

Daily-Diary Evaluated Side-Effects of Conformal versus Conventional Prostatic Cancer Radiotherapy Technique

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Conventional 4-field box radiotherapy technique induces high morbidity for patients with localized prostatic cancer. Using a patient daily diary, the present study compared side-effects after conventional radiotherapy with conformal radiotherapy for prostate cancer. Fifty-eight patients treated with the conventional technique (with or without sucralfate) were compared with 72 patients treated with conformal technique. The patient groups were compared with an age-matched control population. Patients treated with conformal technique were also evaluated regarding acute and late urinary problems. Results showed that patients treated with conformal technique reported significantly fewer side-effects as compared with conventional technique. Patients treated with sucralfate also showed slightly decreased intestinal morbidity in comparison to non-sucralfate group. Acute and late morbidity evaluated by the patients was decreased after conformal radiotherapy as compared with the conventional technique. Sucralfate may be of value if conformal radiotherapy is used for dose escalation in prostatic cancer patients.

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Prostate cancer (PC) is now emerging as one of the most common malignancies in males, and Swedish men have among the highest incidences in PC in the world reaching an age standard incidence of 113/100 000 men (1). External beam radiotherapy, introduced in the 1950s, has been a cornerstone in the treatment of patients with PC. Both early and advanced forms of PC have been rationally treated, and 15 years' bench-marked data are now becoming available (2, 3). Those data shows similar relapse rates as with surgery (4).

Treatment techniques and treated volumes have changed considerable over the years. Historically only an 8 × 8 cm field size was used (5), but in the bulky prostate this field size would miss up to 50% of the vesicles and 25% of the prostate as determined by computer tomography (CT)-scans (6, 7). This leads to larger field sizes with 4-field box techniques during the 1970's, but more normal tissue was unnecessarily irradiated with increased side-effects. A combination of these techniques was developed by Bagshaw (5), who used large fields encompassing the pelvic lymph nodes up to 50 Gy and then decreased field size up to full dose (5).

Data on urinary and intestinal side effects presented during the 1980's indicated a quite high percentage of minor problems from the intestine (blood, mucus) and from the urinary tract (urgency, leakage (8–18)). This was also shown recently with a self-assessment questionnaire (19). In an attempt to decrease these problems Henriksson et al (20) in a prospective, controlled, randomized, double-blind study showed that sucralfate decreased both acute and late intestinal toxicity, in patients treated with radiotherapy where the pelvic area was involved (20, 21). Improved planning of external beam radiotherapy has now rapidly emerged by using a CT-based three-dimensional (3-D) planning and conformal beam radiotherapy (7, 22). This technique permits better sparing of the surrounding normal tissue and gives a better opportunity to increase tumor dose within a limited area. Sandler et al. (7) found no grade III or IV toxicity evaluated by the treating doctor according to the RTOG scale with 19-month medium follow-up of 20 patients who had been treated with a 6-field conformal technique. Reports are now presented regarding decreased acute and late morbidity (7, 23), but these data are all based on the doctor's evaluation and not

on the patient's own evaluation. Others have indicated no differences, and that dose would be the most important factor for toxicity (24). Acute and late morbidity was therefore studied using a patient daily diary in patients treated with conventional 4-field box technique, including pelvic nodes, and compared with patients treated with the 3-D based conformal radiotherapy. These groups were also compared with an age-matched control population.

