IMPROVED SURVIVAL WITH PREOPERATIVE RADIOTHERAPY IN RESECTABLE RECTAL CANCER

SWEDISH RECTAL CANCER TRIAL*

ABSTRACT

Background Adjuvant radiotherapy for rectal cancer has been extensively studied, but no trial has unequivocally demonstrated improved overall survival with radiotherapy, despite a reduction in the rate of local recurrence.

Methods Between March 1987 and February 1990, we randomly assigned 1168 patients younger than 80 years of age who had resectable rectal cancer to undergo preoperative irradiation (25 Gy delivered in five fractions in one week) followed by surgery within one week or to have surgery alone.

Results The irradiation did not increase postoperative mortality. After five years of follow-up, the rate of local recurrence was 11 percent (63 of 553 patients) in the group that received radiotherapy before surgery and 27 percent (150 of 557) in the group treated with surgery alone ($P<0.001$). This difference was found in all subgroups defined according to Dukes' stage. The overall five-year survival rate was 58 percent in the radiotherapy-plus-surgery group and 48 percent in the surgery-alone group ($P=0.004$). The cancer-specific survival rates at nine years among patients treated with curative resection were 74 percent and 65 percent, respectively ($P=0.002$).

Conclusions A short-term regimen of high-dose preoperative radiotherapy reduces rates of local recurrence and improves survival among patients with resectable rectal cancer. (N Engl J Med 1997;336: 980-7.)

THE value of adding radiotherapy to surgery in the treatment of patients with resectable rectal cancer has been assessed in trials using either preoperative[1-6] or postoperative[7-10] irradiation. Lower rates of local recurrence have been found with radiotherapy in most of these trials, especially those using preoperative irradiation. In a randomized trial in the Uppsala region of Sweden, it was found that preoperative irradiation was more effective than postoperative therapy, even though the dose of postoperative radiation was higher.[11] However, no trial has yet shown that, as compared with surgery alone, adjuvant preoperative radiotherapy significantly improves overall survival.[1,2,6,12] A meta-analysis of all the controlled trials on this subject published before 1986 found a marginally positive effect of radiotherapy on survival.[13] A survival benefit was also found with a combination of postoperative radiotherapy and prolonged chemotherapy[9]; in another trial, postoperative chemotherapy alone, but not radiotherapy, improved survival.[8]

Preoperative irradiation is more "dose-effective" than postoperative radiotherapy[14]; that is, a higher dose is needed postoperatively to reduce rates of local recurrence to the same extent as preoperative radiation. Nevertheless, preoperative treatment has not been routinely recommended,[15] mainly because it has not been shown to improve overall survival and because in some trials it has been associated with increased postoperative mortality.[2,6]

We conducted the present trial to determine whether preoperative radiotherapy with a three-beam or four-beam technique could be given to patients younger than 80 years of age without increasing postoperative mortality, to substantiate the previously observed reduction in the rate of local recurrence with radiotherapy, and to investigate the effects of the treatment on survival. In this report, we present rates of local recurrence and survival after a minimal follow-up of five years. The local-recurrence rates after a minimum of two years of follow-up have been reported previously.[16]

METHODS

Randomization

Patients were randomly assigned to treatment groups, with stratification according to hospital, by telephone contact with the trial center in one of the six Swedish health care regions. The patients were assigned either to one week of preoperative irradiation, followed by surgery within the next week (radiotherapy-plus-surgery group), or to surgery with no additional radiotherapy (surgery-alone group).

Sample Size

In order to detect a reduction in the rate of local recurrence from 20 percent to 10 percent with 90 percent probability and a 5 percent significance level, we calculated that a total of 475 patients had to be recruited. To detect an increase in postoperative mortality from 2 percent to 5 percent (again with 90 percent probability and a 5 percent significance level), we needed to recruit 750 patients. To show an increase of 10 percentage points in survival (from 50 percent to 60 percent) after five years with 80 percent probability and a 5 percent significance level, 750 curatively resected patients had to be recruited. Assuming a 10 percent dropout rate and assuming that approximately 20 percent of the patients would be found to have metastatic disease at the time

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of surgery or would have a noncurative local resection, we had to enroll at least 1100 patients.

