at the institution. A formal data monitoring committee was in place to oversee the trial's progress. The National Institutes of Health and the review boards of the RTOG and/or participating institutions approved the study. Local failure was defined as the reappearance of palpable tumor after initial clearance, progression of palpable tumor at any time, persistence of palpable tumor beyond 24 months after study entry, and the biopsy-proven presence of carcinoma of the prostate ≥2 years after study entry. Regional failure was defined as clinical or radiographic evidence of tumor in the pelvis with or without palpable tumor in the prostate. Distant metastasis was defined as clinical or radiographic evidence of disease beyond the pelvis. Disease-free survival or no evidence of disease (NED) survival was defined as survival in the absence of locoregional failure or distant metastases. Disease-free survival was also computed using PSA as an endpoint (either 1.5 ng/mL or 4 ng/mL as the threshold). In these computations, only patients with PSA determinations past 1 year were included in the analysis. Disease-specific mortality was defined as death from prostate cancer or protocol treatment. Patients who died with disease and for whom the cause of death was unknown were also considered to have failure for this endpoint. Absolute survival was defined as death from any cause. Absolute survival and disease-specific mortality were measured from the date of randomization to the date of death or the most recent follow-up evaluation. Persistence of palpable prostate tumor beyond 2 years was recorded as local recurrence as of day 1. The time to distant metastases or local recurrence was measured from the date of randomization to the occurrence of either event. The cumulative incidence approach (2) was used to estimate the time to local failure, time to distant metastases, and time to disease-specific mortality, because it specifically adjusts for other competing risks of failure. The test statistic developed by Gray (3) for comparing cumulative incidence rates was used. NED survival and absolute survival were estimated according to the Kaplan-Meier method (4). Comparisons for these survival endpoints were performed with the log–rank test (5). All statistical comparisons were made with two-tailed tests. Multivariate analyses to look at the treatment effect in the presence of prognostic factors were performed using Cox proportional hazard regression models (6).

RESULTS

Between February 1987 and April 1992, when the study was closed, a total of 977 patients were accessioned. Of these, 488 were entered in the adjuvant arm (Arm I) and 489 in the observation arm (Arm II); 32 patients were retrospectively classified as ineligible and were excluded from the subsequent analysis, leaving 477 analyzable cases in Arm I and 468 in Arm II. The pretreatment characteristics are listed in Table 1. Figure 1 shows the absolute survival for the entire study population. At 10 years, 49% of the patients in Arm I were alive compared with 39% in Arm II ($p = 0.002$). The incidence of disease-specific mortality is show

Table 1. Pretreatment characteristics

	Adjuvant Zoladex ($n = 477$)		Zoladex at relapse ($n = 468$)	
Characteristic	*n*	%	*n*	%
Differentiation				
Well	130	27	125	47
Moderate	234	49	228	49
Poor	113	24	115	24
Centrally reviewed Gleason score				
2–6	125	29	129	30
7	172	39	160	38
8–10	139	32	137	32
Lymph nodes				
Negative	337	71	345	74
Positive	140	29	123	26
Acid phosphatase				
Not elevated	308	65	309	66
Elevated	169	35	159	34
Prostatectomy				
No	406	85	400	86
Yes	71	15	68	14

in Fig. 2, with a rate of 16% and 22% for the adjuvant and control arms, respectively. Table 2 summarizes the endpoints for the entire study population, as well as the absolute survival and disease-specific mortality endpoints for the central Gleason subsets of 2–6, 7, and 8–10. The beneficial adjuvant effect appeared preferentially in patients with a higher Gleason score. At 10 years, the local failure rate in the adjuvant arm was 23% vs. 38% in the control arm ($p < 0.0001$). The incidence of distant metastases was 24% in the adjuvant arm and 39% in the control arm at 10 years ($p < 0.0001$). The NED survival rate was 37% and 23% in the adjuvant and control arms, respectively, at 10 years ($p < 0.0001$). Taking into consideration the PSA level, the NED survival rate with a PSA level of <1.5 ng/mL was 31% in the adjuvant arm and 9% in the control arm at 10 years ($p < 0.0001$). Only patients with a PSA value past 1 year were included in this analysis (438 patients in the adjuvant arm and 429 patients in the control arm. The median follow-up for the entire study population was 7.6 years for all patients and 11.0 years for alive patients. The median follow-up for all patients and alive patients, respectively, within the central Gleason subsets was 9.6 and 12.0 years for central Gleason score 2–6 patients, 7.9 and 11.0 years for central Gleason score 7 patients, and 6.0 and 11.0 years for central Gleason score 8–10 patients.

