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Long-term Symptoms after External Beam Radiation Therapy for Prostate Cancer with Three or Four Fields

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Acta Oncologica Vol. 41, No. 6, pp. 532–542, 2002

The aim of this study was to investigate whether external beam radiation treatment with three or four fields affects the risk of long-term distressful symptoms. The study included 145 patients who had been treated in Stockholm from 1993 to 1996 for localized prostate cancer. Bowel, urinary and sexual function as well as symptom-induced distress were assessed by means of a postal questionnaire 29–59 months after therapy. Among patients treated with a multileaf collimator, defecation urgency, diarrhoea and loose stools were more common after four fields than after three fields, but faecal leakage necessitating the use of pads and distress from the gastrointestinal tract were less common (although not statistically significantly so). Among bowel symptoms, the strongest association with gastrointestinal distress was found for faecal leakage. Three fields without a multileaf collimator entailed a higher risk of defecation urgency than three fields with a multileaf collimator. We conclude that the choice of three or four fields may imply a contrasting risk scenario for defecation urgency or diarrhoea in comparison with faecal leakage.

Received 9 November 2001
Accepted 20 June 2002

The most frequently used approaches to localized prostate cancer are 'watchful waiting', external radiation therapy and radical prostatectomy. The choice of strategy is a decisive issue for both physician and patient, each having its pros and cons in terms of expected survival time and the risk of several different long-term distressful symptoms.

Radiotherapy can sterilize prostate tumours and the higher the radiation therapy dose administered, the greater the likelihood of obtaining local control. But the dose of radiation that can be given is limited by the need to restrict the frequency and severity of undesirable effects. Long-term symptoms can permanently decrease well-being and quality of life. In order to accurately predict the risk of clinically significant chronic damage, we need to correlate radiation details with symptom occurrence, intensity and duration. To set priorities and assist patients in the trade-off between different treatment strategies, we also need to know the relevance of the specific symptoms to emotions and social activities ('symptom-induced distress'). Data are being generated (1), but we need further information before, for example, we can determine reasonable dose or volume thresholds below which no (or reasonably few) late side effects are likely to occur.

Organs at risk when radiating the prostate include the urinary bladder, the anal sphincter, the bowel and the nerves and vessels involved in erectile function. In a randomized study, fewer men developed radiation-induced proctitis and bleeding when given 'conformal' instead of 'conventional' radiotherapy (2). No statistically significant differences were noted for bladder or sexual function between the groups. In a before-and-after study it was observed that there were fewer men with erectile dysfunction when a multileaf collimator was used than when a collimator was not used (3). In a dose-escalating phase I study, the likelihood of chronic urinary bladder symptoms increased considerably when more than 65 Gy was given to at least 30% of the urinary bladder volume (1). No

 ISSN 0284-186X

statistically significant correlation was found between the prescribed dose and the risk of gastrointestinal toxicity, but a rectal volume (anatomically) exceeding 100 cm^3 was associated with an increased risk of bowel toxicity (1). Clearly, treatment techniques influence the risk of long-term distressful symptoms after radiotherapy.

The rapid technological developments in radiotherapy and the need to wait some years before assessing the outcome imply that any observation of side effects is of limited relevance to today's treatments. Still, documentation of historical materials may provide knowledge for improving techniques and predicting the outcome of future radiotherapy. Moreover, such information can be used to help today's patients with post-radiation problems. In the 1990s radiotherapy of prostate cancer was given in Stockholm at two different departments using three or four fields. In this follow-up, we asked whether the choice of three or four fields influenced the risk of long-term distressful symptoms.

MATERIAL AND METHODS

From November 1998 to March 1999 questionnaires including modules assessing sexual function, urinary and bowel symptoms were sent to 158 patients with clinically localized prostate adenocarcinoma treated by external beam radiation therapy in Stockholm in 1993–1996. The study population included all patients who were alive in November 1998, and treated in 1995–1996 at one clinical department, as well as patients who were alive in March 1999 and treated in 1993–1996 at another department in Stockholm, Sweden. The 34 patients treated at the respective departments at the time in question who died before November 1998, or 1 March 1999, respectively, were not included. The regional Ethics Committee approved the study.

As the treatment was given with different treatment planning techniques, including the number of fields and their arrangement, beam collimation, absorbed dose, number of fractions and follow-up time, the patients were divided into four groups: Group I included patients treated with three fields (one anterioposterior (AP) field and two oblique posterior fields) in 1995. Group II comprised patients treated in 1996 with a four-field box technique with two opposing AP-PA fields and two opposing lateral fields. Groups I and II were treated with a multileaf collimator. Group III included patients treated in 1995–1996 and Group IV patients treated in 1993–1994. Groups III and IV were treated using a three-field technique, one AP field and two lateral fields at 90° and 270° using a conventional collimator. The *conventional collimator* technique involved a symmetric collimator to define the target area, resulting in a square or rectangular field. The caudocranial length of the fields was on average 10 cm, the anterioposterior field size was 11 cm in width and the lateral fields were 8 cm in width. The *multileaf collimator* technique uses tumour visualization and a field shaped to match the target volume using 40 leaves to minimize the exposure of healthy tissue (4–8).

The prescribed doses at the reference point were 70.2 Gy for groups I and II and 70 and 68 Gy for groups III and IV. The mean treatment period was 61 days (standard deviation [SD] 4 days) for groups I and II and 48 days (SD 3 days) for groups III and IV. The treatment dose was given as 16 or 18 MV photons in daily fractions of 1.8 Gy, 5 fractions per week for groups I and II. For group III and IV patients, the treatment dose was given with 18 MV photons of 2 Gy, 5 fractions per week. All fields were weighted and given at every treatment occasion.