MATERIAL AND METHODS

Methods

The present study includes two patient groups. One group of patients was treated with conventional 4-field box technique including the pelvic region. Those patients were also included in a double-blind, prospective, randomized study comparing placebo and sucralfate during treatment (21). Seventy patients were included in that study. The study group also contained 7 patient with bladder carcinoma, who were excluded in this study. Four patients were not assessable in the early phase. The remaining numbers of patients with conventional treatment included in this study were 58. The second group of patients ($n = 72$) was treated between 1992 and 1994 with 3-D conformal radiotherapy against localized PC. The included patients had cytologically or histologically verified, localized PC. For each patient a clinical examination, a bone scan, pulmonary x-rays and blood tests indicating no metastatic spread, were performed. A staging operation, routinely via the extraperitoneal approach, was performed on some of the patients for histological examination of pelvic lymph nodes. Thirty-seven patients (64%) in the conventionally treated patient group and 49 (68%) in conformal group had a nodal and tumor status of T0–T4pN0M0. Twenty-one (36%) and 23 (32%) patients had a carcinoma status of T0–T4NXM0 in the conventional and conformal patient groups respectively. From January 1992, after the installation of Helax TMS 3-D dose planning system (Uppsala, Sweden), treatment technique was changed from the conventional 4-field box technique to the 4-field 3-D conformal therapy in our department. The two patient groups were also compared with an age-matched control group of 141 men from the same region as the population of treated patients with PC (19).

The study was approved by the local ethical committee.

Treatment technique

All patients were given five fractions per week, with a daily dose of 2.0 Gy. The treatment was given with a 20/50-MV (Race-track Microtron, Scanditronix, Uppsala, Sweden) or with a 20.9-MV (Microtron, Scanditronix, Uppsala, Sweden). The treatment technique in patients with conventional CT-based 4-field box technique ($n = 58$), included the pelvic area up to 50 Gy and then shrinking field technique after 50 Gy up to total dose in the prostatic

region. Forty-one patients in the conventional group received treatment with shrinking fields. The mean frontal size was 12.5×16.5 cm and the mean lateral field size 9.9×16.5 cm in the conventional treatment group. The mean shrinking field size was $9.0 \times 9.0 \times 9.0$ cm (anterior-posterior-lateral). The CT-based 3-D conformal technique was given with multileaf collimators (Race-track) or with externally blocked field. The mean field size for the conformal group was 11.2×10.3 cm frontal and 10.3×10.3 cm lateral. Mean total dose for the conventional and conformal therapy group was 63.6 Gy and 65.15 Gy respectively. Higher doses were given to the conformal group due to the institutional strategy to increase doses in the prostate.

Evaluation

All patients were given the same daily diary (21) and were instructed to report the daily intestinal function as listed in Table 1. To the 72 patients treated with conformal technique (except the 16 first patients) the daily diary also contained questions about urinary function (Table 1). The patients started with the daily diary on day 1 of treatment and continued for 8 weeks (12 weeks for the patients treated with conformal therapy). A new daily diary was sent out at follow-up 15–16 weeks (2 months after ending radiotherapy) and 52 weeks (1 year) after the end of radiotherapy. In this diary the patients were asked to record their intestinal habits (and urinary habits) during a 2-week period. This diary was mailed back to the administering nurse and fed into a computer. The daily reported values were summarized to weekly mean values. Considering the number of daily stools and the daily consistency during the week the physician consecutively converted intestinal function into a weekly diarrhea score, Table 2. The intestinal and urinary function of the control group was reported on a self-assessment questionnaire (19), and therefore a statistical comparison between control and patient groups was not performed.

Statistical methods

The statistical analyses were performed by using the SPSS ver. 6.1.3 and Status II software package. To evaluate differences between patient and control groups the non-parametric Wilcoxon's rank-sum test was used. Correlation coefficients were calculated according to Pearson and were considered significant when $p < 0.05$.

RESULTS

Patients

Fifty-eight patients in the conventional group completed the early phase diary (week 1–16). The assessable number of patients in the early phase in the conformal group was 64. Regarding the 1-year follow-up period, 53 patients in the conventional group and 36 patients in the conformal group completed the diary.

Table 1
Scores for scales and single items in the daily diary

	No. of items		Score
General part scales			
Medication (Sucralfate, Emepron**)	2	Numbers	0- >
Symptom scales			
Intestinal problems			
Stool frequency (day, night)	2	Numbers	0- >
Consistency	1	Likert	1-4*
Mucus	1	No/Yes	1-2
Blood	1	No/Yes	1-2
Abdominal cramps	1	Likert	0-3 #
Urinary problems**			
Urinary frequency (day, night)	2	Numbers	0- >
Starting problems	1	Likert	0-3 #
Urgency	1	Likert	0-3 #
Pain	1	Likert	0-3 #
Blood	1	No/Yes	1-2
Total	14		

* Likert scale where 1 = Watery, 2 = Loose, 3 = Firm, 4 = Hard.

