Pre- or Postoperative Radiotherapy in Rectal and Rectosigmoid Carcinoma

Report from a Randomized Multicenter Trial

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Between October 1980 and December 1985, 471 patients with a resectable rectal carcinoma entered a randomized multicenter trial for comparison of pre- and postoperative irradiation. Two hundred thirty-six patients were allocated to receive high-dose fractionated preoperative irradiation (total dosage, 25.5 Gy in five to seven days) and 235 patients to receive postoperative irradiation to a very high dosage level with conventional fractionation (60 Gy in a total 8 weeks). The postoperative treatment was delivered only to a high-risk group of patients (Astler-Coller stages B_2, C_1, and C_2). The preoperative irradiation was well tolerated, with no immediate irradiation-related complications and no increased postoperative mortality (3%, 7 of 217 patients, compared to 5%, 10 of 215 patients in the postoperatively irradiated group). More patients in the preoperative irradiation group had perineal wound sepsis after abdominoperineal resection and this prolonged the stay in hospital after surgery. In 50% of the patients the postoperative treatment could not be commenced until more than 6 weeks after surgery. The postoperative treatment was not as well tolerated as the preoperative one. The local recurrence rate was statistically significantly lower after preoperative than after postoperative radiotherapy (12% *versus* 21%; $p = 0.02$). In both groups more patients developed a local recurrence if the bowel was perforated at surgery or if the resection line was microscopically close to the tumor. To date, with a minimum follow-up of 3 years and a mean follow-up of 6 years, there is no difference in survival rates between the two groups.

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LOCAL RECURRENCES AFTER curative surgery for rectal carcinoma are common, although the rates reported in the literature have varied from less than 10% to as much as 65%.[1-6] The skill of the surgeon,[5] patient selection, and/or different follow-up routines have been discussed as reasons for this variability. With perioperative radiotherapy, provided the dosage level has been sufficiently high (> 40 Gy in 3 to 4 weeks, or a comparable dosage level with other fractionation schedules), the local recurrence rate has been substantially reduced.[7-9] One major question is whether an additional treatment should preferably be given before or after operation, or both. With postoperative radiotherapy, groups of patients found to be at low risk of local recurrence can be excluded from therapy, whereas at present this is not possible when preoperative therapy is used.

In 1980 a trial for comparison of preoperative radiotherapy at a high dosage level with a postoperative radiotherapy regimen to an even higher dose given only to high-risk groups of patients was initiated. The primary aim of the trial was to investigate whether the local recurrence rate differs between the two treatment modalities. A secondary aim was to compare the survival. An interim report on the trial was published shortly before the end of the inclusion of the patients.[10] This second report will focus on the acute effects of the treatment, the local recurrence rate, and the survival after a minimum follow-up of 3 years (mean, 6 years).

Materials and Methods

Patients

Between October 1980 and December 1985 all patients with a tumor in the rectum or rectosigmoid (18 to 20 cm or less from the anal verge as measured at rigid sigmoidoscopy) were recruited to the trial from a defined area of Sweden. Patients with primarily operable tumors in whom an anterior resection or an abdominoperineal resection was considered, were randomly allocated either to a preoperative group, in which all patients were to have radiotherapy, or to a postoperative group in which the radiotherapy was to be given only to high-risk groups of patients (Fig. 1).

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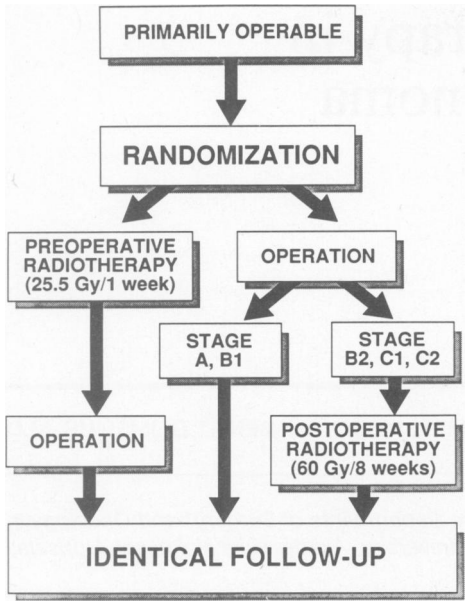

FIG. 1. Treatment protocol for rectal carcinoma.