The gross target volume (GTV) was the entire prostate gland and, in most patients, the seminal vesicles as visualized on the planning computerized tomography (CT) scan. The clinical target volume (CTV) was not distinguished from the GTV. The planning target volume (PTV) was the GTV plus a 2.0 cm margin around it, with the exception of at the apex, where the margin was 2.5 cm to allow for positioning errors, and mobility and uncertainty about the microscopic spread outside the GTV. To ensure the accuracy of the set-up, portal films were taken. Patients were treated in the supine position in both departments. Patients in groups I and II were advised to empty the urinary bladder before treatment, the rationale being to reduce target movement. In groups III and IV, the patients were instead advised to have a full bladder (the rationale being to reduce the dose to the bladder and small intestine). Portal films were taken to ensure the accuracy of the set-up. For patients in groups III and IV, the treatment technique involved the placing of Foley catheters and contrast in the bladder and rectum during a CT scanning procedure.

The dose planning was guided by CT scanning using a TMS 3-dimensional (3-D) treatment planning system (TMS, MDS Nordion) in groups I and II and a Theraplan 3-D treatment planning system in groups III and IV.

Information on the external beam radiation therapy, disease stage and grade was retrieved from the hospital records (Table 1). Additional data were collected with a follow-up questionnaire that was posted to all patients. Patients who failed to return the questionnaire within four weeks were contacted by telephone.

The questionnaire, which had been developed on the basis of successive in-depth interviews with patients and clinicians, was similar to our previously used questionnaires (9–11) and contained 80 questions. The modules assessed bowel, urinary and sexual functions. Each symptom was assessed separately, followed by an assessment of the extent to which the symptom distressed the patient. The bowel questions addressed diarrhoea or loose stools, constipation, defecation urgency, blood or phlegm in stools

Table 1

Characteristics of patients prior to external beam radiotherapy for prostate cancer

Characteristics	Group I	Group II	Group III	Group IV
Total no. of treated patients	47	34	50	63
Dead at follow-up—no./total no. (%)	4/47 (9)	3/34 (9)	5/50 (10)	22/63 (35)
Not included—no./total no. (%)	1/47 (2)	1/34 (3)		
Reasons for not participating—no./total no. (%)	2/42 (5)		1/45 (2)	
No contact established	4/42 (10)		2/45 (4)	2/41 (5)
Refusal		1/30 (3)	1/45 (2)	
Patient's health				
Total answering the questionnaire—no./total no. (%)	36/42 (86)	29/30 (97)	41/45 (91)	39/41 (95)
Treatment technique				
Mean dose at isodose centre	70.2 Gy	70.2 Gy	70 Gy	68 Gy
No. of fields	3.0	4.0	3.0	3.0
No. of sessions	39	39	35	34
Dose per session	1.8 Gy	1.8 Gy	2.0 Gy	2.0 Gy
Treatment period				
Mean—days (SD, standard deviation)	61 (4)	60 (5)	47 (2)	48 (3)
Median—days (range)	61 (53–68)	60 (52–69)	47(45–55)	48(44–59)
Beam collimator	Multileaf[1]	Multileaf	Conventional	Conventional
Initial potency status—no./total no (%)				
Satisfactory erectile function	17/36 (47)	11/29 (38)	24/40 (60)	22/39 (56)
Nearly satisfactory erectile function	10/36 (28)	8/29 (28)	8/40 (20)	8/39 (23)
Median age				
At follow-up—yrs (range)	72.6 (54–82)	70 (61–81)	72 (57–79)	73 (55–84)
At treatment—yrs (range)	69.5 (52–79)	67 (58–78)	69.5 (55–75)	69 (50–78)
Follow up time—yrs (range)	3.2 (2.0–3.9)	2.4 (1.9–2.9)	3.0 (2.2–3.9)	4.9 (4.0–6.0)
Mean age				
At follow-up—yrs (SD)	72 (6.6)	71 (5.3)	71 (5.5)	73 (6.1)
At treatment—yrs (SD)	69 (6.5)	68 (5.2)	68 (5.4)	68 (5.9)
Follow-up time—yrs (SD)	3.2 (0.4)	2.4 (0.3)	3.0 (0.5)	4.9 (0.5)
Marital status—no./total no (%)				
Married or living with a partner	32/34 (94)	4/28 (86)	35/40 (88)	31/38 (82)
Single	2/34 (6)	4/28 (14)	5/40 (13)	7/38 (18)
Mean volume				
Anal sphincter—cm^3 (SD)	21 (3.0)	24 (5.0)		
Rectum wall—cm^3 (SD)	40 (9.0)	44 (9.0)		
Bowel-lower part exposed to a dose of ≥ 30 Gy—cm^3 (SD)	51 (49)	65 (41)		
Rectum length—cm (SD)	8.9 (0.9)	9.6 (0.7)		
Anal sphincter length—cm	3.0	3.0		
Stage—no./total no. (%)				
T0	1/36 (3)	0/29 (0)	0/41 (0)	0/39 (0)
T1	2/36 (6)	1/29 (3)	1/41 (2)	2/39 (5)
T2	10/36 (28)	7/29 (24)	16/41 (39)	13/39 (33)
T3	21/36 (58)	20/29 (69)	22/41 (54)	24/39 (62)
T4	1/36 (3)	1/29 (3)	1/41 (2)	0/39 (0)
T?	1/36 (3)	0/29 (0)	1/41 (2)	0/39 (0)
Grade—no./total no. (%)				
GI	4/36 (11)	5/29 (17)	4/41 (10)	4/39 (10)
GII	21/36 (58)	16/29 (55)	23/41 (56)	23/39 (59)
GIII	10/36 (28)	8/29 (28)	14/41 (34)	12/39 (31)
GIV	1/36 (3)	0/29 (0)	0/41 (0)	0/39 (0)
History of TURP—no./total no. (%)	7/36 (19)	4/28 (14)	7/41 (17)	6/39 (15)
History of radical prostatecotmy—no./total no. (%)	6/36 (17)	2/28 (7)	1/41 (2)	1/38 (3)
Orchidectomy—no./total no. (%)	2/36 (6)	1/28 (4)	0/41 (0)	2/39 (5)