= Likert scale where 0 = None, 1 = A little, 2 = Quiet a bit, 3 = Very much.

** = Urinary problems only evaluated in the conformal group with a daily diary (except the first consecutive conformal patients).

Intestinal side effects during radiotherapy (acute effects)

Mean numbers of daily stools 1 to 8 weeks after initiation of radiotherapy treatment are shown in Fig. 1. The frequency of daily stools significantly increased in all three groups during radiotherapy treatment. Both the conformal radiotherapy technique and the conventional radiotherapy with sucralfate treatment significantly decreased the mean numbers of daily stools as compared with conventional treatment, but the numbers were still clearly increased compared with the stool frequency of the control population (19).

Diarrhea score, combining both the stool frequency and consistency of the stools (Table 2), increased significantly in all patient groups during the radiotherapy period. During conformal radiotherapy, the diarrhea score was significantly decreased compared with that by conventional treatment technique (Fig. 2). During the last week of treatment, 3-D conformal technique caused less problems (ns) with loose stool consistency compared with the 4-field box technique both with or without sucralfate (Fig. 3).

A significant decrease 5 weeks after radiotherapy start, in high diarrhea score (2 + 3), occurrence of mucus and

abdominal cramps, was observed for patients treated with the conformal technique (Table 3). Patients in the conformal group and in the sucralfate group used less anti-diarrhea medicaments (Table 3).

Late intestinal side-effects

Both patients treated with the conformal radiotherapy technique and the conventional technique with sucralfate had significantly lower mean numbers of daily stools at 1-year follow-up compared with those treated with the conventional box technique (19) (Fig. 1), almost reaching the stool frequency of age-matched men (1.5/24 h) in northern Sweden (19). After completion of radiotherapy, a rapid decrease in stool frequency was seen in both groups already after 2 months (at 15-16 weeks). Thereafter stool frequency in the conformal group continued to decrease, and did not differ significantly from values prior to the start of treatment at 1-year follow-up.

In patients treated with conformal radiotherapy the diarrhea score indicated significantly less side-effects at 15-16 weeks and 1-year follow-up compared with those treated with conventional box technique (Fig. 2). Up to 1 year the diarrhea score in the conformal group continued to decrease and was also significantly lower than in the sucralfate group. Compared with diarrhea scores reported at the start of treatment all three groups showed significantly higher diarrhea scores at 1-year follow-up.

In both conventional and conformal groups, stool consistency was normalized at 15-16 weeks and at 1-year follow-up compared with the start values (Fig. 3). Patients in the placebo group reported looser consistency at 1-year follow-up than at the start of radiotherapy. Patients

Table 2

Description of the diarrhea score value

Scale	Description
0	No change in bowel habit (normal)
1	A small increase in frequency and soft stools
2	A more pronounced increase in frequency and loose stools
3	Marked increase in frequency and watery stools

