Preoperative Radiotherapy as Adjuvant Treatment in Rectal Cancer

Final Results of a Randomized Study of the European Organization for Research and Treatment of Cancer (EORTC)

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A randomized clinical trial was conducted by the European Organization for Research and Treatment for Cancer (EORTC) Gastrointestinal Cancer Cooperative Group to study the effectiveness of irradiation therapy administered in a dosage of 34.5 Gy, divided into 15 daily doses of 2.3 Gy each before radical surgery for rectal cancer (T2, T3, T4, NX, MO). Four hundred sixty-six patients were entered in the clinical trial between June 1976 and September 1981. Tolerance and side effects of preoperative irradiation were acceptable. The overall 5-year survival rates were similar in both groups. When considering only the 341 patients treated by surgery with a curative aim, the 5-year survival rates were 59.1% and 69.1% in the control group and in the combined modality group, respectively (p = 0.08). The local recurrence rates at 5 years were 30% and 15% in the control group and the adjuvant radiotherapy group, respectively (p = 0.003). Although this study did not show preoperative radiotherapy to have a statistically significant benefit on overall survival, it does have a clear effect on local control of rectal cancer. Therefore, before performing radical surgery, this adjuvant therapy should be administered to patients who have locally extended rectal cancer.

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IT HAS BEEN KNOWN for a long time that radiation therapy shrinks the volume of large tumors of the rectum and enhances their resectability.[1] However, the benefit of radiotherapy as adjuvant treatment to surgery with a curative aim of rectal cancers is still under much discussion. Its effectiveness does not appear evident if one considers only the results of the prospective randomized clinical trials that have been published thus far.[2-8]

Postoperative radiotherapy, combined with chemotherapy, has been shown to improve the recurrence rate and the disease-free interval.[6] It may also have an impact, albeit smaller, on survival.[9] Unfortunately, postoperative radiotherapy is poorly tolerated in 5% of the patients and can lead to ileitis and other serious side effects. Its toxicity is compounded by the toxicity of chemotherapy when the two are given in combination.[6]

Preoperative radiotherapy has appeared ineffective at doses lower than or equal to 20 Gy.[4] At higher doses, radiotherapy has clear contraindications, as we reported in a previous study of preoperative radiotherapy using 34.5 Gy.[10] We observed that this adjuvant treatment should not be administered to elderly patients, nor to patients with atherosclerosis, cardiac deficiency, or risk of thromboembolic disease.

In 1976, the European Organization for Research and Treatment of Cancer (EORTC) Gastrointestinal (G.I.) group activated a prospective multicenter phase III clinical trial to study the effectiveness of preoperative radiation therapy at the dose of 34.5 Gy. In an interim analysis[11] that was made after a mean follow-up time of 3 years, we reported that this adjuvant treatment had no significant impact on the postoperative morbidity and mortality rates, had relatively minor side effects, and had a marked effect on the local recurrence rate. This clinical trial was closed in 1981. Today, the mean follow-up period is over 6 years and the number of deaths specified in the trial protocol

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has been exceeded. The purpose of this paper is to report final results of this controlled trial of a high dose of preoperative radiation therapy (34.5 Gy) in terms of time to local recurrence, distant metastases, overall disease progression, and overall survival.

Methods

Eligibility Criteria for Patients' Entry

Patients entering this study were required to have a histologically proven, potentially resectable adenocarcinoma of the rectum located within 15 cm of the anal margin and no clinical or surgical evidence of distant metastases. The tumor had to be classified as either a T2, T3, T4, NX, or MO resectable tumor* (International Union Against Cancer Committee, 1968 TNM classification). Patients had to be fit for major surgery without any previous treatment for any other malignant diseases or for the present lesion, apart from colostomy or exploratory laparotomy.

Treatment Regimens

Patients were randomized at the EORTC Data Center by telephone or by telex into two regimens.