Exclusion criteria included

(1) locally inextirpable tumors, *i.e.*, tumors fixed to the pelvic wall or genitourinary organs (excluding the vagina) and large bulky tumors that were not really mobile;
(2) previous radiotherapy to the pelvis;
(3) high age and/or poor condition (no upper age limit was used);
(4) advanced generalized disease; and
(5) other malignant generalized disease.

Of a total 471 patients from whom informed consent was obtained, 236 patients were randomly allocated to the preoperative group and 235 to the postoperative group. The age and sex distributions are given in Table 1.

During the same time period, a primary adenocarcinoma of the rectum was diagnosed in 123 additional patients. Fifty-nine of these patients had a tumor that was considered locally inextirpable and 64 had an extirpable tumor. Those patients were not included in the trial because of a high age or poor condition (29 patients), advanced distant metastases (9 patients), previous radiotherapy to the pelvic region (6 patients), other malignant disease (9 patients), refusal of treatment (8 patients), and inconclusive preoperative biopsy (7 patients).

TABLE 1. *Age and Sex Distributions of the Initially Included 471 Patients*

	Preoperative Group			Postoperative Group		
		Age			Age	
	n	Median	Range (yrs)	n	Median	Range (yrs)
Men	134	71	(42–84)	138	70	(40–83)
Women	102	72	(44–87)	97	69	(39–87)

Surgery and Histopathology

Standard surgical procedures were used and the choice of operative procedure rested on the surgeon. Locally radical surgery included a bowel with a radically resected tumor with free margins at histopathologic examination. If the bowel was damaged during surgery but a free margin was observed histopathologically, the operation was considered radical. The operative specimen was classified according to a modification of Dukes' staging system:

A = tumor limited to the mucosa and submucosa; negative lymph nodes;
B_1 = tumor extension into but not through the muscularis propria; negative lymph nodes;
B_2 = tumor extension through the muscularis propria; negative lymph nodes;
C_1 = tumor extension into but not through the muscularis propria; positive lymph nodes; and
C_2 = Tumor extension through the muscularis propria; positive lymph nodes.

This is a slightly modified version of what has been referred to as the Astler-Coller modification of Dukes' staging system.[11]

Irradiation

The irradiation technique has been described previously.[12] Briefly, the target volume included the whole dorsal part of the pelvic cavity from the anus up to L4. The irradiation was given with one mid-dorsal and two angled dorsal portals with the patient in a prone position (Fig. 2). The relative biologic effect of the irradiation on

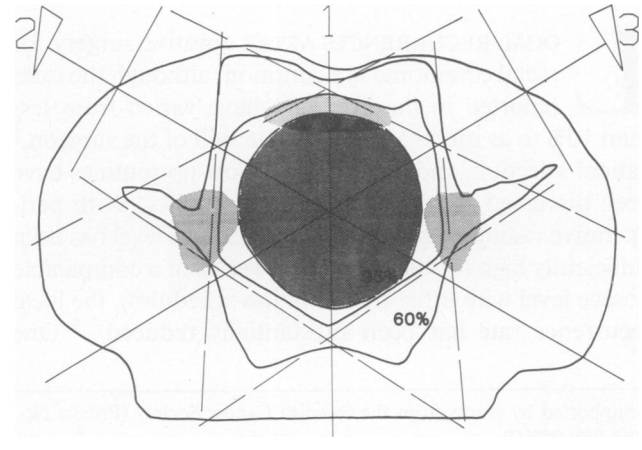

FIG. 2. Plan of irradiation. Transverse section through S3 with the patient in a prone position. The target area is closely encompassed by the 95% isodose curve.

normal cells was calculated according to the CRE (cumulative radiation effect) concept,[13] with corrections for late effects on normal tissue (corrected CRE) as suggested by Turesson.[14]

Preoperative irradiation. All patients allocated to this treatment group should receive a total tumor dose of 25.5 Gy in five fractions of 5.1 Gy daily over five to seven days. The corrected CRE values for five days and seven days were 15.4 and 14.9, respectively, corresponding to 47 to 49 Gy given with fractions of 2 Gy daily (10 Gy/week). The patients were operated on within 1 week after radiotherapy.