Patients

Between March 1987 and February 1990, we recruited patients with resectable rectal carcinoma for whom abdominal surgery was planned. Patients were eligible for the trial if they were less than 80 years old, had a histopathologically proved adenocarcinoma situated below the promontory, as shown on a lateral projection on barium enema, and gave informed consent for their participation. The protocol was approved by the regional ethics committees.

The criteria for exclusion were a locally nonresectable tumor; a plan to perform only local excision; known metastatic disease; previous radiotherapy to the pelvis; and other malignant disease (except squamous-cell carcinoma of the skin).

Of 1168 patients from 70 hospitals throughout Sweden who were randomly assigned to treatment groups, 908 (78 percent; 454 in each group) were treated with curative intent (Table 1). The patients' characteristics are described in the first report from this trial.[17] There is some overlap between the current Swedish Rectal Cancer Trial and the so-called Stockholm II trial,[18] in that 316 patients who were enrolled in Stockholm from March 1987 through February 1990 are also included in the current trial, whereas the patients enrolled after February 1990 in Stockholm (238 patients) are not included in this analysis.

Irradiation Technique

The clinical target volume, estimated according to the International Commission on Radiation Units and Measurements report 50 (ICRU 50), included the anal canal, the primary tumor, the mesorectal and presacral lymph nodes, the lymph nodes along the internal iliac vessels, the lumbar lymph nodes up to the level of the upper border of the fifth lumbar vertebra, and the lymph nodes at the obturator foramina. The plan was to deliver treatment with three beams with the patient in a prone position, as previously described,[19] or with a four-beam "box" technique with the patient lying either supine or prone. Shielding of tissues not at risk of containing tumor cells was stipulated in the protocol.[20]

The protocol called for the delivery of 25 Gy in five fractions with 5 to 16 megavoltage photons in one week. The dose was defined as that delivered at the intersection of the central axes of the three or four beams. This radiation schedule was designed to correspond approximately to a dose of 45 Gy given with conventional fractionation (i.e., 2 Gy daily five days a week). Originally, the cumulative-radiation-effect (CRE) formula of Kirk et al.,[21] with corrections for late effects as described by Turesson and Notter,[22] was used to estimate short-term and late effects of different radiation schemes. According to the original CRE concept, this treatment corresponds approximately to a total dose of 42 Gy when given in fractions of 2 Gy five times a week. With corrections for late effects,[22] the corresponding dose is approximately 48 Gy. Using the linear–quadratic time model (LQ formula[23]), a dose of five fractions of 5 Gy each also corresponds to approximately 42 to 50 Gy in 2-Gy fractions. Uncertainties about the precise correspondence remain, however, because of insufficient knowledge of the size of the coefficients of the LQ formula for various tumors and normal tissues.[14,20]

Surgery and Histopathological Analysis

Anterior resection or abdominoperineal excision was to be performed within one week after the completion of radiotherapy. Surgery was considered locally curative if both the surgeon and the histopathologist considered the margins of the resected tissue to be free of tumor, even if the bowel was perforated during surgery. The locally curative nature of surgery was defined as uncertain when either the surgeon or the pathologist reported a questionable margin. In all other cases, the treatment was considered not locally curative.

TABLE 1. SELECTION OF THE STUDY COHORT.

PATIENT CATEGORY	RADIOTHERAPY-PLUS-SURGERY GROUP	SURGERY-ALONE GROUP
	no. of patients	
Randomized	583	585
Ineligible	10	11
Eligible	573	574
Refused surgery	1	0
No resection performed	19	17
Local resection performed	553	557
Distant metastases found	42	41
Locally noncurative surgery	14	19
Local cure uncertain	43	43
Curatively treated	454	454

The resected specimens were examined by a pathologist in the region where the center was located, who classified the tumor according to the original staging system of Dukes and Bussey.[24] When the rate of local recurrence was calculated in relation to tumor stage, the local Dukes' stage was used even when distant metastases were known to exist. The pathologist also classified the resection as locally curative, of uncertain curativeness, or not locally curative. The treatment was considered curative if the resection was locally curative and no distant metastases were found during surgery.

Follow-up

A clinical evaluation twice a year during the first five years after surgery was stipulated in the protocol. Any clinically detectable tumor, whether morphologically verified or not, within the dorsal parts of the pelvis, including the urinary bladder, was considered a local recurrence. Laboratory tests, imaging, and biochemical tests were performed only if a local or distant recurrence was suspected.