Patients of the first group were treated by surgery immediately after randomization. The most important consideration of this treatment was a complete exeresis of the tumor and the lymphatic drainage by a radical resection. When anterior resections were performed, measures had to be taken to minimize cancer cells contaminating the operating field and the anastomosis. To minimize cancer emboli, primary vascular ligation of inferior mesenteric vessels had to be performed. Radical resection with a curative aim was performed at the discretion of the surgeon at the end of laparotomy, provided that no gross residual neoplastic tissue was left in the abdominal cavity.

Patients of the second group (combined modality) were treated by radiotherapy before surgery. Treatment fields included the primary tumor, the adjacent lymph node drainage area in the pelvis, and the regional nodes along the superior hemorrhoidal vessels. Each daily treatment was to be administered by megavoltage machines (betatron or linear accelerators) by two parallel opposing anterior and posterior fields extending from the lower border of the obturator foramina to the upper border of the second lumbar vertebra. The lateral border was 1 cm from the bony margin of the true pelvis at its widest point, and was close to the tips of the transverse processes in the lumbar region. These treated volumes were believed to contain most of the areas of locoregional failures.[12] The total tumor dose was 34.5 Gy, delivered in 15 daily doses of 2.3 Gy each, over a period of 19 days. Dosage was prescribed at the midplane of the anterior-posterior central diameter of the field. This dosage, corresponding to 1304 rets in the NSD formulation currently in common use, was considered as being of the moderate dose range, as compared with other regimens used for this disease.[13] Moreover, the EORTC G.I. group showed previously that this regimen approaches the upper tolerance limits that permit operation without delay.[14] After administering this dosage, surgery was then performed as in the first group.

Patients underwent surgery with a mean delay of 11 days between the end of radiotherapy and surgery. (Range of 1–69 days, upper quartile 14 days).

Follow-up

Follow-up evaluations of both treatment groups took place monthly during the first 3 months, every 3 months until the end of the second year, and yearly thereafter. Evaluations included physical examination, determination of blood counts, and blood chemistries, including carcinoembryonic antigen level in the serum. Liver computed tomography (CT) scan or liver ultrasonography or scintigraphy, chest x-ray films, barium enema, and proctoscopy needed to be performed at least once per year.

When possible, suspect lesions were biopsied to confirm metastatic or recurrent disease. Liver scans were accepted as proof of tumor recurrence. Perineal recurrences after abdominoperineal resection had to be proven by biopsy or by pelvic CT scan.

Registration, Characteristics of the Tumors, and Surgical Procedures

Four hundred sixty-six patients were entered in the trial by 13 European institutions over a period of 5 years. Sixteen patients were not eligible for the following reasons: two patients had small tumors classified as T1 by the TNM classification system, five patients had a histology other than carcinoma. One patient had a synchronous tumor. Three patients had tumors located more than 15 cm from the anal margin. Five patients had a tumor location other than the rectal location, and six patients were lost to follow-up before starting their assigned treatment (three of each group).

Seven patients did not undergo surgery, for various reasons. In the control group, two patients refused surgery. In the combined modality group, two patients refused surgery, one patient refused all therapy, and two patients were unable to receive therapy (one patient, 80 years of age, was considered too old to receive treatment, and the other had respiratory insufficiency).

Of the 437 remaining patients, 341 (175 of the control group and 166 of the combined modality group) can be

* International Union Against Cancer Committee, 1968 TNM classification.

TABLE 1. *Distribution of Patients Treated Palliatively According to Treatment Group*

	Surgery	Radiotherapy + Surgery	Total
Local residual neoplastic tissue	19	18	37
Distant metastases	27	30	57
Bowel obstruction (colostomy only)	0	2	2
Total	46	50	96

considered as adequately treated following the protocol. Ninety-six patients were treated palliatively (46 of the control group and 50 of the combined modality group).