Postoperative irradiation. Patients with a tumor in stage A or B_1 as evaluated at the postoperative histopathologic examination did not receive any radiation, even though they were randomly allocated to the postoperative group. According to the intended schedule, the postoperative radiotherapy should ideally have been started within 4 to 6 weeks after surgery. Irradiation was delivered in a dose of 2 Gy daily, five days per week for 4 weeks. After an interval of 10 to 14 days, further radiation was given for a period of 2 weeks to a total dose of 60 Gy. The target volume was reduced during the last 10 Gy. This dose corresponds to a CRE value of 17.0 to 17.2, the variation depending on the length of the interval.

Follow-up Routines

The patients were followed clinically every third month during the first postoperative year, every fourth month in the second year, and twice a year up to at least 5 years. Since the fifth year, the patients have been followed yearly. Computed tomography (CT) of the pelvic region was performed at least once, 6 to 9 months after surgery. Several patients have been examined repeatedly.[15] Supplementary CT investigations were carried out if there was any clinical suspicion of recurrence. In the event of any clinical or roentgenologic suspicion of local recurrence, *e.g.*, if a mass was observed at CT, a fine-needle and/or true-cut biopsy directed to the region in question was performed. Only patients with a morphologically proved recurrent cancer within the pelvic cavity were recorded as having local recurrence. According to the protocol, a morphologic diagnosis should be the objective.

Statistics

Patients were randomly allocated to the two groups according to a self-adjusting randomization plan.[16] The material was stratified according to oncological department, sex, and tumor level (low tumors 0 to 10 cm, high tumors 11 to 20 cm). A total 441 patients had to be included to detect a difference in the local recurrence rate of 10% (from 10% to 20%), with a significance level of 0.05 and a probability of a successful test of 0.9. The power calculation was done with 10% drop-outs. Differences in local recurrence rate and survival were evaluated by the log-rank test.[17] In the survival calculations all patients were included, whereas only patients with locally radically resected tumors were included when differences in local recurrence rates were evaluated. Postoperative mortality was calculated among all patients who underwent a resection.

Results

Treatment

In the preoperative group all patients but one received the intended radiation, and in all but 14 the treatment was given according to schedule, *i.e.*, during five to seven days. In these 14 patients the treatment was prolonged for one to three days, mainly because of holidays. The preoperative radiotherapy was extremely well tolerated without any radiation-related adverse effects during the treatment period. Surgery was performed as scheduled within 1 week (seven days) after the end of the irradiation in all but 21 patients; in these patients it was performed between 8 to 22 days, except in two patients who had no surgery (Table 2). In 209 (89%) of the patients in the preoperative group the operation was locally curative (Table 2).

In the postoperative group, 204 (87%) patients had a resection that was locally curative (Table 2). Of these 137 had a tumor in local stage B_2, C_1, or C_2 and therefore should have been referred to postoperative irradiation. Radiotherapy was started, however, in only 115 patients (84%). The other 22 patients did not receive radiotherapy for the following reasons: postoperative death (9 patients), prolonged postoperative recovery (8 patients), advanced distant metastases (4 patients), and treatment refusal (1 patient). None of the patients in stage A and B_1 received radiotherapy.

