significantly during the radiation course. The scores had not fully returned to pretreatment values at week 15 ($p = 0.07$). If the 25% percentile was arbitrarily used as a cut off for clinical significance, only five patients (11%) scored consistently below this during the RT course. One patient scored consistently 0 throughout the RT.

Grade 3 RTOG/EORTC acute gastrointestinal toxicity occurred in four patients: in three at week 6 and in one at week 9. None experienced grade 4 toxicity (Table 2). 19 patients had maximum RTOG/EORTC grade 2 symptoms, and 30 patients had maximum grade 1 symptoms, while 43 patients had no or only minor symptoms, not recorded by the RTOG/EORTC toxicity scale. From week 2 no significant change was observed in RTOG/EORTC grade.

Endoscopy

All patients examined had normal pretreatment endoscopic findings (Fig. 5). Scores of radiation injury were maximal after two weeks. Two weeks after cessation of radiation

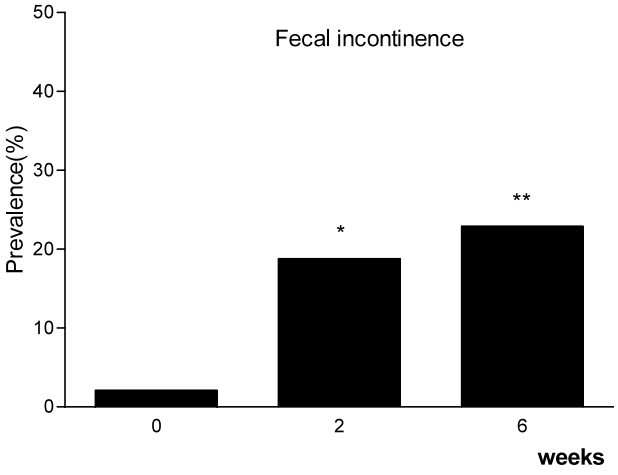

Fig. 3. Fecal incontinence before and during radiotherapy. ** = $p < 0.01$, * = $p < 0.05$. No follow-up data from week 15 were available.

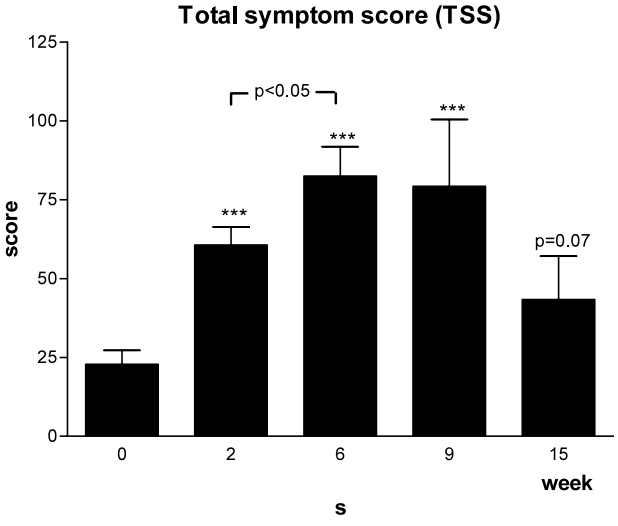

Fig. 4. The total symptom scores (TTS) before, during (weeks 2 and 6), and after (weeks 9 and 15) radiotherapy. The p-values refer to pretreatment. *** = $p < 0.001$.

(week 9) a significant reduction compared to week 6 was observed ($p < 0.01$).

Biopsies

The histopathologic changes have been published previously (12), showing an early, statistically significant increase in inflammation, with attenuation after week 2 despite ongoing RT. At week 6 inflammatory parameters were not significantly different from pretreatment.

DISCUSSION

The present study gives a detailed, sequential, and overall picture of the acute side effects of pelvic RT for prostate cancer. Most symptoms of acute radiation toxicity increase early during ongoing pelvic RT and are not attenuated until several weeks after the end of treatment. The individual symptoms as well as the total toxicity burden caused by these symptoms are significant and have an impact on daily well-being.