Table 1 (Continued)

Characteristics	Group I	Group II	Group III	Group IV
Diabetes mellitus—no./total no. (%)	4/36 (11)	5/29 (17)	0/41 (0)	5/39 (13)
Hypertension—no./total no. (%)	9/36 (25)	9/29 (31)	11/41 (27)	14/39 (36)
Testosterone depletion—no./total no. (%)	6/36 (17)	9/28 (32)	15/40 (37)	7/39 (18)
Before radiotherapy	0/36 (0)	4/28 (14)	8/40 (20)	0/39 (0)
At least one year before the fellow-up time	2/36 (6)	3/28 (11)	3/40 (8)	2/39 (5)
Less than one year before or during the fellow-up period time	4/36 (11)	2/28 (7)	4/40 (10)	5/39 (13)
Claudicatio intermittens—no./total no. (%)	1/36 (3)	4/29 (14)	1/41 (2)	4/39 (10)
Angina pectoris—no./total no. (%)	4/36 (11)	5/27 (19)	8/36 (22)	7/38 (18)
Disease in joints or muscles—no./total no. (%)	4/34 (12)	5/29 (17)	6/41 (15)	3/35 (8)
History of heart attack—no./total no. (%)	2/35 (6)	6/29 (21)	5/41 (12)	3/39 (8)
Depressed previous 6 months—no./total no. (%)	6/36 (17)	5/29 (17)	8/41 (20)	7/39 (18)
Depressed before diagnosis—no./total no. (%)	3/36 (8)	2/29 (7)	2/40 (5)	4/39 (10)
Using any medical devices to improve erection stiffness—no./total no. (%)	4/30 (13)	10/24 (42)	4/37 (11)	4/34 (12)

[1] Three patients treated with a conventional collimator.
Abbreviations: TURP = transurethral resection of the prostate; MUSP = major urologic surgical procedure.

faecal leakage. Urinary questions addressed the frequency of urination during the day and night, incomplete bladder evacuation, urinary control, straining to initiate micturition, weak stream, urinary urgency and urinary leakage. The frequency/intensity of the symptom was assessed using six response alternatives including 'no symptom', 'less than once a week', 'once a week', 'twice or three times a week', 'four to six times a week' and 'seven times a week or more'. The questionnaire also included questions about quantity of urinary and faecal leakage and if any protective devices had been used. Parts of the 'Radiumhemmet Scale of Sexual Functioning' (10) were used to assess sexual symptoms. This scale contains questions on three functional aspects of sexuality including desire, erection and orgasm, using from five to eight ordinal categories as response alternatives. The scale also includes questions about various factors to measure possible confounders, including intermediate diseases that may affect sexual function. '*Potency*' was defined as an erection 'sufficiently stiff for intercourse most of the time' or better during sexually stimulated erections, night/morning erections or spontaneous erections (10).

The level of symptom distress was assessed with a 'verbal' 4-category scale (none/little/moderate/much) (9).

In the analysis, we primarily compared group I with groups II and III, as the time from treatment to follow-up is similar in these groups. In addition, the categories were collapsed to any frequency: less than once a week or more and at least twice a week or more. Patients reporting the same frequency/intensity of symptoms (or very little progression) at follow-up and pretreatment were classified as 'Symptom-free'.

The relative risk of having symptoms was calculated as the percentage of patients in the respective groups II or III or IV reporting the particular problem divided by the percentage of patients in group I reporting the same symptom. A corresponding 95% confidence interval (CI) was calculated using the Mantel–Haenszel method (12, 13).

Dose-planning treatment data were stored for all patients and the questionnaires were coded; the data for all patients in groups I and II were restored from the archive in the TMS system. The rectal wall was defined anatomically as extending from the sigmoid flexure to the anal verge. The anal sphincter area was determined by the muscle layer around the rectal aperture. The anal sphincter area and the lower bowel tract were delineated on each CT image for each patient. In addition, the structure of the rectum wall was outlined by the interior and exterior borders. The caudal–sagittal length of the rectum and the anal sphincter were defined as 8.0–11.0 cm and 3.0 cm, respectively. Most of the lower bowel tract was defined on one or two slices only, which included an at least 50% isocentre dose (14). The rectal wall, anal sphincter and lower bowel tract differentiated absolute volumes of the dose-volume histogram (DVH), defined at 0.5 Gy intervals, were generated for each patient.

In order to assess the difference between DVHs for patients treated with either three fields or four fields, the mean percentage DVH for each treatment technique group was calculated.

The differential and cumulative DVHs of the rectum and the anal sphincter were assessed for each patient. The cumulative volume was normalized to the total volume of

Table 2

Bowel symptoms, occurrence and symptom distress, relative risks previous 6 months