In order to avoid statistical bias, all randomized patients were considered in the survival analysis, despite the fact that they included clear protocol violations. The distribution of patients for whom palliative surgery was performed is detailed in Table 1. The distributions of age, sex, T category, tumor location, surgical technique, and Dukes' classification for patients with a curative resection are shown in Table 2. The histologic examination of the surgical specimen revealed a tumor sterilization in five patients of the preoperative radiotherapy group.

TABLE 2. *Distribution by Age, Sex, Tumor Location, Surgical Technique, and Dukes' Classification According to Treatment Group in Patients with Curative Resection*

	Surgery	Radiotherapy + Surgery	Total (%)
Age			
Minimum	24	28	24
Maximum	83	78	83
Median	62	58	60
Male/female	99/76	107/59	206/135
Sex ratio	1.30	1.81	1.52
T2	77	79	156 (46%)
T3	89	79	168 (49%)
T4	9	8	17 (5%)
From the anal verge			
1–5 cm	73	66	139 (41%)
6–10 cm	79	88	167 (49%)
11–15 cm	23	12	35 (10%)
Abdomino-perineal resection	135	142	277 (81%)
Anterior resection	24	19	43 (13%)
Pull-through technique	13	5	18 (5%)
Hartmann procedure	3	0	3 (1%)
Dukes' A	18	18	36 (11%)
Dukes' B	98	88	186 (54%)
Dukes' C	59	55	114 (33%)
No residual tumor after preoperative irradiation therapy	—	5	5 (2%)
Total	175	166	341 (100%)

TABLE 3. *Distribution of Noncompliance to Adjuvant Therapy by Treatment Group*

Patients	Surgery	Radiotherapy + Surgery	Total
Received radiotherapy	3	—	—
No radiotherapy	—	3	3
Excluded from radiotherapy treatment (70 years of age or older, liver metastases, bowel obstruction)	—	5	5
Received 5-FU	—	1	1
Total	3	9	12

Postoperative Mortality and Postoperative Morbidity

The postoperative mortality rate was 3.8% (3.4% in the control group, 4.2% in the combined modality group). The causes of death were reported in a previous paper.[11] Postoperative morbidity was reported slightly more frequently and at higher degrees of severity after preoperative irradiation therapy. Overall, however, the difference was not statistically significant.[11] The perineal wound healing duration and the median duration of hospitalization tended to be longer for irradiated patients.[11]

Noncompliance to Adjuvant Irradiation Therapy

Twelve patients did not comply with the adjuvant treatment protocol. Three patients of the control group received radiation therapy, eight of the combined modality group did not receive radiotherapy, and one patient was given chemotherapy in combination with radiotherapy (Table 3).

Toxicity and Side Effects of Radiotherapy

Radiation therapy had to be discontinued for four patients. Therapy was interrupted after 25 Gy for leukopenia and poor tolerance (with the patient dying of renal insufficiency 3 months after radiation therapy and radical surgery); therapy was also interrupted after 9.2 Gy for one patient's refusal (without explanation) to receive treatment; for the third patient, therapy was interrupted after 22.5 Gy because of diarrhea and colitis, and for the fourth patient, therapy was interrupted after 30 Gy because of the patient's poor physical condition, related to old age (this 83-year-old patient died 2 months later in cachexia).

Although long-term tolerance was fairly good, most of the patients treated by preoperative irradiation therapy suffered from diarrhea during the third week of the administration of irradiation; diarrhea, infection, and genitourinary disorders were more frequently reported in the group treated by preoperative irradiation therapy, as already described in a previous publication.[10]