All case-record forms were checked by an independent observer against the clinical records during an audit in 1995. The causes of death of all patients who died were checked against the National Causes of Death Registry by computerized linkage. Living patients had been followed up for a median of 75 months (range, 60 to 96 months) as of March 1995.

Statistical Analysis

The significance of differences in proportions was calculated with the chi-square test, and that of differences between means with Student's t-test. P values of less than 0.05 were considered to indicate statistical significance. Analyses of postoperative mortality and overall survival were based on all eligible patients (Table 1), whereas rates of postoperative morbidity and local recurrence were based only on those who underwent resection. All comparisons between the treatment groups were made on the intention-to-treat principle. Survival and cumulative incidence were estimated with actuarial methods. Distributions of factors were analyzed with the log-rank test. A multivariate analysis of survival according to assigned treatment was performed with use of the Cox proportional-hazards regression model, with both the assigned treatment and the Dukes' stage included as independent variables.

Before the trial started, it was stipulated that postoperative mortality and morbidity should be reported when the last patient had been enrolled. Rates of local recurrence were to be analyzed

after two and five years of follow-up, and survival after a minimum of five years.

RESULTS

Treatment and Postoperative Mortality

Of the 573 eligible patients who were randomly assigned to receive preoperative radiotherapy, 555 (97 percent) received up to 25 Gy of irradiation; no patient in the surgery-alone group received preoperative radiotherapy. In 3 percent of the patients in both groups, the tumor was not resected, because it either was unresectable or was found to be metastatic at surgery (Table 1). Similar proportions in the two groups underwent surgery classified as noncurative (Table 1). In-hospital mortality was 4 percent (22 of 573 patients) in the radiotherapy-plus-surgery group and 3 percent (15 of 574) in the surgery-alone group ($P=0.3$). However, in the group of patients irradiated with two beams, in-hospital mortality was considerably higher (15 percent [7 of 48 patients]) than in those irradiated as stipulated in the protocol with three or four beams (3 percent [13 of 507], $P<0.001$). The distribution of the Dukes' stages in two groups is shown in Table 2 and described in detail in our first report.[17]

Rates of Local Recurrence

After follow-up for a minimum of five years, the local-recurrence rates were significantly lower after combined radiotherapy and surgery than after surgery alone in all groups of patients (Table 2). In the irradiated group, 11 percent (63 of 553 patients) had a local recurrence, as compared with 27 percent (150 of 557) in the group undergoing surgery alone ($P<0.001$). The corresponding figures were 9 percent (41 of 454 patients) and 23 percent (106 of 454) among the curatively treated patients ($P<0.001$). As shown in Table 2, a significant reduction in the rate of local recurrence was found among patients with all three Dukes' stages who underwent preoperative radiotherapy. Figure 1 shows the proportion of local failures observed after different amounts of follow-up. The reduction in the rate of local recurrence with radiotherapy was 58 percent (95 percent confidence interval, 46 to 69 percent). The same reduction in the rate of local recurrence with the addition of radiotherapy was also noted after different surgical procedures (Table 3).

Overall Rates of Recurrence

At follow-up, 28 percent of the curatively treated patients (125 of 454) in the radiotherapy-plus-surgery group had signs of recurrent disease, as compared with 38 percent (171 of 454) in the surgery-alone group ($P<0.001$). In the radiotherapy-plus-surgery group, 22 patients (5 percent) had only a local recurrence, and 84 (19 percent) had only distant metastases. The corresponding figures in the surgery-alone group were 59 patients (13 percent) and 65 patients (14 percent), respectively. Both local and distant recurrences were seen in 19 patients (4 percent) in the radiotherapy-plus-surgery group and in 47 patients (10 percent) in the surgery-alone group.

Survival

Both overall survival in all patients (Fig. 2) and cancer-specific survival (Fig. 3) among patients in whom curative surgery was performed were significantly higher in the radiotherapy-plus-surgery group than in the group treated with surgery alone. The relative hazard of death from all causes in the radiotherapy-plus-surgery group was 0.79 (95 percent confidence interval, 0.66 to 0.92), and that of death due to cancer was 0.69 (95 percent confidence interval, 0.55 to 0.83). Overall five-year survival rates in these two groups were 58 percent (95 percent confidence inter-

TABLE 2. RATES OF LOCAL RECURRENCE ACCORDING TO DUKES' STAGE AND SURGICAL OUTCOME AMONG PATIENTS WITH RESECTED TUMORS ASSIGNED TO RADIOTHERAPY PLUS SURGERY OR SURGERY ALONE.