Among the 115 patients who were given radiotherapy after operation, the length of time from surgery to radia-

TABLE 2. *Outcome in the Two Groups*

	n
Preoperative group	236
Refused treatment	1
Patients irradiated	235
Refused surgery	1
Wrong preoperative histopathological diagnosis	1
No surgery because of poor condition	1
No resection because of liver metastases	12
Locally inextirpable at surgery	3
Locally nonradical surgery	8
Locally curative surgery	209
Postoperative group	235
Wrong preoperative histopathological diagnosis	6
No resection because of liver metastases	10
Locally inextirpable at surgery	7
Locally nonradical surgery	11
Locally curative surgery	204

TABLE 3. *Histopathologic Stage and Surgical Procedure in the Two Groups*

	Preoperative Group			Postoperative Group		
Local Stage	APR	AR	Total	APR	AR	Total
A	13 (1)	2 (1)	15 (2)	8	5	13
B_1	31 (2)	21 (1)	52 (3)	26 (4)	18 (3)	54 (7)
B_2	45 (6)	26 (3)	71 (9)	40 (10)	26 (7)	66 (17)
C_1	4	2	6	9 (2)	4 (1)	13 (3)
C_2	42 (10)	23 (2)	65 (12)	35 (8)	23 (8)	58 (16)
Locally nonradical	5 (1)	3 (2)	8 (3)	8 (3)	3 (1)	11 (4)
No resection			19			19
Total	140 (20)	77 (9)	236 (29)	136 (27)	79 (20)	235 (47)

Figures denote numbers of patients and figures in parentheses denote number of local recurrences.

APR, abdominoperineal resection; AR, anterior resection.

tion was 6 weeks or less (≤ 42 days) in 62 patients (54%), between 7 and 8 weeks (43 to 56 days) in 26 patients (23%), and more than 8 weeks (range, 56 to 95 days) in 27 patients (23%). In the majority of patients in whom radiotherapy was not started within 6 weeks, the reason for this was prolonged postoperative recovery (fatigue, nonhealed perineal wound). In some patients practical reasons such as not wanting to start therapy immediately before a big holiday or in the middle of a vacation also contributed. The tolerance to the postoperative radiotherapy was not as good as to the preoperative treatment. In nine patients the treatment was interrupted prematurely (4 to 36 Gy), the reason being fatigue in 3 patients, infectious complications in 4, a cerebrovascular lesion in 1, and a synchronous generalized renal carcinoma in 1 patient. Most of the patients had mild to moderate symptoms such as diarrhea, fatigue, nausea, skin reactions, and urinary tract disorders, particularly during the end of the first radiation period (see also Påhlman et al.[10]). Only in nine patients could the treatment be completed without any adverse effects.

Histopathology and Type of Surgery

There was no difference between the two groups with respect to the surgical procedure or histopathologic stage (Table 3). Of 209 patients with locally radical surgery in the preoperative group, 17 had distant metastases. Among the 204 patients with locally radical surgery in the postoperative group this figure was 15.

Complications of Surgery

Seven of the 209 patients with locally curative surgery in the preoperative group died after operation (3%). In the postoperative group, this proportion was 9 of 204 (4%). Based on all resected patients, *i.e.*, including those with a locally nonradical resection, the postoperative mortality rate was 3% in the preoperative group (7 of 217 patients) and 5% in the postoperative group (10 of 215 patients).

Postoperative complications (Table 4) were equally distributed between the two groups, with one exception—that perineal wound sepsis after abdominoperineal resection occurred more often in the preoperative than in the postoperative group (33%, 45 of 135 patients *vs.* 18%, 23 of 128 patients; $p < 0.01$). This infection was treated with simple drainage and left open for secondary healing, and in all but three patients (two patients in the preoperative group and one patient in the postoperative group) the wound healed within 3 months. As seen in Table 5, the increased number of infected perineal wounds among preoperatively treated patients who underwent an abdominoperineal resection also affected the length of hospital stay because the longer stay among patients who received preoperative therapy was restricted to the group of patients who had this form of surgery.