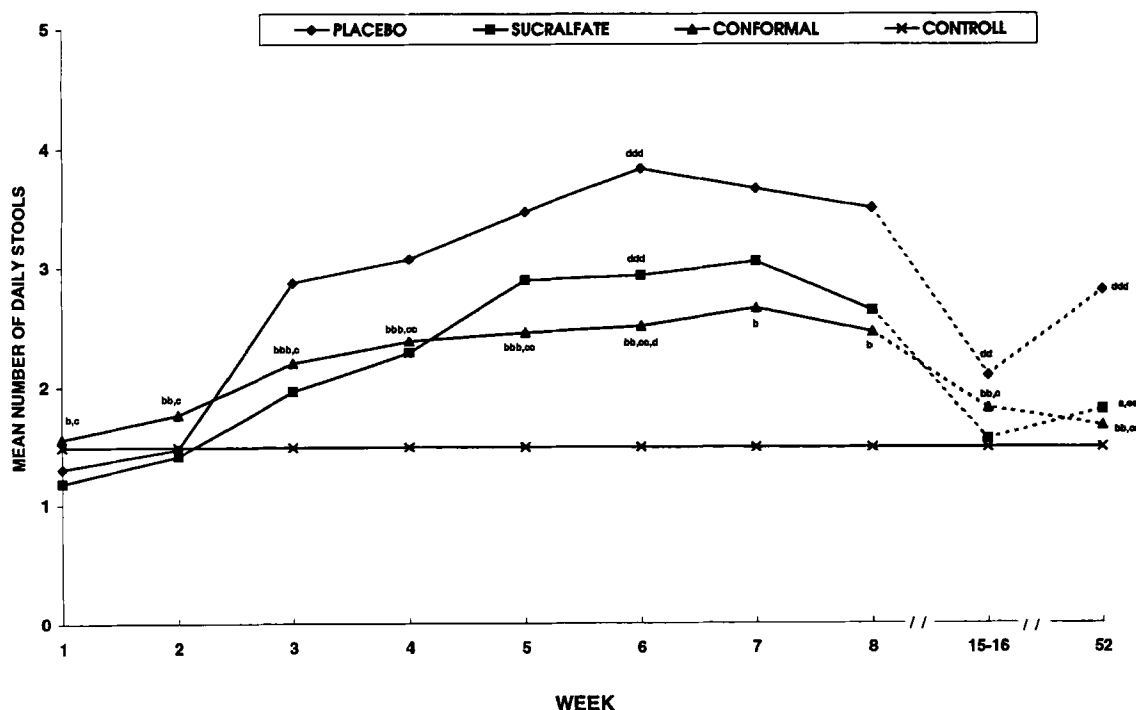


Fig. 1. Mean number of daily stools in the conventional (placebo or sucralfate) and conformal patient groups and a control group, 1 to 8 weeks, 15–16 weeks and 52 weeks after initiation of radiotherapy treatment.

Sucralfate vs. placebo group; a = $p < 0.05$.

Conformal vs. placebo group; b = $p < 0.05$; bb = $p < 0.01$; bbb = $p < 0.001$.

Conformal vs. sucralfate group c = $p < 0.05$; cc = $p < 0.01$.

Difference from stool frequency at the start of radiotherapy; d = $p < 0.05$; dd = $p < 0.01$; ddd = $p < 0.001$.

Difference from stool frequency at the end of radiotherapy; e = $p < 0.05$; ee = $p < 0.01$; eee = $p < 0.001$.

treated with conformal therapy reported significantly looser stools than the box-treated groups at 2–3 months' follow-up but at 1-year follow-up this was normalized.

Table 4 shows parameters regarding late side-effects 1 year after initiation of radiotherapy. Patients treated with conformal radiotherapy included a significantly lower number of patients with high diarrhea score and less occurrence of mucus. The results (Table 4) also show that all parameters were in favor of the conformal group compared with the conventional radiation treatment group.

Urinary problems

Urinary symptoms were only recorded for the conformal group. The mean urinary frequency (during 24 h) increased significantly from 8.8/24 h to 11.7/24 h during the radiotherapy treatment period from week 1 to the end of treatment at week 7 ($p = 0.004$). A rapid normalization of urinary frequency, 8.9/24 h, occurred, not significantly different from pretreatment frequency, already within 2–3 months' follow-up after radiotherapy and continued to decrease up to 1 year (mean 8.2/24 h), not significantly different from the frequency at the start of treatment. However, a higher urinary frequency was reported than that of an age-matched control population (6.2/24 h) (19).