SURGICAL OUTCOME	RADIOTHERAPY PLUS SURGERY				SURGERY ALONE			
	DUKES' STAGE A	DUKES' STAGE B	DUKES' STAGE C	TOTAL	DUKES' STAGE A	DUKES' STAGE B	DUKES' STAGE C	TOTAL
	number with recurrence/total number (percent)							
Distant metastases	0/5	0/11	5/26 (19)	5/42 (12)	1/4 (25)	3/12 (25)	8/25 (32)	12/41 (29)
Locally noncurative surgery	0	3/6 (50)	1/8 (12)	4/14 (29)	0	0/8	10/11 (91)	10/19 (53)
Local cure uncertain	0/2	6/13 (46)	7/28 (25)	13/43 (30)	0/3	5/8 (62)	17/32 (53)	22/43 (51)
Curative surgery	8/174 (5)	11/165 (7)	22/115 (19)	41/454 (9)	17/147 (12)	31/145 (21)	58/162 (36)	106/454 (23)
Total	8/181 (4)*	20/195 (10)†	35/177 (20)‡	63/553 (11)‡	18/154 (12)	39/173 (23)	93/230 (40)	150/557 (27)

*$P=0.02$ for the comparison with the same subgroup in the surgery-alone group.

†$P=0.002$ for the comparison with the same subgroup in the surgery-alone group.

‡$P<0.001$ for the comparison with the same subgroup in the surgery-alone group.