Variable	Group I (n = 36) 3 fields 95	Group II (n = 29) 4 fields 96	p-value*	Group III (n = 41) 3 fields 95/96	p-value*	Group IV (n = 39) 3 fields 93/94
Defecation urgency, change to two times a week or more—no./total no. (%)[1]	2/36 (6)	8/29 (28)		8/40 (20)		10/39 (26)
Relative risk, others vs. group I.	1.0 (ref.)	4.5 (1.1–21)	0.02	3.5 (0.8–16)	0.09	4.6 (1.1–20)
Blood or phlegm in stools, change to two times a week or more—no./total no. (%)[1]	4/36 (11)	6/29 (21)		11/41 (27)		5/39 (13)
Relative risk, others vs. group I	1.0 (ref.)	1.9 (0.6–6.0)	0.32	2.4 (0.8–6.9)	0.09	1.2 (0.3–4.0)
Diarrhoea or loose stools, change to two times a week or more—no./total no. (%)[1]	0/36 (0)	7/29 (24)		2/40 (5)		3/39 (8)
Relative risk, others vs. group I	1.0 (ref.)	∞ (not done)	0.002	∞ (not done)	0.50	∞ (not done)
Constipation, change to every week or more —no./total no. (%)[1]	1/36 (3)	0/29 (0)		0/41 (0)		3/39 (8)
Relative risk, others vs. group I.	1.0 (ref.)	0.0 (not done)	1.0	0.0 (not done)	0.47	2.8 (0.3–25)
Fecal leakage, no to yes—no./total no (%)[a]	11/35 (31)	8/29 (28)		13/41 (32)		10/39 (26)
Relative risk, others vs. group I	1.0 (ref.)	0.9 (0.4–1.9)	1.0	1.0 (0.5—2.0)	1.0	0.8 (0.4–1.7)
Using any kind of pads, diapers or other devices, no to yes—no./total no. (%)[1]	5/36 (14)	2/29 (7)		8/41 (20)		3/39 (8)
Relative risk, others vs. group I	1.0 (ref.)	0.5 (0.1–2.4)	0.45	1.4 (0.5—3.9)	0.56	0.6 (0.2–2.2)
Distress/much if current leakage were to persist—no./total no. (%)[1]	5/36 (14)	2/29 (7)		8/41 (20)		2/39 (5)
Relative risk, others vs. group I	1.0 (ref.)	0.5 (0.1–2.4)	0.45	1.4 (0.5—3.9)	0.56	0.4 (0.1–1.8)
Distress/much if current problems from gastrointestinal tract were to persist—no./total no. (%)[1]	9/36 (25)	2/29 (7)		11/41 (27)		9/39 (23)
Relative risk, others vs. group I	1.0 (ref.)	0.3 (0.1–1.2)	0.09	1.0 (0.5–2.3)	1.0	0.9 (0.4–2.1)

[1] Respondents included only subjects with the symptom.
* Fisher's exact test (2-tailed) as compared with group I.

the rectum or anal sphincter. The mean percentage DVHs for each patient group was then calculated.

RESULTS

Out of a total of 158 available patients, 145 (92%) answered and returned the questionnaire. Most of the patients had answered all the questions included in the questionnaire. The reasons given by patients for not participating in the study are presented in Table 1, along with relevant patient characteristics.

Tables 2–5 present the prevalence and the relative risk (other vss group I) of bowel, urinary and sexual dysfunction.

Bowel symptoms

Defecation urgency twice a week or more was reported by 28% of the patients in groups II and 20% of the patients in group III. Only 6% of the patients in group I reported such urgency. The relative risk compared with group I was statistically significant for group II (4.5) (95% CI 1.1–21.0) (Table 2).

Twenty-three percent (18/79) of the patients in groups III and IV reported defecation urgency compared with 6% in group I corresponding to a relative risk of 4.1 (95% CI 1.0–16.0) (p = 0.03) (not in the Table).

Seven out of 29 (24%) patients in group II reported diarrhoea or loose stools twice a week or more. This symptom was reported by 5% of the patients in group III and 8% of those in group IV. None of the patients in group I reported this symptom (Table 2).

Eleven out of 41 (27%) patents in group III and 9 out of 39 (23%) in group IV reported moderate or considerable distress owing to the persistence of current problems involving the gastrointestinal tract. Nine out of 36 (25%) patients in group I reported moderate or considerable distress, compared with only 2 out of 29 (7%) patients in group II (Table 2).

Four percent (2/55) of the total number of patients under 71 years of age were using a protective device because of faecal leakage compared with 17% (16/90) of patients aged 71 years or more. The relative risk was 4.9 (95% CI 1.3–20.0) on comparing patients under 71 with those aged 71 years or older (p = 0.02) (not in the Table).

The distress caused by bowel symptoms in general in relation to each specific bowel symptom is assessed in Table 5. The most distressful bowel symptom was faecal leakage; 47% of the patients with this symptom reported that they were distressed or greatly distressed by bowel symptoms (Table 5).

Mean percentage DVHs of the rectum wall and anal sphincter are available for group I and II patients only and are shown in the Fig. 1 (panels a and b, respectively). The mean DVH of the rectum wall indicated that 57% of the

Table 3

Urinary symptoms, occurrence and symptom distress, relative risks, most recent 6 months