TABLE 4. *Complications in Connection with Surgery**

Complication	Preoperative Group (n = 217)	Postoperative Group (n = 215)
Postoperative mortality		
Heart failure	3	5
Anastomotic dehiscence	2	1
Infectious complication	1	1
Ileus		2
Respiratory insufficiency	1	
Hematemesis		1
Perineal wound sepsis	45	23
Anastomotic dehiscence	14	13
Ileus-subileus	10	6
Postoperative fever	10	6
Abdominal wound sepsis	5	4
Abdominal wound rupture	7	4
Intra-abdominal abscesses or septicaemia	3	4
Thromboembolic disturbances	3	2
Stomal necrosis	4	4
Cardiovascular complications	2	3
Surgical mishaps	4	6
Pneumonia	—	1
Hematemesis	—	1

* Locally nonradical resections included.

TABLE 5. *Length of Stay After the Operation at the Department of Surgery, in Days*

	Preoperative Group				Postoperative Group				
	Range	Median	Mean	SD	Range	Median	Mean	SD	p Value
APR	9–146	28	38	25.3	9–79	25	28	14.6	$p < 0.001$
AR	7–100	17	23	18.9	7–100	16	22	19.1	$p > 0.05$
Total	7–146	25	33	23.6	7–100	20	26	16.6	$p < 0.01$

APR, abdominoperineal resection. AR, anterior resection.

Local Recurrence Rate

Statistically significantly more patients in the postoperative than in the preoperative group developed local recurrence (21%, 43 of 204 patient, *vs.* 12%, 26 of 209 patients, $p = 0.02$; Fig. 3, Table 6). This difference was noted in Astler-Coller stages B_2, C_1, and C_2. In stages A and B_1 the number of recurrences was small in both groups. Because of the small number of patients followed for more than 5 years (53 in the preoperative group and 45 in the postoperative group) an analysis of the differences in the local recurrence rate was performed on the findings at 5 years. The accumulated probability of developing a local recurrence at this time was 14.3% in the preoperative group and 26.8% in the postoperative group. The difference in local recurrence rate at 5 years was 12.5%, with a 95% confidence interval of 5% to 20%. Among patients in whom the bowel was perforated at surgery or in whom the resection line was close to the tumor microscopically, a local recurrence occurred significantly more often both in the preoperative ($p < 0.01$) and in the postoperative group ($p < 0.05$) than among those in whom the surgery was more definitely locally radical (Table 6). There was no difference between the two groups regarding the length of time between surgery and the development of a local recurrence (Fig. 3). Local recurrence developed in 3 of 17 patients with distant metastases in the preoperative group and in 2 of 15 in the postoperative group. Three of eight patients with locally nonradical surgery in the preoperative group displayed local recurrence, and 4 of 11 in the postoperative group. All patients with locally nonradical surgery in whom local recurrence did not develop died of cancer (nine patients) or intercurrent disease (three patients) within 18 months (median, 8 months) after surgery.

Distant Metastases and Survival

As seen in Figure 4, there was no difference between the two groups concerning the length of time that elapsed from surgery to the occurrence of a distant metastasis. So far there is no difference in overall survival between the two groups as calculated on the total material, or in cancer-specific survival estimated on the basis of patients operated on for total cure (Figs. 5 and 6).

Discussion

When discussing radiotherapy as an adjuvant to surgery, it is essential to remember that the minimum dose level required to kill micrometastases with a probability exceeding 90% is about 45 Gy in 4 weeks or a comparable dose level (CRE about 14.0) with other fractionation schedules.[18] With this figure in mind, influence on the