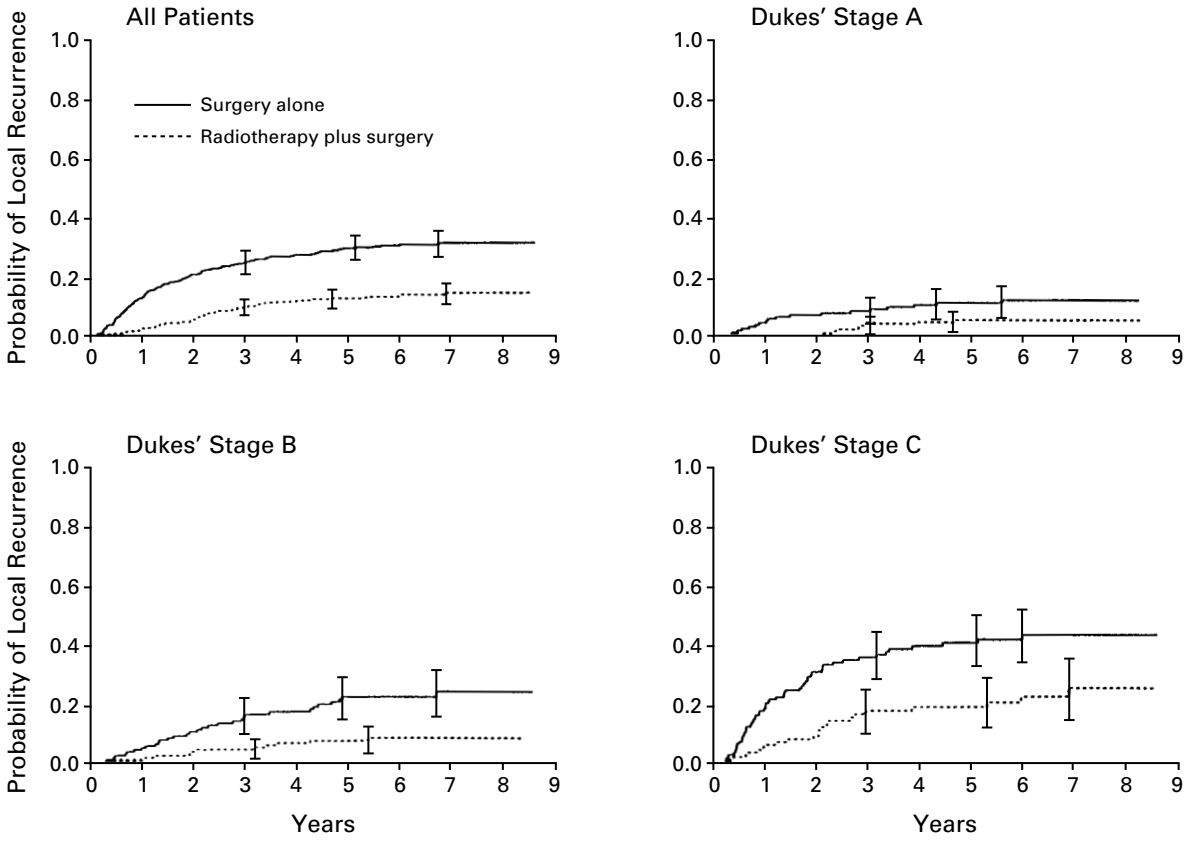

Figure 1. Rates of Local Recurrence among All Patients Undergoing Resection, According to Dukes' Stage and Treatment Assignment. The bars indicate 95 percent confidence limits.

TABLE 3. RATES OF LOCAL RECURRENCE ACCORDING TO SURGICAL PROCEDURE AMONG PATIENTS ASSIGNED TO RADIOTHERAPY PLUS SURGERY OR SURGERY ALONE.

PROCEDURE	RADIOTHERAPY PLUS SURGERY			SURGERY ALONE		
	ANTERIOR RESECTION	ABDOMINOPERINEAL RESECTION	OTHER*	ANTERIOR RESECTION	ABDOMINOPERINEAL RESECTION	OTHER*
	number with recurrence/total number (percent)					
Noncurative surgery	5/37 (14)	17/61 (28)	1/1 (100)	11/33 (33)	32/66 (48)	2/4 (50)
Curative surgery	18/206 (9)	22/243 (9)	1/5 (20)	41/194 (21)	65/256 (25)	1/4 (25)
Total	23/243 (9)†	39/304 (13)†	2/6 (33)	52/227 (23)	97/322 (30)	3/8 (38)

*"Other" includes Hartmann's procedure and proctocolectomy.

†$P<0.001$ for the comparison with the same subgroup in the surgery-alone group.