Variable	Group I (n = 36) 3 fields 95	Group II (n = 29) 4 fields 96	p-value*	Group III (n = 41) 3 fields 95/96	p-value*	Group IV (n = 39) 3 fields 93/94
Incomplete bladder evacuation, change to half of the time or more—no./total no. (%)[1]	1/35 (3)	4/28 (14)		1/40 (3)		3/39 (8)
Relative risk, others vs. group I	1.0 (ref.)	5.0 (0.6–42)	0.16	0.9 (0.1–13)	1.0	2.7 (0.3–24)
Excluding patients with radical prostatectomy	1/29 (3)	4/26 (15)		1/39 (3)		2/38 (5)
Relative risk, others vs. group I	1.0 (ref.)	4.5 (0.5–37)	0.18	0.7 (0.0–11)	1.0	1.5 (0.1–16)
Urination at least every other hour, change to half of the time or more—no./total no. (%)[1]	4/35 (11)	6/29 (21)		4/40 (10)		5/39 (13)
Relative risk, others vs. group I	1.0 (ref.)	1.6 (0.6–5.8)	0.49	0.9 (0.2–3.2)	1.0	1.1 (0.3–3.9)
Excluding patients with radical prostatectomy	3/29 (10)	5/27 (19)		4/39 (10)		4/38 (11)
Relative risk, others vs. group I	1.0 (ref.)	1.8 (0.5–6.8)	0.46	1.0 (0.2–4.1)	1.0	1.0 (0.2–4.2)
Unintentional micturition stops, change to half of the time or more—no./total no. (%)[1]	1/36 (3)	3/29 (10)		2/40 (5)	1.0	1/38 (3)
Relative risk, others vs. group I	1.0 (ref.)	3.7 (0.4–34)	0.32	1.8 (0.2–19)		0.9 (0.1–14)
Excluding patients with radical prostatectomy	0/30 (0)	3/27 (11)	0.10	2/39 (5)	0.50	1/38 (3)
Weak stream, change to half of the time or more—no./total no. (%)[1]	3/35 (9)	9/29 (31)		6/40 (15)		5/39 (13)
Relative risk, others vs. group I	1.0 (ref.)	3.6 (1.1–12)	0.03	2.0 (0.5–6.5)	0.49	1.5 (0.4–5.8)
Excluding patients with radical prostatectomy	2/29 (7)	7/27(26)	0.07	6/39 (18)	0.45	5/38 (13)
Relative risk, group I vs. others	1.0 (ref.)	3.9 (0.9–17)		2.2 (0.5–10)		1.9 (0.4–9.1)
Straining to initiate micturition, change to half of the time or more—no./total no. (%)[1]	3/36 (8)	4/29 (14)		3/40 (8)		1/39 (3)
Relative risk, others vs. group I	1.0 (ref.)	1.7 (0.4–6.8)	0.69	0.9 (0.2–4.2)	1.0	0.3 (0.1–2.9)
Excluding patients with radical prostatectomy	1/30 (3)	4/27 (14)		3/39 (8)		1/37 (3)
Relative risk, others vs. group I	1.0 (ref.)	4.4 (0.5–37)	0.17	2.3 (0.3–21)	0.63	0.8 (0.1–12)
Nocturia, change to two times or more—no./total no. (%)[1]	1/35 (3)	2/29 (7)		2/41 (5)		2/39 (5)
Relative risk, others vs. group I	1.0 (ref.)	2.4 (0.2–25)	0.59	1.7 (0.2–18)	1.0	1.8 (0.2–19)
Excluding patients with radical prostatectomy	0/29 (0)	2/27 (7)	0.23	2/40 (5)	0.50	2/38 (5)
Urinary urgency, change to half of the time or more—no./total no. (%)[1]	3/35 (9)	5/28 (18)		6/39 (15)		3/39 (8)
Relative risk, others vs. group I	1.0 (ref.)	2.1 (0.5–8.0)	0.45	1.8 (0.5–6.6)	0.49	0.9 (0.2–4.2)
Excluding patients with radical prostatectomy	1/29 (3)	3/26 (12)		5/38 (13)		3/38 (8)
Relative risk, others vs. group I	1.0 (ref.)	3.3 (0.4–30)	0.34	3.8 (0.5–31)	0.22	2.3 (0.3–21)
Distress/much if current urinary urgency would persist—no./total no. (%)[1]	11/36 (31)	6/29 (21)		15/41 (37)		11/39 (28)
Relative risk, others vs group I	1.0 (ref.)	0.7 (0.3–1.6)	0.41	1.2 (0.6–2.3)	0.64	0.9 (0.5–1.9)
Excluding patients with radical prostatectomy	7/30 (23)	5/27 (19)		15/40 (38)		10/38 (26)
Relative risk, others vs. group I	1.0 (ref.)	0.8 (0.3–2.2)	0.75	1.6 (0.8–3.4)	0.30	1.1 (0.5–2.6)
Urinary leakage, change to every week or more frequently—no./total no. (%)[1]	6/35 (17)	3/29 (10)		4/40 (10)		3/39 (8)
Relative risk, others vs. group I	1.0 (ref.)	0.6 (0.2–2.2)	0.49	0.6 (0.2–1.9)	0.5	0.4 (0.1–1.7)
Excluding patients with radical prostatectomy	3/29 (10)	3/27 (11)		4/39 (10)		2/38 (5)
Relative risk, others vs. group I	1.0 (ref.)	1.1 (0.2–4.9)	1.0	1.0 (0.2—4.1)	1.0	0.5 (0.1–2.8)
Using any kind of pads, diapers or other devices, no to yes—no./total no. (%)[1]	8/36 (22)	3/29 (10)		4/41 (10)		2/39 (5)
Relative risk, others vs. group I	1.0 (ref.)	0.5 (0.1–1.6)	0.32	0.4 (0.1–1.3)	0.2	0.2 (0.1–1.0)
Excluding patients with radical prostatectomy	5/30 (17)	2/27 (7)		4/40 (10)		1/38 (3)
Relative risk, others vs. group I	1.0 (ref.)	0.4 (0.1–2.1)	0.42	0.6 (0.2–2.0)	0.48	0.2 (0.0–1.3)
Distress/much if current leakage would persist—no./total no. (%)[1]	7/36 (19)	5/29 (17)		5/41 (12)		3/39 (8)
Relative risk, others vs. group I	1.0 (ref.)	0.9 (0.3–2.5)	1.0	0.6 (0.2–1.8)	0.53	0.4 (0.1–1.4)
Excluding patients with radical prostatectomy	5/30 (17)	5/27 (19)		5/40 (13)		2/38 (5)
Relative risk, others vs. group I	1.0 (ref.)	1.1 (0.4–3.4)	1.0	0.8 (0.2–2.4)	0.74	0.3 (0.1–1.5)
Distress/much if current LUTS were to persist—no./total no. (%)[1]	7/36 (19)	7/29 (24)		7/41 (17)		7/39 (18)
Relative risk, others vs. group I	1.0 (ref.)	1.2 (0.5–3.1)	0.76	0.9 (0.3–2.3)	1.0	0.9 (0.4–2.4)
Excluding patients with radical prostatectomy	5/30 (17)	7/27 (26)		7/40 (18)		6/38 (16)
Relative risk, others vs. group I	1.0 (ref.)	1.6 (0.6–4.3)	0.52	1.1 (0.4–3.0)	1.0	0.9 (0.3–2.8)

[1] Respondents include only subjects with the symptom.