The results of the multivariate analyses are shown in Table 3. The following variables were used in the multivariate analyses: treatment (Arm I vs. Arm II), prostatectomy (yes vs. no), nodal involvement (no vs. yes), central Gleason score (2–6 vs. 7–10), age (<70 vs. ≥70 years), and clinical stage (A-B vs. C). Treatment remained statistically significant in favor of the adjuvant arm on multivariate analysis for all endpoints. In addition to treatment, the following

The introduction of 3DCRT has led to the expectation that exposure of less normal tissue would reduce toxicity (2). Retrospective and prospective analyses of conformal radiotherapy in prostate cancer published in recent years suggested a low percentage of serious toxicity even when using high tumor doses (3–11). In the study by Hanks *et al.* (3) a 20% reduction in grade 2 acute toxicity was found. In another study (10), comparing historical patient groups, a 20% and 27% reduction of grade 2 acute toxicity was suggested for intestinal symptoms using computed tomography (CT)-based and beam's eye view–based radiotherapy techniques instead of conventional techniques.

However, in two randomized studies (7, 9), these differences in acute toxicity have not been confirmed. In the preliminary report of the M.D. Anderson Hospital (7) acute toxicity (grade $>$ 2) after conventional radiotherapy (RT) (70 Gy, $n = 31$) vs. conformal therapy (79 Gy, $n = 29$) was 0% and 10%, respectively, for bladder symptoms ($p > 0.4$) and 0% and 3%, respectively, for rectal symptoms ($p > 0.4$). In the Royal Marsden study (9) including prostate ($n = 138$), bladder ($n = 110$), and rectal cancer ($n = 11$), acute toxicity was identical using a patient questionnaire. Fifty percent and 23% of patients, respectively, reported more than "quite a bit" of bowel and bladder toxicity ($p = 0.3$ and 0.6). The authors were not able to score toxicity, for example, according to the European Organization for Research and Treatment of Cancer/Radiation Therapy Oncology Group (EORTC/RTOG) toxicity scoring systems. Another problem in this study was the nonuniform fractionation scheme and dose. Our study was performed in a homogeneous group of patients treated with a homogeneous tumor dose and fractionation scheme. In the presented analyses a possible volume–toxicity correlation was studied using the EORTC/RTOG score, with special attention to the medication prescribed. We therefore feel that this study provides additional information to clarify possible mechanisms of acute toxicity caused by the conservatively dosaged radiotherapy schemes.

METHODS AND MATERIALS

General information

From June 1994 to March 1996, 266 patients were enrolled in a randomized study. Inclusion criteria were: $T_{1\text{-}4}N_0M_0$ prostate carcinoma without prior radiotherapy to the pelvic region. Patients with a history of other malignancies were excluded. As the primary aim of this study was to investigate a possible reduction in toxicity, any tumor stage, grade, and prostate-specific antigen (PSA) level was accepted. Hormonal (neo)adjuvant therapy was not used at the time of this study. The pelvic lymphatics were not treated intentionally. There are no significant differences in patient characteristics for both study arms (Table 1). Three patients were excluded from further analysis, as they refused further treatment or because they appeared to have regional and/or distant metastases during pretreatment screening.