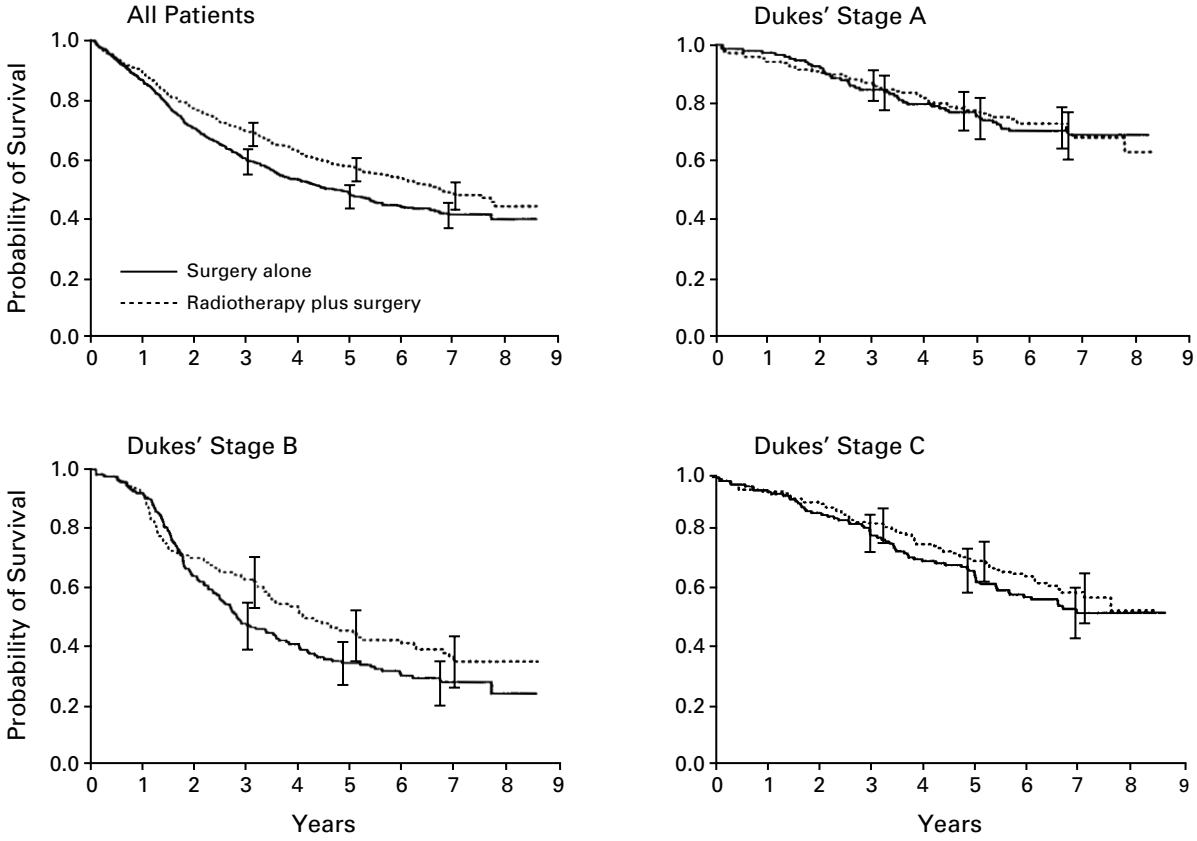

Figure 2. Overall Survival among All Eligible Patients Undergoing Surgery, According to Dukes' Stage and Treatment Assignment. The bars indicate 95 percent confidence limits.

val, 54 to 62 percent) and 48 percent (95 percent confidence interval, 44 to 52 percent), respectively ($P = 0.004$); radiotherapy was thus associated with an increase of 21 percent (95 percent confidence interval, 8 to 34 percent) in overall survival.

As shown in Table 2, more patients had a tumor in Dukes' stage A or B in the radiotherapy-plus-surgery group than in the surgery-alone group, a statistically significant difference ($P = 0.008$), which is most likely due to a "down-staging" effect of preoperative irradiation.[17] To test whether the survival difference persisted after adjustment for the imbalance in Dukes' stage — that is, whether it was due to chance — we performed a Cox regression analysis including age, sex, Dukes' stage, and treatment group as variables. In this analysis the relative hazard of death from all causes changed only marginally, to 0.81 (95 percent confidence interval, 0.67 to 0.94).

DISCUSSION

We designed this trial to detect even a small but clinically relevant survival benefit associated with the use of preoperative radiotherapy in patients with resectable rectal cancer. We found that preoperative radiotherapy not only reduced the rate of local recurrences but also improved survival. Moreover, the survival benefit, 21 percent (95 percent confidence interval, 8 to 34 percent), is of the same magnitude as that reported by three North American trials of postoperative chemotherapy[8] or chemoradiotherapy[9,10] in rectal cancer and is not significantly different from that obtained with chemotherapy alone in patients with Dukes' stage C colon cancer.[25,26]

The results of randomized trials worldwide of adjuvant radiotherapy for rectal cancer indicate that preoperative radiotherapy is more effective than postoperative radiation in reducing rates of local failure.[14,27] If the dose of radiation is moderately high, the reduction is at least 50 percent,[1,2,4,6] as we also found. A reduction of this magnitude has not been found with lower preoperative doses[3,5,28,29] or with even higher doses delivered postoperatively.[7-10] Only one trial has compared preoperative and postoperative radiotherapy; the patients given preoperative radiotherapy received the same dose as those in our study.[11] The patients who were treated postoperatively (only those