* Fisher's exact test (2-tail) as compared with group I.

Abbreviation: LUTS = lower urinary tract symptoms and /or leakage.

Table 4

Sexual symptoms, occurrence and symptom distress, relative risks prior to treatment and most recent 6 months

Variable	Group I (n = 3 6) 3 fields95	Group II (n = 29) 4 fields96	p-value*	Group III (n = 41) 3 fields. 95/96	p-value*	Group IV (n = 39) 3 fields 93/94
Proportion reporting that sex was important or very important before prostate cancer diagnosis—no./total no. (%)[1]	19/36 (53)	18/29 (62)		24/40 (60)		22/39 (56)
Proportion reporting that sex was important or very important after treatment—no./total no. (%)[1]	32/36 (89)	19/29 (66)		31/40 (78)		32/39 (82)
Relative risk, others vs. group I	1.0 (ref.)	0.7 (0.6–1.0)	0.03	0.9 (0.7–6.0)	0.23	0.9 (0.8–1.1)
Erection stiffness before prostate cancer diagnosis 'seldom sufficient for intercourse or less' (impotent)—no./total no. (%)[1]	9/36 (25)	8/27 (30)		8/40 (20)		8/39 (21)
Relative risk, group I vs. others	1.0 (ref.)	1.2 (0.5–2.7)	1.0	0.8 (0.3–1.9)	0.78	0.8 (0.4–1.9)
Prevalence of 'erectile dysfunction' in previously 'potent' patients after treatment—impotent patients no./potent patients no. (%)[1]	21/27 (78)	17/19 (89)		22/32 (67)		28/31 (90)
Relative risk, others vs. group I	1.0 (ref.)	1.2 (0.9–1.5)	0.43	0.9 (0.6–1.2)	0.56	1.2 (0.9–1.5)
Excluding all potential confounding factors—impotent after treatment no./no. of previously potent patients no. (%)[2]	7/12 (58)	7/9 (78)		15/21 (71)		17/18 (94)
Relative risk, others vs. group I	1.0 (ref.)	1.3 (0.7–2.4)	0.64	1.2 (0.7–2.1)	0.47	1.6 (1.0–2.6)
Proportion reporting distress or considerable distress if erectile dysfunction were to persist no./total no. (%)[1]	19/36 (53)	18/29 (63)		21/40 (53)		22/39 (56)
Relative risk, others vs. group I	1.0 (ref.)	1.2 (0.8–1.8)	0.61	1.0 (0.6–1.5)	1.0	1.1 (0.7–1.6)

[1] Respondents include only subjects with the symptom.
[2] Potential confounding factors include radical prostatectomy, orchidectomy, testosterone depletion less than one year before or during the fellow-up period, depressed previous 6 months, using any medical device to improve erection stiffness.
* Fisher's exact test (2-tailed) as compared with group I.

Table 5

Proportion reporting moderate or considerable distress due to 'bowel symptoms' among patients reporting, or not reporting, five different specific symptoms

Variable	Distress				
	Not having symptom	Having symptom at any grade	p-value*	Having symptom at least twice a week or more	p-value*
Diarrhoea or loose stools, no. with bowel distress/total no. (%)[1]	16/93 (17)	15/51 (29)		3/11 (27)	
Relative risk, yes vs. no.		1.7 (0.9–3.2)	0.10	1.6 (0.5–4.6)	0.4
Constipation, no. with bowel distress/total no. (%)[1]	12/70 (17)	19/75 (25)		3/4 (75)	
Relative risk, yes vs. no.		1.5 (0.8–2.8)	0.31	4.4 (2.0–9.4)	0.02
Defecation urgency, no. with bowel distress/total no. (%)[1]	6/63 (10)	25/82 (30)		12/28 (42)	
Relative risk, yes vs. no.		3.2 (1.4–7.3)	<0.001	4.5 (1.9–10.9)	<0.001
Blood or phlegm, no. with bowel distress/total no. (%)[1]	10/78 (13)	21/67 (31)		11/26 (42)	
Relative risk, yes vs. no.		2.4 (1.5–5.0)	0.01	3.3 (1.6–6.9)	0.003
Faecal leakage no. with bowel distress/total no. (%)[1]	10/100 (10)	21/45 (47)		11/15 (73)	
Relative risk, yes vs. no.		4.7 (2.4–9.1)	<0.001	7.3 (3.8–14.2)	<0.001

[1] Respondents included only subjects with the symptom.
* Fisher's exact test (2-tail).