Regarding urgency and pain related to urination, an expected and significant increase in problems was reported during the treatment period. Twenty-nine percent ($n = 16/55$) indicated some kind of urgency (mean = 0.6) at the start of treatment and 55% ($n = 29/53$) at the end (mean = 1.1). Twenty-four percent ($n = 13/55$) reported pain (mean = 0.2) in relation to urination at the start of radiotherapy and 40% ($n = 21/53$) at the end (mean = 0.9). Thirty-six percent ($n = 20/55$) of the patients indicated some kind of starting problems (mean = 0.7) at the beginning of radiotherapy treatment and 51% ($n = 27/53$) reported problems at end of treatment (mean = 1.0). The problems were of low magnitude as reported on the Likert scale with a range from 0 to 3. All three types of urinary problems had decreased significantly already 2 months after ending the treatment. At 1-year follow-up, the numbers of patients that indicated any problems (>0) with urgency, pain related to urination and starting problems, were very low; 16%, 9% and 17% respectively. In comparison to the initiation of radiotherapy a significant decrease of starting problems (mean = 0.2) and urgency (mean = 0.2) was seen at 1-year follow-up.

Two patients (4%) reported macroscopic hematuria at the start of radiotherapy, and one patient (2%) reported blood week 4 during radiotherapy and 1 year after therapy. No correlations were found between T-stage and

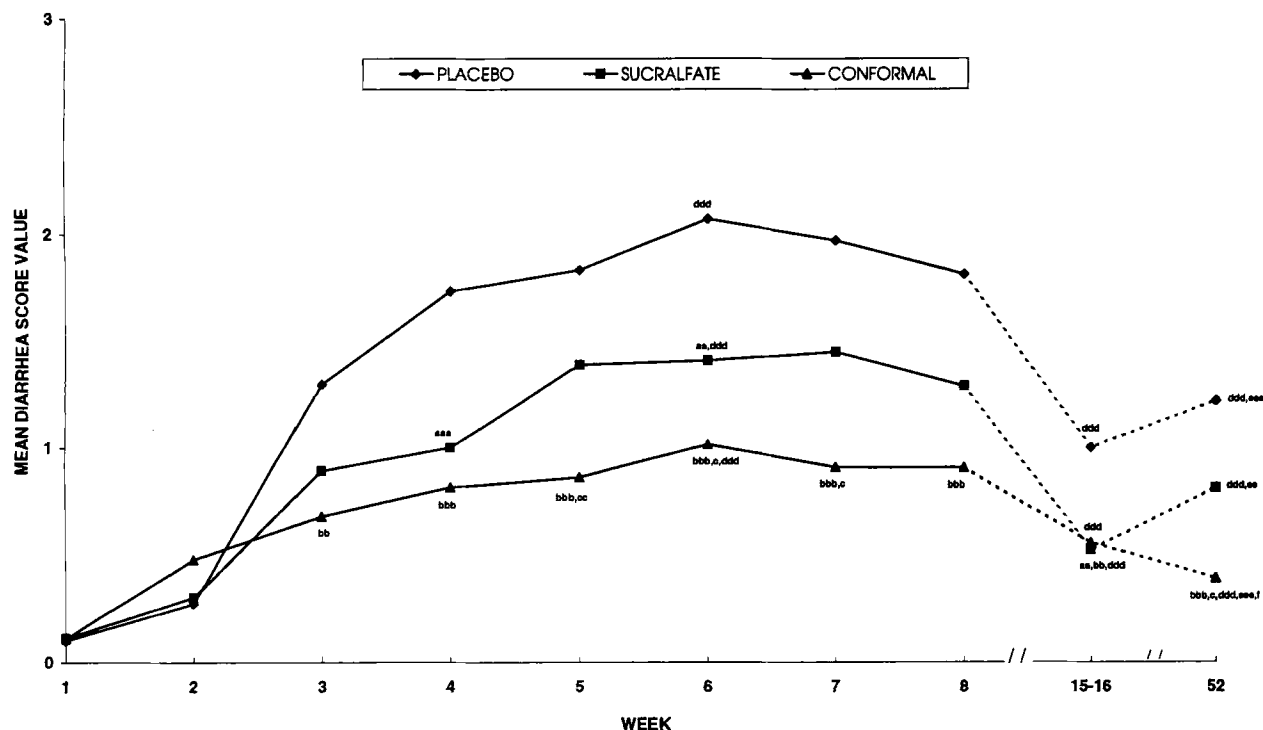


Fig. 2. Mean diarrhea score according to Table 1 in the conventional (placebo or sucralfate) and conformal patient groups, 1 to 8 weeks, 15–16 weeks and 52 weeks after initiation of radiotherapy treatment.