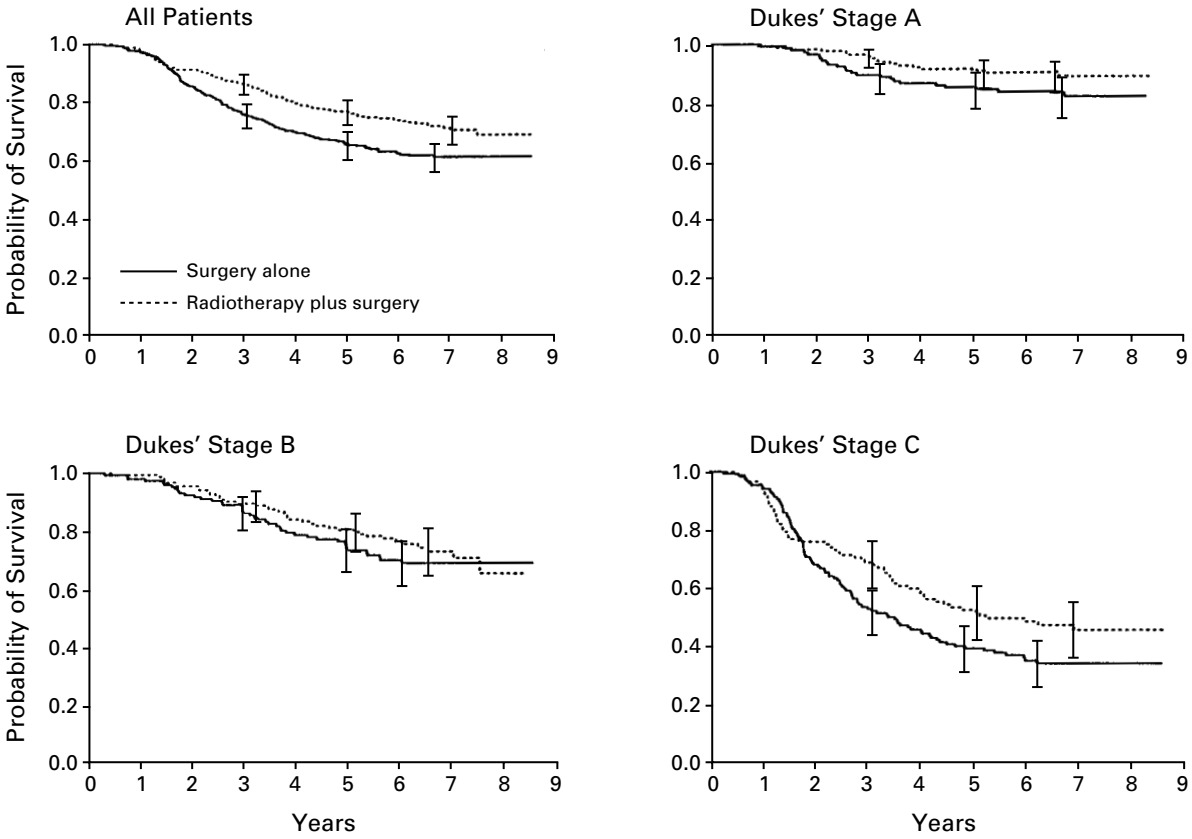

Figure 3. Cancer-Specific Survival among All Patients Undergoing Curative Operations, According to Dukes' Stage and Treatment Assignment.

The bars indicate 95 percent confidence limits.

in this group with tumors in Dukes' stage B or C underwent radiotherapy) received the highest dose used in an adjuvant setting (60 Gy given over seven to eight weeks). Nevertheless, the preoperatively irradiated group had a significantly lower rate of local recurrence (12 percent vs. 25 percent, $P = 0.02$).[11,30]

Concern has been expressed about the short- and long-term toxic effects of high fractional doses of radiation.[31] Doses higher than 1.8 to 2.0 Gy per fraction, such as the 5-Gy fraction administered in this and other trials,[2,4,6] may lower the therapeutic ratio, particularly with respect to late toxic effects.[31] Higher fractional doses imply shorter treatment periods and thus have practical and economic advantages. The tumor-cell–killing effect of a dose of 25 Gy in one week (5 Gy daily for five days) corresponds approximately to that of 42 to 50 Gy (2 Gy daily for five days a week) over four to five weeks according to older concepts such as the CRE formula[21] used in our study, the nominal standard dose,[32] and the possibly more accurate LQ formula.[23]

We stress the importance of the irradiation technique, which must prevent unnecessary irradiation of tissues outside the tumor-containing areas. Our results and those of the Uppsala trial[11] show that five doses of 5 Gy each can be given preoperatively to patients younger than 80 years without any significant increase in the number of complications in the immediate postoperative period. The toxicity associated with a large radiation volume was our chief reason for undertaking this study. Two beams cannot spare surrounding tissues to the same extent as three or four beams.[20] Increased postoperative mortality, mainly among elderly patients, was found in both the Stockholm–Malmö trial,[6] in which five fractional doses of 5 Gy each were also given, but with two beams extending above L2, and the British Imperial Cancer Research Fund trial,[2] in which three 5-Gy fractions were given with anterior–posterior beams to the entire pelvic cavity. In another British trial, by the Northwest Region Rectal Cancer Group, four 5-Gy fractions were given with a rotational three-field wedge technique without any increase in postoperative mortality, further emphasizing the importance of the radiation technique.[4]