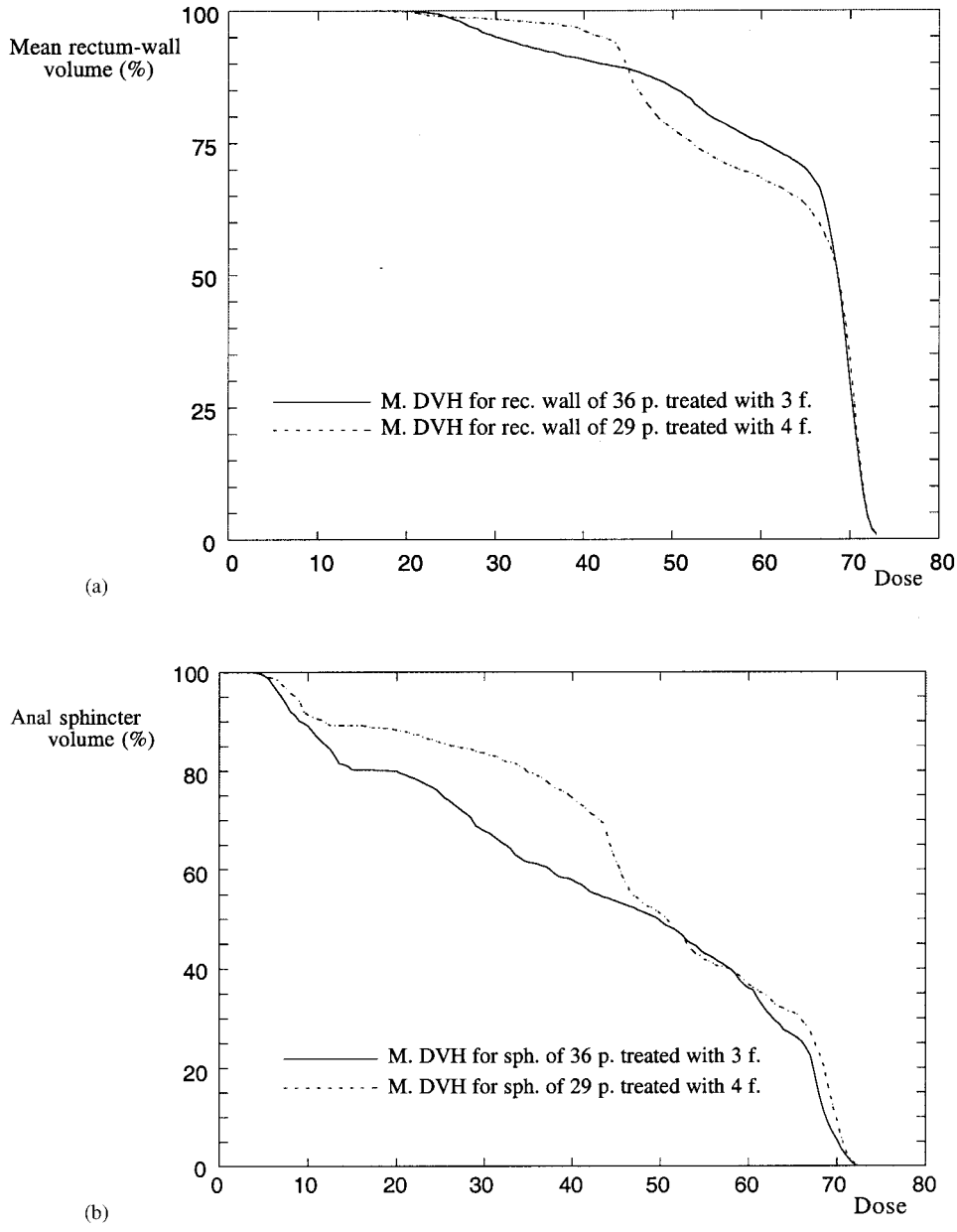

Fig. 1. (a) Mean dose-volume histogram (DVH) for rectum wall of 36 patients treated with three fields and 29 patients treated with four fields normalized by the sum of the mean dose volume of each group. (b) Mean DVH for the anal sphincter of 36 patients treated with three fields and 29 patients treated with four fields normalized by the sum of the mean dose volume of each group.

rectum wall volume received a dose ≥ 68 Gy for both groups. The mean volume of the anal sphincter receiving a dose of ≥ 40 Gy for group II was 78% compared with 60% for group I (see Fig. 1, a and b). For patients treated with the four-field box technique, the mean volume of the lower bowel tract receiving a dose of ≥ 35 Gy was 51 cm^3 compared with 65 cm^3 for patients treated with three fields (not in table).

Urinary symptoms

No statistically significant differences were detected between the groups regarding urinary symptoms, with the exception of increased prevalence of a weak urinary stream in group II compared with group I (Table 3).

When patients with radical prostatectomy were excluded, the prevalence of urinary symptoms decreased more often in group I than in the other groups. In group

I there were more patients who had undergone radical prostatectomy than in the other groups (Table 3).

Sexual function

In the different groups, 53–62% of the patients reported that sex had been important or very important to them before they were diagnosed with prostate cancer. Eleven to 34% of the patients reported a waning importance of sex after the treatment.

Of all 'potent' patients before treatment, 67–90% reported that erection stiffness had diminished to being 'seldom sufficient for intercourse or less' (i.e. erectile dysfunction) at the time of follow-up (Table 4). No statistically significant difference between the groups was found in this respect.

Of the 'potent' patients before treatment who reported 'erectile dysfunction' after treatment, 67% (59/88) reported being distressed or very distressed owing to waning erection stiffness (not in the Table).

DISCUSSION

In this follow-up comprising information from 145 patients followed for 29–59 months after radiotherapy, few differences in symptom prevalence could be detected between patients who had been treated with four as opposed to three fields. Among those treated with a multileaf collimator, four fields entailed a higher risk for defecation urgency and diarrhoea compared with three fields. However, the risk was (not statistically significantly) lower for pad-requiring faecal leakage and distress from the gastrointestinal tract. Faecal leakage ranked highest when gastrointestinal distress was related to occurrence of specific bowel symptoms. Three fields with a conventional collimator entailed a higher risk of defecation urgency than the three-field technique with a multileaf collimator. Major limitations of the comparisons that were made include the small number of subjects and the influence of patient selection.