Table 1. Comparison of conventional and conformal radiotherapy study arms for patient characteristics and dose information

		Conventional	Conformal
No. of patients		134	129
Mean age		69 (SD 7)	69 (SD 6)
T classification	T1	16	15
	T2	66	57
	T3	47	54
	T4	5	3
Histology	grade I	44	37
	grade II	65	59
	grade III	22	28
	grade x	3	5
PTV dose	mean	66.3 (SD 0.8)	66.2 (SD 0.7)
PSA at start		26 (SD 38)	21 (SD 20)
iPSA	$<$10	41	41
iPSA	10–20	39	40
iPSA	$>$20	50	47
iPSA	unknown	4	1

iPSA = initial PSA.

Radiotherapy protocol

All patients were treated to a dose of 66 Gy in the International Commission on Radiation Units and Measurements (ICRU) reference point (12), using the same treatment planning procedure, treatment technique, linear accelerator, and portal imaging procedure. Patients in the conventional arm were treated with rectangular, open fields; conformal radiotherapy was performed with conformally shaped fields using a multileaf collimator (MLC). Patients were asked to have a full bladder and empty rectum at the time of the planning CT scan and during treatment. For the CT scan 5-mm slices were used with a 5-mm width. The responsible radiation oncologist contoured the gross target volume (GTV), the lower intestinal structures, and the bladder. The GTV was limited to the prostate in T1 tumors, whereas in all other patients it encompassed both the prostate and the seminal vesicles. The length of the intestinal structures analyzed was limited by the superior and inferior field borders. The anus was reconstructed from these contours being (by definition) the most caudal 3.0 cm. The remaining intestines were defined to be the rectum/sigmoid (Fig. 1). The bladder was contoured entirely. The planning target volume (PTV) was constructed using an automated (uniform) 3D expansion of the GTV volume (13), adding 5 mm for microscopic disease (clinical target volume [CTV]) and another 10 mm for positioning errors and CTV mobility. These margins were chosen on the basis of the first reports on the internal movement of the CTV (14–20). All contours were checked by the study coordinator, to guarantee a uniform description of the contoured volumes.

In the planning protocol a strict planning procedure was prescribed to guarantee a standard treatment plan for both treatment groups. A three-field technique (one anterior and two oblique laterals) was used. All treatment plans were made with a 3D treatment planning system (CADPLAN). In

of the study, following the precepts of the CONSORT statement (27), and from then on, no other patients were excluded, as can be seen in Figure 1. All patients adhered to the treatment assignment, and there were neither side effects nor intolerance related to the use of synbiotics or placebo. Groups were homogeneous regarding age and body mass index. There was no significant difference in the cumulative radiation doses and in the irradiated rectal volume, as can be seen in Table 1 and Figure 2.

Proctitis symptoms plus quality of life scores

Both groups showed an increasing sum of points obtained from questions 1 to 21 ($P=.01$; within-groups comparison) (Fig. 3A). The median sum of points was 21 in both groups before treatment. Then it increased to 21.5 (range, 21-25) in week 1, 23 (21-30) in week 2, 23 (21-32) in week 3, and 23.5 (21-30) in week 4 in the synbiotic group. In the placebo group this increase was significantly higher in the second (26.5 [22-34]; $P<.05$) and third weeks (27.5 [24-32]; $P<.01$). This higher increase of points in the placebo group was mostly due to a greater number of points seen in questions 6 (need to get up at night to open bowels), 13 (intensity of tenesmus), and 14 (urgency for a bowel movement during urination) of the questionnaire ($P<.01$; ANOVA for repeated measures). No difference was seen in the first (placebo group, 22 [21-37]) and fourth weeks (placebo group, 27[21-35]) of radiation therapy (Table 2). Comparing the 2 groups by repeated-measures ANOVA, the score of the placebo group was significantly higher ($P<.01$) than that of the synbiotic group (Fig. 3A).