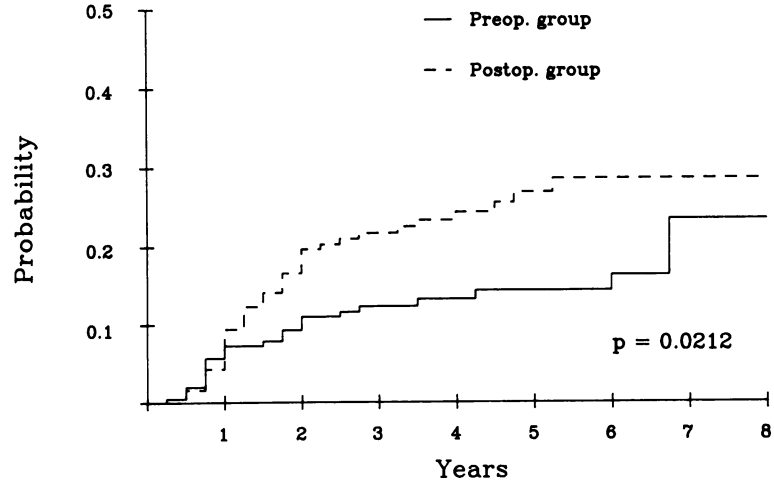

FIG. 3. Local recurrence rate after locally curative surgery in the two treatment groups.

TABLE 6. *Local Recurrences in Relation to the Findings at Histopathology and the Radicality of the Operation*

Group	Locally Satisfactory Surgery	Perforated Bowel	Histopathologically Close to Resection Line	Total
Preoperative				
A	11 (2)	4	—	15 (2)
B_1	45 (1)	6 (2)	1	52 (3)
B_2	57 (6)	8 (2)	6 (1)	71 (9)
C_1	6	—	—	6
C_2	47 (6)	10 (4)	8 (2)	65 (12)
Total	166 (15)	28 (8)	15 (3)	209 (26)
Postoperative				
A	9	4	—	13
B_1	47 (5)	7 (2)	—	54 (7)
B_2	52 (13)	12 (2)	2 (2)	66 (17)
C_1	11 (1)	2 (2)	—	13 (3)
C_2	38 (9)	17 (6)	3 (1)	58 (16)
Total	157 (28)	42 (12)	5 (3)	204 (43)

Figures denote number of patients (local recurrences).

local recurrence rate should not be expected in trials in which low dosage levels are used, and this has in fact been found to be the case.[19-23] In trials with higher dosage levels, a reduced local recurrence rate has been noted. In the EORTC trial preoperative irradiation to a comparably high dose level (CRE 13.0) reduced the local recurrence rate significantly.[7] An even larger reduction was achieved in the Stockholm trial,[8] in which a dose similar to our own (25 Gy in 1 week) was administered. In a Danish trial, in which a dose of 50 Gy in 5 weeks (CRE 15.2) delivered postoperatively was compared with surgery alone, no significant reduction in the local recurrence rate was found, except possibly in Dukes' B cases.[24] A slight reduction in the local recurrence rate was also observed in a GITSG study in which radiotherapy was given after operation to about 45 to 50 Gy in 4 to 5 weeks.[9] In that trial an even better effect was noted when radiotherapy was combined with chemotherapy.

Taken together results from trials using a surgery-alone arm as control indicate that preoperative irradiation at comparable, or even lower dosage levels, is more efficient in reducing the local recurrence rate than postoperative irradiation. This conclusion was strongly supported by the results of the present trial. Further in this trial we have used an unconventional preoperative treatment designed to be easy to deliver and to be a tempting alternative both for the patient and surgeon. On the other hand the treatment used in the postoperative group was designed to be the most satisfactory treatment that could be given as adjuvant therapy to patients with rectal tumors. In no other trial has such a high dosage level been used. In light of this it is interesting that a significantly lower local recur-