The development of radiation sequelae in a specific organ depends on the dose and irradiated volume (15, 16). When large fields are used for the irradiation of tumours in or near the abdominal cavity, painful cramps in the abdomen, difficulty in digesting fat and fluctuation between diarrhoea and constipation occur with varying degrees of severity. Tubiana et al. suggest that a dose of at least 40 Gy is required before the risk of complications in the 'abdominal cavity' increases (16). In our study, the mean volume of anal sphincter to receive a dose ≥ 40 Gy for patients treated with the four-field technique was 50% higher than that for patients treated with three fields ($0.75 \times 24 = 18$ cm^3 and $0.58 \times 21 = 12$ cm^3). Furthermore, the mean volume of anal sphincter that received a dose ≥ 60–70 Gy for patients treated with the four-field technique was 14–100% higher than that for patients treated with three fields. Some of the reported stool blood may originate from tissue in and adjacent to the anal sphincter, so the documented difference in dose may partly explain the higher prevalence of rectal bleeding symptoms in patients treated with a four-field technique. Both the anatomical volume of the bowel, and the percentage that is irradiated, may influence symptom occurrence (17). The mean rectum wall volume that received a dose ≥ 60 Gy for both groups was the same ($0.68 \times 44 = 30$ cm^3 and $0.75 \times 40 = 30$ cm^3). The mean DVH of the rectum wall indicated that at least 60% of the rectum volume received a dose of ≥ 67 Gy in both groups I and II. The mean lower bowel tract volume that received a dose of ≥ 35 Gy for patients treated with four fields was 27% higher than that for patients treated with the three-field techniques. The higher prevalence of defecation urgency and loose stools in patients treated with a four-field technique may be due to the higher mean dose volume of the lower bowel tract for patients treated with four fields than those treated with the three-field technique.

Difficulties in comparing the results of our study with those of previous studies include the methodological and technical differences involved, such as the treatment dose, the method used to assess bowel, urinary and sexual dysfunction and the follow-up time.

Adolfsson and co-workers previously found a prevalence of 4% of faecal leakage and 10% of (any degree) defecation urgency symptoms in the general Stockholm population (18). In a separate study from Stockholm, population controls reported a prevalence of 2% of faecal leakage (at least once a month) and 2% of defecation urgency (every other time or more). In addition, the authors found a prevalence of 11% of diarrhoea and 2% of blood or phlegm in stools (at least once a month) (19). The prevalence of symptoms of faecal leakage, defecation urgency, diarrhoea and blood or phlegm in stools in all four groups in the present study was higher than the previously found background occurrence in the Stockholm population. Thus, current data indicate that radiotherapy for prostate cancer in Stockholm during 1993–1996 probably increased the long-term risk of symptoms of faecal leakage, defecation urgency, diarrhoea and blood or phlegm in the stools. Similar results were obtained in Umeå (Sweden), where irradiated prostate cancer patients and controls showed differences in the prevalence of faecal leakage (27% vs. 2%), abdominal cramps (14% vs. 5%) and mucus in the stools (38% vs. 4%) after an average follow-up time of 48 months, ranging from 24–56 months (20). We know of no other comparative study.

The results of previous studies have demonstrated different late side effects after external beam, conventional or conformal radiation therapy for prostate cancer. Rectal bleeding and diarrhoea were reported by respectively 14% (8/57) and 25% (14/57) of patients treated with a four-field

box (multileaf collimator, 64–66 Gy) (21). However, rectal bleeding and diarrhoea were reported in respectively 34% (39/114) and 9% (10/114) of patients treated with three fields (using customized cerrobend blocks to shape the radiation beam) and a treatment dose of 60–64 Gy (2). More than one-third of patients treated with a four-field box (using a conventional collimator and a treatment dose of 70 Gy) (22) have reported urgent bowel movements. In addition, 20% (37/189) and 7% (17/189) of patients who received the same treatment with a dose of 66 Gy reported rectal urgency and faecal leakage (23).

We did not find any statistically significant differences between the groups relating to urinary symptoms after radiotherapy, with the exception of the increased prevalence of a weak urinary stream in the group II compared with the group I patients. This finding may be explained by the fact that the bladder base, urinary anal sphincter and urethra when using both the three- and four-field technique lie within the radiation target volume. We have no explanation for the observation that all relative risks for obstructive urinary symptoms are above 1.0. The numbers are small and random variation may explain the finding or this may be due to the treatment conformality with a multileaf collimator (4–8).

The figure for the preservation of potency in the present patient population treated with the three-field technique using a multileaf collimator and 70.2 Gy was lower than that previously reported at a 1–1.5-year follow-up (3) but similar to results of a 4.5-year follow-up (3). In the latter study, patients were treated with a similar treatment protocol, using the same method for assessing erection stiffness as in the present study. The time to follow-up probably increases the risk of erectile dysfunction. In the current study the potential confounding factors predicting erectile function were not similarly distributed among patient groups (24–28). Still, no statistically significant differences were found between the groups.

We did not include the effects of set-up errors and organ motion; there, errors on average deviate from the relative risks presented towards unity. However, the anal sphincter is more fixed than the rectum (29–32).

Stratifying the data to assess the potential confounding effect of age and follow-up time or excluding patients reporting intercurrent diseases that may confound the relationship did not change the results.

The results for group IV patients are shown in the last column of Tables 2–4. We did not calculate relative risks for this group because the length of the follow-up was greater than for the other groups and information on about 38% of the patients in this group was lost owing to death or refusal to participate in the study. However, no clear differences in prevalence between groups III and IV were found.

Many patients wish to be informed about the side effects of a specific type of treatment, and it is a challenge to communicate such data to men with clinically localized prostate cancer where several treatment options are available (33). One probably cannot say that three fields are 'better' than four fields, or visa versa, since the two approaches entail contrasting risk scenarios and varying symptoms cause distress in subjects differently. On average, faecal leakage is the most distressing bowel symptom and three fields probably implies a higher risk for this symptom than four fields.

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