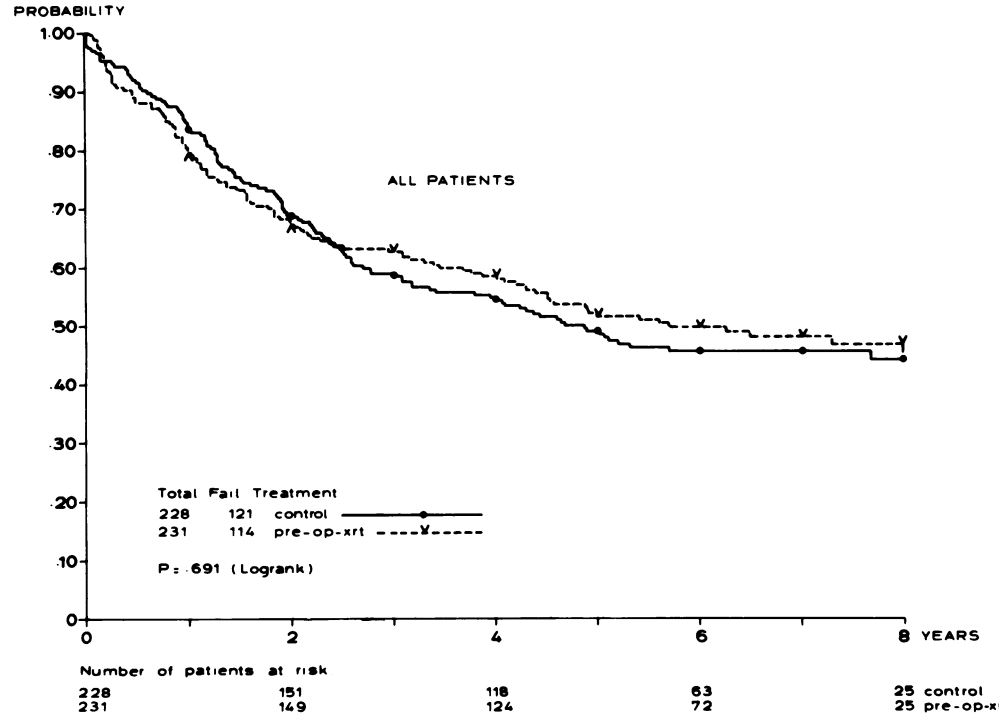

FIG. 1. Survival curves for all eligible patients according to group.

Statistical Methods

Survival was measured from the date of randomization to the date of death, irrespective of its cause. Time to progression was measured from the date of surgery to the date of progression, either local or distant. Survival and time to progression curves were estimated by the product-limit procedure of Kaplan and Meier,[15] and were compared through the use of the log-rank test.[16] Comparisons were retrospectively adjusted for prognostic factors, using a stratified log-rank test. All statistical tests were two-tailed.

Results

All living patients have been followed-up, with the exception of six patients lost to follow-up before therapy. The mean follow-up for both groups is 75 months.

Survival

Survival curves were first estimated for all 466 randomized patients (including protocol violations). The 5-year survival rates are 49.0% and 51.6% for the control group and the combined modality group, respectively (p = 0.69, Fig. 1).

When considering only the 341 patients treated by surgery with a curative aim, the 5-year survival rates are 59.1% and 69.1% for the control group and the combined modality group, respectively (p = 0.08, Fig. 2). The treatment comparison is not statistically significant, even after adjustment for age, Dukes' grade, T classification, and location of the tumor in the rectum has been made. One subgroup analysis shows a remarkable treatment difference; in patients younger than 55 years of age (n = 103), the 5-year survival rates are 48% and 80% for the control group and the combined modality group, respectively (p = 0.004).

The causes of death according to Dukes' grade and treatment for the patients who underwent surgery with a curative aim are detailed in Table 4. One patient, who had no residual tumor in the resected surgical specimen after preoperative radiation therapy, died of distant metastases in the lung. Three patients with a Dukes' A tumor died of malignant disease after radical surgery alone. In all 56 of 175 patients of the control group, died of rectal cancer, as compared with 36 of 166 patients of the preoperative radiation group (Table 4).