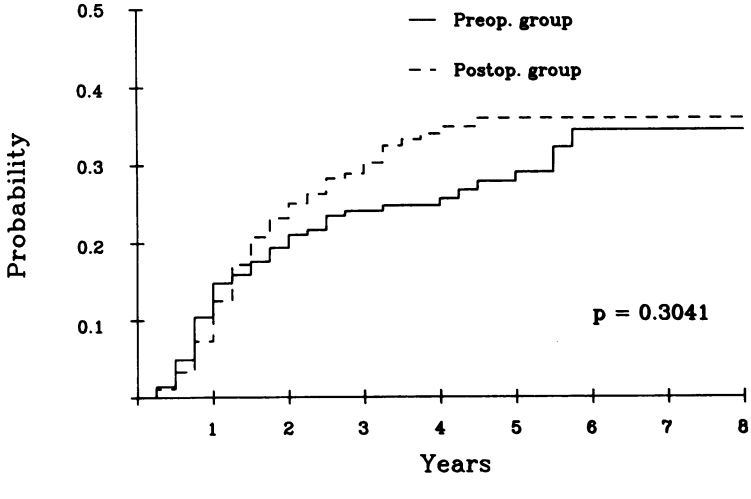

FIG. 4. Probability of development of distant metastasis after curative surgery in the two groups.

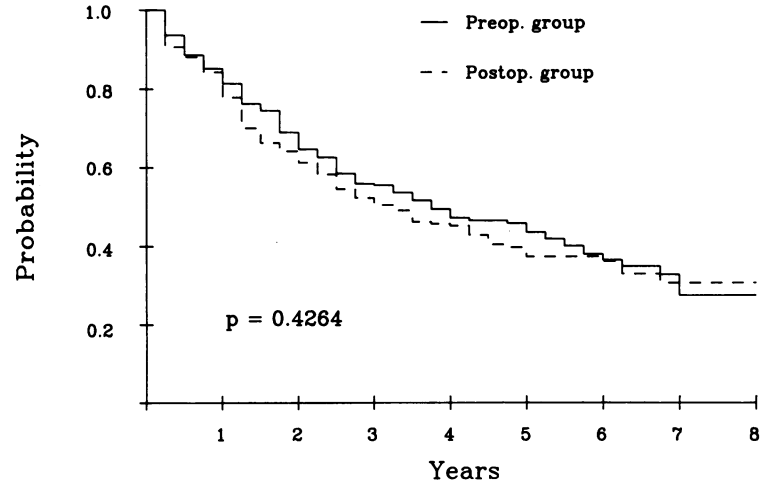

FIG. 5. Overall survival regardless of cause of death in the two groups.

rence rate was noted after the semi-optimal preoperative treatment than after the probably optimal postoperative treatment. The results support the idea that higher dosages are necessary to kill micrometastases in surgically disturbed tissue than in nondisturbed tissue.[18,25]

Another finding in this trial is an increased local recurrence rate among patients in whom the bowel was perforated at surgery or in those patients in whom the margin of clearance was microscopically minimal. Similar results with an increased local recurrence rate after bowel perforation have been found in series of patients treated with surgery alone.[26,27] Whether a minimal margin of clearance is deleterious is more questionable. In a large series from St Mark's Hospital, no difference in the recurrence rate was noted comparing those with a microscopically minimal or unclear (less than 2 mm) margin of clearance to those with a larger margin.[28] In that trial, only the distal margin of clearance was taken into account. If, however, the specimen was carefully examined concerning the lateral spread, Quirke et al.[29] found that the local recurrence rate was increased if the lateral margin was not clear. In the present material, the doubtful microscopic clearance was either lateral or distal.

The radiation technique used in this trial differed from that used in most other trials. With three or four radiation portals, one can largely avoid irradiation of other parts of the pelvis and abdomen than the tumor-containing target volume. If the irradiation is given with two opposed anterior-posterior portals, as in most trials, the irradiated volume is considerably larger. This difference in the radiation technique could well explain the higher postoperative mortality rate noted in the Stockholm trial[8] and in the small trial from St. Mark's Hospital.[30] This was not observed in the present series. The increased postoperative mortality rate in the two mentioned series was restricted to patients older than 75 years and referred mainly to those with generalized disease at surgery. It is tempting to believe that a large irradiated volume may be deleterious in this age group. With the irradiation technique used in this trial, we have established that preoperative radio-