Table 2

RTOG grading during and after radiotherapy

RTOG grade	Week 2 Patients (%)	Week 6 Patients (%)	Week 9 Patients (%)
0	63 (66)	41 (43)	55 (57)
1	26 (27)	35 (36)	27 (28)
2	7 (7)	17 (18)	13 (13)
3	0 (0)	3 (3)	1 (1)
4	0 (0)	0 (0)	0 (0)

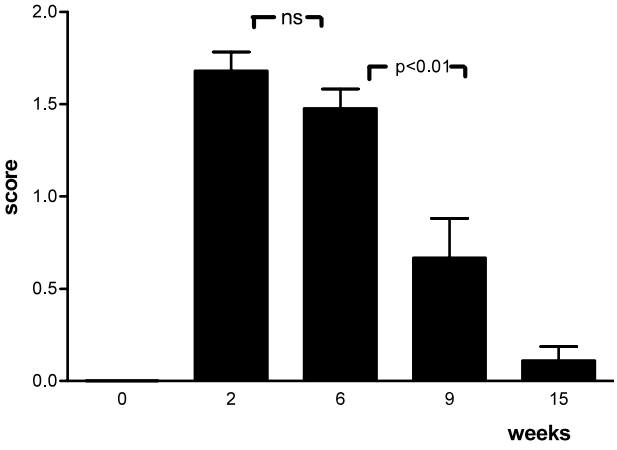

Fig. 5. Endoscopy scores before and during radiotherapy.

Loose stools are common and cause considerable and continuing discomfort, while bloating, nausea, and abdominal pain do not cause much concern. Rectal bleeding does occur in a small proportion, usually without causing anemia, and apparently unrelated to inflammation. Fecal incontinence is a very troublesome symptom in a significant number of patients during and after RT. The frequency increases after the end of treatment (13), and is one of the most incapacitating symptoms in chronic radiation proctitis.

The RTOG/EORTC acute toxicity scoring system (10) provides a global assessment and does not differentiate between the prevalent symptoms. When expressed by this system, toxicity appears low, as shown in previous studies (14–16). Koper et al. (17) found no grade 3 or 4 acute toxicity among 266 prostate cancer patients. Only 5–10% of patients will experience symptoms of RTOG/EORTC grade 3 or 4 (18, 19). In our study only four patients (4%) had grade 3, and none grade 4. The four grade 3 patients had high TSS scores. In contrast to the single asymptomatic patient with no increase in TSS, 43% scored RTOG/EORTC = 0.

The use of the ad hoc grading system as a severity index assumes that the symptoms considered were of equal clinical importance. This assumption and the lack of formal validation limit the applicability of the system. However, it demonstrates a steady increase in the total toxicity burden throughout the treatment course. Two months after cessation of RT, the TSS had abated and was not significantly different from pretreatment values, which is in agreement with other studies (8, 18, 20). However, not all patients were symptom-free at week 15, a trend was observed ($p = 0.07$) towards persistence of symptoms, of which loose stools and abdominal pain were dominant. In contrast to the RTOG/EORTC score system, our method appears more feasible for the clinical setting by showing a differentiated picture and by quantifying the total toxicity burden even in patients who do not present increased RTOG/EORTC scores. The results underline the need for more sensitive registration of acute pelvic radiation toxicity. High sensitivity score systems are important tools when comparing different treatment regimes. Recently, after the completion of the current study, an elaborate, prostate cancer specific, questionnaire-based programme (21), encompassing urinary, gastrointestinal, and sexual functions has been proposed. Validation of the programme demonstrates high reliability and responsiveness. This programme has recently been used in a prospective evaluation after conformal RT for prostate cancer in 287 patients (22) and in 267 patients treated by the urethral catheter BeamCath® technique (20).

The development of acute clinical radiation toxicity is multifactorial and should be sought in the pathogenesis of the intestinal injury. Important mechanisms considered are: (1) inflammation; (2) malabsorption/hypersecretion; (3) dysmotility; and (4) changes in luminal factors. These mechanisms are interdependent through an extensive 'cross-talk' involving neural, endocrine, and paracrine signalling.