Sucralfate vs. placebo group; a = $p < 0.05$; aa = $p < 0.01$; aaa = $p < 0.001$.

Conformal vs. placebo group; bb = $p < 0.01$; bbb = $p < 0.001$.

Conformal vs. sucralfate group c = $p < 0.05$; cc = $p < 0.01$.

Difference from diarrhea score at the start of radiotherapy; ddd = $p < 0.001$.

Difference from diarrhea score at the end of radiotherapy; ee = $p < 0.01$; eee = $p < 0.001$.

Difference from diarrhea score at 15–16 weeks follow-up; f = $p < 0.05$.

urinary symptoms but there was high correlations between starting problems and urgency ($r = 0.80$; $P < 0.001$) and between urgency and pain ($r = 0.80$; $P < 0.001$).

DISCUSSION

The present study demonstrated that patients treated for PC with conformal radiotherapy, when evaluated with a daily diary, clearly had decreased morbidity compared with those treated with conventional 4-field box technique including the pelvic area. Sucralfate also reduces intestinal discomforts in patients treated with pelvic fields (20, 21, 25). Data are comparable since the only change in treatment technique was the conversion to conformal radiotherapy technique, including the prostate, with a 2-cm margin. No studies have been published on self-assessment daily diary-reported side-effects comparing conformal therapy with conventional radiotherapy of patients with PC, while some studies with self-assessment questionnaire have reported side effects after the 4-field box technique (19–21, 26). The present study using a patient daily diary also clearly showed decreased side-effects with the 3-D technique as compared with the 4-field box technique. Two previous studies where side-effects were evaluated (24, 27),

did not report decreased morbidity with smaller treatment volumes, but dose was an important factor regarding treatment-related side-effects.

Dose escalation studies using conformal techniques are now starting. Memorial Sloan-Kettering Cancer Center has completed the initial group with a minimum described dose in the prostate with 75.6 Gy and the dose will then be escalated, monitoring safe guard permitted in 5.4 Gy increments. The technique used is mainly 6–8 portal treatment and inhomogenous dose distribution. Excellent results are reported with very low morbidity despite increased dose (28). At the University of Michigan, Sandler et al. (7) are also using a 6-field technique with 45–50 Gy to the pelvis and trying to reach a maximum dose 74 to 84 Gy to the prostate. The Fox Chase Cancer Center is also currently completing a study with minimum dose of 75 Gy (23).

A dose-response relationship has been reported for tumor control, but the increase of dose escalation was previously hampered by the increase in toxicity that was seen with doses higher than 70 Gy (29). With the development of conformal radiotherapy the goal is to deliver higher doses while maintaining acceptably low levels of complications. Initial dose escalation results show that the conformal technique with decreased treatment volume

Table 3

Comparison of acute side-effects 5 weeks after start of radiotherapy in conventional treatment patients and patients treated with conformal technique

Parameter	Treatment			p-value*
	Conventional		Conformal (n = 64)	
	Placebo (n = 30)	Sucralfate (n = 28)		
Diarrhea score				bbb,cc
0 + 1	27%	61%	88%	
2 + 3	73%	39%	12%	
Stool consistency				b
Normal	83%	84%	92%	
Loose	17%	16%	8%	
Occurrence of mucus	53%	43%	16%	
Occurrence of blood	3%	11%	5%	
Abdominal cramps	33%	32%	16%	
Loperamide consumption	20%	8%	11%	

* The p-values are compared in the following order:

b = placebo vs. conformal, b = $p < 0.05$, bbb = $p < 0.001$.

c = sucralfate vs. conformal, cc = $p < 0.01$.

causes less grade 2 morbidity (2; according to RTOG-EORTC grading criteria for lower gastrointestinal and genitourinary acute toxicity), but still high morbidity was reported with conventional margins using conformal therapy (27). It has also been shown that special rectal shielding are probably of importance to get acceptable toxicity with higher doses (30).