Disease Recurrence and Progression

Table 5 shows the type of first disease recurrence according to treatment group after surgical resection with a curative aim. The number of local recurrences is much lower after preoperative radiotherapy. Indeed, the local recurrence rates at 5 years are 30% and 15% for the control group and the preoperative radiation therapy group, respectively (p = 0.003, Fig. 3).

Taking into account all randomized patients, the 5-year local recurrence rate is still significantly lower for the group receiving preoperative radiotherapy (p = 0.023, Fig. 4). There is no difference between the treatment groups

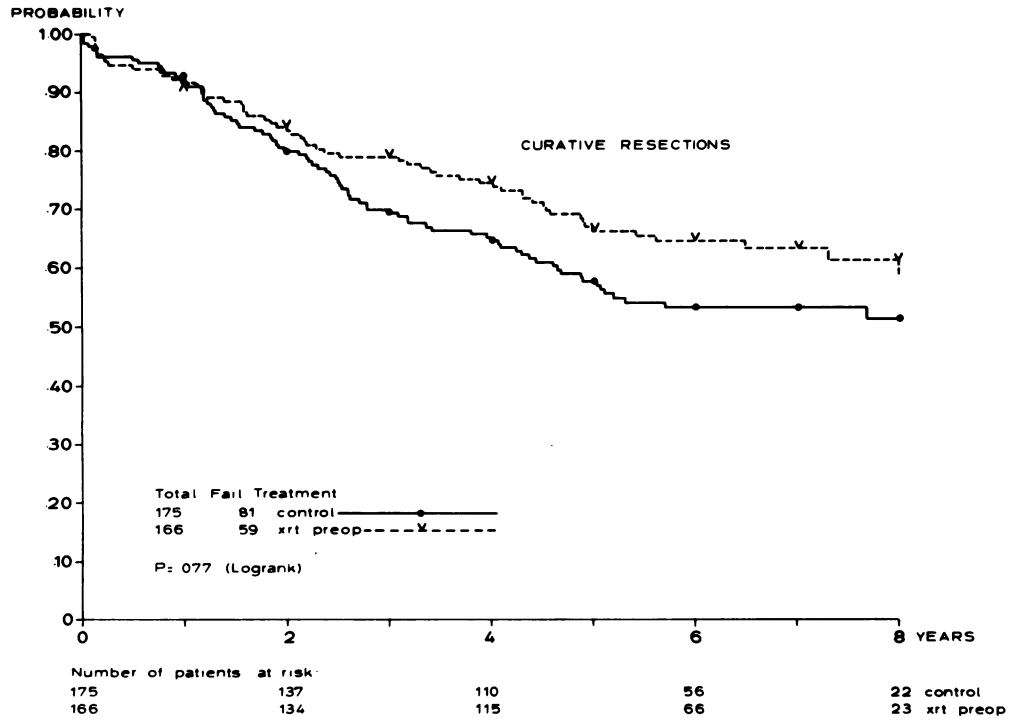

FIG. 2. Survival curves for eligible patients operated on with a curative aim according to treatment group.

in terms of time to distant metastases, as shown in Figure 5. Of the 341 patients who underwent surgery with a curative aim, 78 had distant metastases as a first sign of recurrence (39 in both groups). For most patients, the site of distant metastases was the liver (Table 6). Nevertheless, twelve patients had lung metastases as the first site, with six of these patients having their primary tumor located within the last 5 cm of the rectum, and with the remaining six having it located between 6 and 10 cm from the anal margin. Overall, the time to disease progression for all randomized patients is similar for the two treatment groups (Fig. 6).