1) *Inflammation*. Endoscopically, inflammation is rapidly attenuated after cessation of RT (Fig. 5). Histopathologically, the inflammation in the superficial mucosal layers decreases from week 2 in contrast to the time-dependent development of symptoms. However, persisting inflammation was demonstrated in the lamina propria and the glands (12), possibly contributing to the clinical picture. Following a single radiation dose, thickening of the muscularis mucosae has been demonstrated (23), but no systematic data exist on inflammatory changes in or around the smooth muscle layers or in the ganglia of the enteric nervous system during fractionated RT.
2) *Malabsorption/hypersecretion*. Radiation-induced impairment of water and electrolyte absorption has been demonstrated in rat experiments (24). Injury of the small bowel may result in malabsorption of bile acids, vitamin B12, fat, and glucose.
3) *Dysmotility*. There are few reports on motility studies in patients with acute radiation enteropathy. Radionucleic absorption tests (25) lend support to motility disturbances, probably through local neuroendocrine mechanisms. Changes in gastric emptying rate are independent of radiation field (pelvic, thoracic, abdominal) (26), suggesting neurogenic mechanisms. Most studies on motility have concentrated on the small intestine. Results from such studies may, however, to a certain extent be applicable to colonic phenomena. Experimental animal studies do not necessarily reflect the situation in humans undergoing highly fractionated RT. Usually, in animal studies radiation is given in one dose to the abdomen, resulting in profound motility changes (27). An increased incidence of giant colonic migrating contractions coinciding with episodes of diarrhoea is seen during fractionated radiation (28, 29). Release of 5-HT induces vomiting and diarrhoea. The antiemetic and antidiarrhoeic effects of specific 5-HT3 receptor antagonists during RT indicates an increased 5-HT release (30, 31).
4) *Luminal factors.* Most probably, hostile luminal factors (bacteria, viruses, enzymes, antigens) influence the morphologic and functional changes in the gut wall during radiation. No study on colonic intraluminal microbiological milieu during radiation is available. Radiation-induced decrease in fecal bifidus excretion was reversed by oral application of *L. acidophilus* (32), and patients receiving oral *L. acidophilus* prophylaxis had reduced incidence of diarrhoea during pelvic RT (33).

A new categorization of intestinal radiation injury has recently been proposed (34), in which three basic effects are described that alone or in combination underlie the pathophysiology and the clinical picture. The *cytocidal* effects occur within few days after radiation exposure in tissues with rapid cell renewal, such as epithelial surfaces. *Indirect* effects occur as results of damage to other tissue structures or as 'by-stander' phenomena, while *functional* effects reflect changes in molecular and gene expression in damaged tissue. Radiation injury occurs as a result of interaction of several mechanisms. The acute inflammation reflects both cytocidal, functional, and indirect effects, namely rapid development of injury, activation of stress protein genes, and upregulation of cytokines, growth factors, and chemokines.

The progression from acute to chronic radiation injury occurs in 5–20% (5) and is of great clinical significance. Detailed studies of the acute reaction is of basic importance in this issue as modifications by pharmacotherapy or other measures during the acute response may influence the risk of developing late injury. Two or more simultaneously occurring biomolecular changes may have opposite effects

on gut motility, the significance of changes in morphology and/or function in different cells and compartments is unknown, and the 'cross-talk' between cells and tissues is only partly understood. Therapeutic and prophylactic intervention strategies depend on characterization of mechanisms of injury at a cellular and molecular level.

In summary, we have demonstrated a differential development of acute pelvic radiation toxicity symptoms during and immediately after the radiation course, and an increasing total symptom burden in most patients, not readily picked up by the conventional RTOG/EORTC registration system. A simple but detailed and clinically feasible registration method has been used. Most of the symptoms may reflect motility disturbances, some of which may be secondary to radiation induced inflammation, but for the majority not directly related to the inflammatory changes. A detailed description of the individual symptoms illustrates different pathogenic mechanisms as targets for development of specific pharmacotherapy and prophylaxis and may give clues for future research.

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