Acute side-effects

Measured with a patient daily diary, conformal radiotherapy decreased irradiation-induced acute side effects during the treatment period in comparison with the conventional technique. Previous studies using the same daily diary have shown that sucralfate might decrease the side-effects of irradiation-induced intestinal problems at least with the conventional technique including the pelvic region (20, 21). The mean numbers of daily stools and diarrhea score (Tables 2, 3) are also in favor of conformal therapy during the acute phase. Soffen et al. (22) showed that acute morbidity after 3-D conformal radiotherapy decreased both medication and interruptions of treatment with up to 50% compared with conventional treatment to the prostate. Vijayakuwar et al. (31) and Hanks et al. (2) noticed less grade 2 acute toxicities for patients treated with conformal radiotherapy compared with those treated with the conventional box technique.

Late side-effects

The present study showed a rapid decrease in side effects within 2 months after ending radiotherapy and a tendency to further decrease in side effects up to one year after treatment with conformal therapy compared with conventional 4-field box technique. A slightly looser consistency

of the stool was reported in the conformal group at 2–3 months' follow-up after radiotherapy, but this was normalized at 1 year. This could possibly be due to the slightly higher dose (65.15 Gy vs. 63.60 Gy) in the conformal treated group. As previously reported (20, 21, 25) sucralfate may also decrease intestinal side-effects after treatment with the conventional technique. Sandler et al. (7) did not detect any high-grade toxicity (RTOG grade III or higher) in 20 patients with 19 months' follow-up treated with a 6-field conformal dose escalation technique to a maximum of 76 Gy in the prostate. It may be possible to reach even higher doses without significant increased side-effects (28). However, it should be noted that Borghede & Sullivan (26) found higher urinary problems in patients treated with a combination of external beam radiotherapy and brachytherapy than in patients treated with radiotherapy alone. One study from the Fox Chase Cancer Center (23) showed that the high grade toxicity rate was decreased to less than 1% in the conformal treatment group at 13 months' follow-up in comparison with 6.3% in 156 patients treated with the conventional technique. A recent study by Lennernäs et al. (32) has shown that conformal therapy with smaller margins was the most important factor to decrease the dose delivered to the organs at risk, rectum and bladder, and the smaller margins were more important than the 5- or 6-field technique.

Urinary side-effects

Previous studies have indicated that conformal radiotherapy reduces genitourinary (GU) morbidity (2). In the present study few patients indicated any kind of problems remaining one year after treatment with urgency (16%), starting problems (9%) or pain during urination (19%).