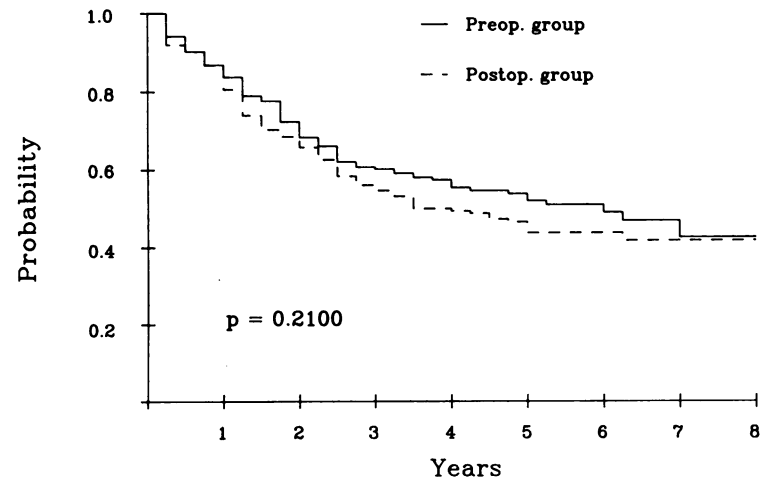

FIG. 6. Cancer-specific survival after curative surgery in the two treatment groups.

therapy to a high dosage level (CRE above 14.5) can be delivered without affecting the postoperative mortality rate. However, as in other trials[7,8] using preoperative radiotherapy, the postoperative morbidity was increased in one respect, *i.e.*, there was an increased frequency of infections in the perineal wounds after abdominoperineal resection. This increase in perineal wound sepsis prolonged the hospital stay. In the long term, however, this is no problem for the patient because the perineal wound healed within 3 months in virtually all patients.

Another question is whether additional therapy will cause a long-term increase in morbidity (intestinal obstruction, urinary or skin reactions). All patients with a minimum follow-up of 5 years in this trial were re-examined with respect to late adverse effects of radiation. After this follow-up evaluation, no differences were found between those who were given preoperative radiotherapy, postoperative radiotherapy, or surgery alone concerning bowel obstruction or other possible late adverse effects (manuscript in preparation).

The follow-up of this trial is still too short to estimate if there will be any survival benefits. Radiotherapy to the primary tumor area cannot affect occult metastases in the liver, for instance. On the other hand, if the local recurrence rate is decreased, and if such a recurrence is the only residual tumor, preoperative radiotherapy will, after a prolonged follow-up, have an impact on survival. In the Stockholm trial, when the survival curves were corrected for postoperative deaths, the survival was increased in the group of patients who received preoperative radiotherapy.[31] This difference is statistically significant. Similarly, in the EORTC trial, the survival curves are diverging with longer follow-up.[32] Taken together, however, the improvement of the local control by preoperative radiotherapy, even at higher dosage levels, does not translate into any substantially improved survival. This lack of any major survival benefit prompts the question of whether the radiotherapy should be postponed until a local recurrence has developed rather than be given to all patients before operation. The answer to this question is not known. However a local recurrence is usually a tragedy for the patient because of symptoms like pain, soiling, and/or fistulation. Local radiotherapy may give pain relief in most patients, whereas other symptoms respond less well. Also symptoms usually recur after a median time of 6 to 8 months. Radiotherapy, even if given at a very high dosage and combined with chemotherapy and/or surgery, is rarely curative; 5-year survival figures seldom excede 5%.[33–35] It is not known to what extent optimal treatment may keep a patient with a local recurrence locally symptom free for his or her remaining life span. The question whether preoperative radiotherapy for all patients is advantageous from a quality-of-life point of view, or if no additional radiotherapy at surgery but with an optimized treatment also including radiotherapy if a local recurrence develops is best, is addressed in an ongoing trial.

The data from this trial together with available data from the literature indicate that additional radiotherapy in patients with primarily resectable rectal carcinoma should be given before operation. This approach will be even more attractive if patients with a low risk of recurrence (such as Dukes' stage A cases) can be excluded before operation by transanal ultrasonography.[36,37]

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