Proctitis symptoms scores

There was a significant increased scores in questions 1 to 15 of the EORTC QLQ-PRT23 questionnaire in the 2 groups along the 4 weeks ($P=.01$; within-groups comparison) (Fig. 3B). Groups showed similar scores before treatment (synbiotic group, 15 [15-19] and placebo group, 15 [15-23]; $P=.80$). However, the sum of points increased to a median (range) of 15.5 (15-19) in week 1, 16.5 (15-20) in week 2, 17 (15-23) in week 3, and 16.5 (15-22) in week 4 in the synbiotic group. In the placebo group this increase was significantly higher in the second (19.5 [16-25]; $P<.05$) and third weeks (19 [17-24]; $P<.01$). No difference was seen in the first (placebo group, 16 [15-25]) and fourth weeks (placebo group, 20 [15-26]) of radiation therapy (Table 3). The score of the placebo group was significantly higher (repeated-measures ANOVA; $P<.01$) than that of the synbiotic group (Fig. 3B).

Table 1 Demographic and clinical characteristics of the 2 groups

Variable	Symbiotic group	Placebo group	*P*
Age (y)	64.3 (7.5)	70.4 (8.3)	.10
BMI (kg/m^2)	30.0 (5)	27.4 (3.8)	.23
Radiation dose (Gy)			
1st week	10 (10-14)	10 (6-14)	.67
2nd week	20 (18-24)	21 (18-26)	.21
3rd week	30 (28-34)	31 (28-38)	.10
4th week	40 (38-42)	40 (38-56)	.30
Irradiated rectal volume (%)*			
V10	77.1 (64.1-97.9)	84.6 (47.9-99.7)	.48
V20	66.9 (37.4-95.4)	77.5 (39.6-96)	.43
V30	31.3 (21.2-43.3)	26 (23.2-53.4)	.74
V40	14.8 (4.6-18.1)	11.9 (5.8-22.7)	.74

Abbreviation: BMI = body mass index.Values of age and BMI are mean and SD (Student's T-test). Values of radiation dose and irradiated rectal volume are median and range (Mann-Whitney test).

* Percentages of rectal volume that received 10 Gy (V10), 20 Gy (V20), 30 Gy (V30), and 40 Gy (V40) after radiation accumulated doses of 40 Gy.

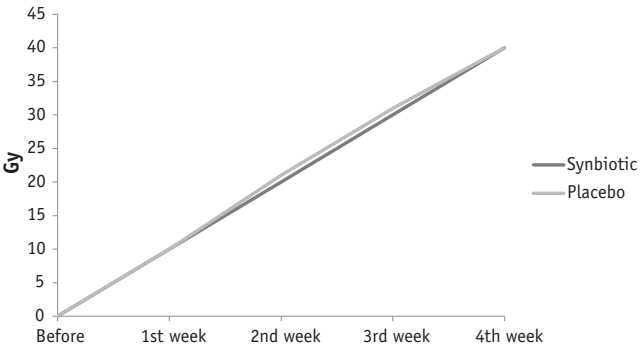

Fig. 2. Evolution of cumulative radiation doses in the 2 groups during the 4 weeks of follow-up. Data represent the median. $P>.05$ in all comparisons between groups.

Bowel movements

There was no significant difference among the groups during the period of study. Bowel movements ranged from a median of 2 to 3 in each week (data not shown).

Discussion

The overall results showed that early prescription of synbiotics had an important role in both proctitis symptoms and quality of life during the first 4 weeks of radiation therapy for prostate cancer. Not only did the scores related to the combined proctitis symptoms plus quality of life questions of the EORTC QLQ-PRT23 questionnaire increase less in the synbiotic group, but the scores of proctitis symptoms alone also presented the same pattern. The homogeneity between the 2 groups regarding demographic data, dose of radiation, and irradiated rectal volume was quite important to ensure that the only difference between the 2 groups was the use or not of synbiotics and thus to confirm the initial hypothesis. These results suggest that synbiotics might help in preventing the upsetting collateral rectal symptoms that are often present during the initiation of radiation therapy.