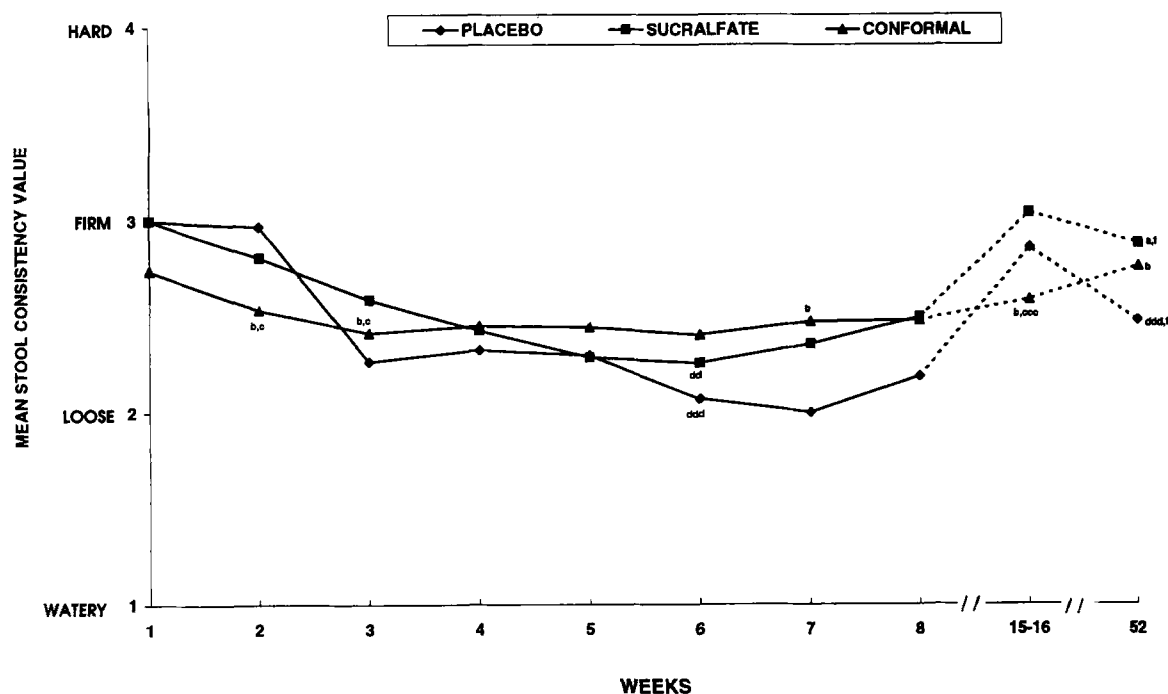


Fig. 3. Mean stool consistency in the conventional (placebo or sucralfate) and conformal patient groups, 1 to 8 weeks, 15–16 weeks and 52 weeks after initiation of radiotherapy treatment.

Sucralfate vs. placebo group; a = $p < 0.05$.

Conformal vs. placebo group; b = $p < 0.05$.

Conformal vs. sucralfate group c = $p < 0.05$; ccc = $p < 0.001$.

Difference from diarrhea score at the start of radiotherapy; dd = $p < 0.01$; ddd = $p < 0.001$.

Difference from diarrhea score at 15–16 weeks follow-up; f = $p < 0.05$.

These problems were of very low magnitude on the Likert scale. Compared with symptoms prior to radiotherapy, a significant decrease of symptoms was actually found at 1-year follow-up in the conformal group. This could sug-

gest that symptoms prior to radiotherapy were due to the function, but could also be related to hyperplasia. Using another questionnaire with similar GU questions, more GU problems were reported at 4 years' follow-up after

Table 4

Comparison of late side-effects 52 weeks after start of radiotherapy in conventionally treated patients and patients treated with conformal techniques

Parameter	Treatment			p-value*
	Conventional			
	Placebo (n = 27)	Sucralfate (n = 26)	Conformal (n = 36)	
Diarrhea score				
0 + 1	70%	85%	100%	bbb,cc
2 + 3	30%	15%	0%	
Stool consistency				
Normal	100%	100%	100%	bbb
Loose	0%	0	0%	
Occurrence of mucus	52%	27%	10%	bb
Occurrence of blood	26%	15%	4%	
Abdominal cramps	30%	19%	10%	bb
Loperamide consumption	33%	15%	3%	

* The p-values are compared in the following order:

b = placebo vs. conformal, bb = $p < 0.01$, bbb = $p < 0.001$.

c = sucralfate vs. conformal, ccc = $p < 0.001$.

treatment with the conventional box technique than with conformal radiotherapy (19). The lower incidence of GU morbidity could also be due to the relatively short time after treatment (1 year), since Schultheiss et al. (27) showed that GU morbidity has longer latency than intestinal problems. Also the total dose below 70 Gy could explain the low GU morbidity, but Hanks et al (2) did not find any significant difference of grade 2 morbidity above 70 Gy in conformally treated patients. Regarding GU problems and T-stage we could not see any significant correlations.

To conclude, evaluation of side-effects using a patient daily diary showed a decreased acute morbidity using conformal 3-D radiotherapy compared with using the conventional 4-field box techniques. The late morbidity (>1 year) was also decreased, the stool frequency was almost as low as that in an age-matched control group. Whether sucralfate will decrease side-effects in PC patients treated with conformal therapy with or without dose escalation remains to be elucidated.

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