It is too early to evaluate the late adverse effects

of the short-term, high-dose preoperative radiotherapy protocol used in this trial. A preliminary analysis of responses to a questionnaire about anal function sent to all recurrence-free patients who had a sphincter-saving procedure and were alive in 1996 (at least five years after treatment) indicates that patients who underwent irradiation have more problems with the number of bowel movements, incontinence, urgency, and soiling than those who were assigned to surgery alone. However, their quality of life is good and is not significantly different from that of the patients who had surgery alone (unpublished data). To minimize disturbance of bowel function, the routine inclusion of the anal canal in the irradiated volume in proximal rectal tumors, as was standard in our trial, should probably be avoided. Anal function after postoperative chemoradiotherapy has not been studied prospectively, but recent data suggest a worse outcome after postoperative than after preoperative treatment.[33,34]

Prospective follow-up over a 10-year period (still a rather limited period) in the Uppsala trial (in which five fractions of 5 Gy each were delivered with three beams, with the upper level of the irradiated field at mid-L3) showed no increased risk of late adverse effects.[28] The projected 10-year rate of small-bowel obstruction was 5 percent among patients irradiated preoperatively, 6 percent among nonirradiated patients, and 11 percent among those who received postoperative irradiation (30 fractions of 2 Gy each). The number of patients followed for more than 10 years was small, however. The Stockholm–Malmö trial, in which the radiation dose was the same but the irradiated volume was considerably larger (upper level above L2 with two beams), found an increase in thromboembolic events, femoral-neck and pelvic fractures, delayed perineal wound healing, and intestinal obstruction.[18] In that study, pelvic fractures occurred only among the patients treated in Stockholm, perhaps because the stipulated shielding was not used routinely in Stockholm. In the Stockholm II trial, which partly overlaps with our trial, there was a significantly increased rate of hospitalization for delayed perineal wound healing, but not for other complications.[18]

As compared with the group treated with surgery alone, there were significantly more patients in Dukes' stage A and fewer patients in Dukes' stage C in the group given preoperative radiotherapy ($P=0.008$). This is most likely due to a down-staging effect of radiotherapy. Down-staging has also been observed in trials with longer treatment periods and with an interval of several weeks between the end of irradiation and surgery.[1,3] Analysis of more than 1500 patients, including those in the present trial and the Uppsala trial,[11] has shown that the tumors were significantly smaller and the number of positive lymph nodes fewer in the preoperatively irradiated group.[35] This down-staging effect may arouse concern on the part of physicians who routinely administer postoperative chemotherapy to patients with Dukes' stage B or C tumors. However, when we analyzed survival separately among patients with the various Dukes' stages, we found improvement in all groups, although a statistically significant effect of treatment was evident only in the group with tumors in Dukes' stage C (Fig. 2). Moreover, this benefit persisted when the Dukes' stage was taken into account in a Cox regression model.

Should all patients with a primary resectable rectal cancer receive preoperative radiotherapy? Some surgeons claim they can achieve very low rates of local recurrence and good survival without radiotherapy, provided the surgical technique is optimal.[36] In this trial, the local-recurrence rate of 27 percent after five years of follow-up in the surgery-alone group is similar to the findings in all the other controlled trials on this topic, in which the local-recurrence rates in the surgery-alone groups have varied from 20 percent to 40 percent (average, 28 percent).[1,3-7,10,12,26,27] These figures are unacceptably high in the light of the morbidity associated with local failure. Optimal surgery, such as total mesorectal excision for rectal cancer,[36] might yield lower rates of local recurrence than standard surgery, but no randomized comparison of these surgical methods has been reported. Perhaps a combination of radiotherapy and total mesorectal excision can improve the results even further.[37]

Of concern in all cases in which neoadjuvant treatment is used is the overtreatment of patients with Dukes' stage A lesions, which can be recognized fairly easily and with reasonably high accuracy by preoperative endorectal ultrasonography.[38] However, in this trial the proportional reduction in the rates of local recurrence was of the same magnitude among patients with tumors in all Dukes' stages. This has also been reported from the Stockholm–Malmö trial.[6] If surgery is optimal, preoperative ultrasonography can be used to exclude patients from preoperative radiotherapy. Nevertheless, in patients with an anatomically very low tumor — especially in men in whom an abdominoperineal excision is planned — preoperative radiotherapy should be considered irrespective of tumor size, since such patients are at high risk for local failure even if surgery is optimal.

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APPENDIX

This study was performed in collaboration with the six Regional Oncological Centers in Sweden.

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