TABLE 4. *Cause of Death by Dukes' Grade and Treatment Group After Resection with a Curative Aim*

	Surgery	Radiotherapy + Surgery	Total
No tumor found			
Malignant disease	—	1	1
Other causes	—	—	—
Dukes' A			
Malignant disease	3	—	3
Other causes	1	2	3
Dukes' B			
Malignant disease	24	13	37
Other causes	13	14	27
Dukes' C			
Malignant disease	29	22	51
Other causes	11	7	18
Total (All Dukes' grades)			
Malignant disease	56	36	92
Other causes	25	23	48

Discussion

The purpose of this study was to discover whether radiation therapy has any beneficial effect when administered before surgical resection with a curative aim of cancer of the rectum. Indeed, we know that only slightly more than half of the patients who have been operated on for such a cancer have a life expectancy of 5 years. For quite some time we have also known that preoperative radiotherapy enhances the resectability of advanced tumors of the rectum—that is, tumors fixed to neighboring organs.[1,17,18] It seemed interesting, therefore, to investigate the effect of radiotherapy on the survival time, and on the frequency of local recurrences or distant metastases

TABLE 5. *Type of First Disease Recurrence According to Treatment Group After Resection with a Curative Aim*

	Surgery	Radiotherapy + Surgery	Total (%)
No recurrence	103	113	216 (63%)
Local	33	14	47 (14%)
Distant	23	29	52 (15%)
Both local and distant	16	10	26 (8%)
Total	175	166	341 (100%)

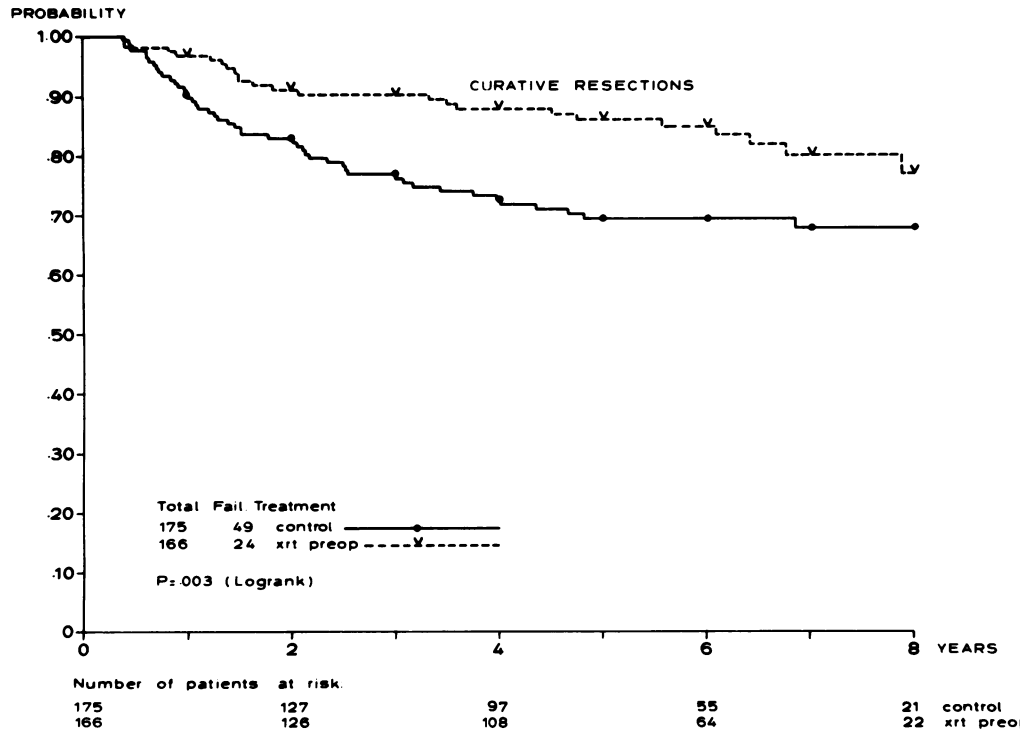

FIG. 3. Time to local recurrence curves for eligible patients operated on with a curative aim according to treatment group.

in patients with rather advanced tumors, such as T2, T3 and T4 (based on the 1968 TNM classification). Moreover, if preoperative radiotherapy is effective, it is essential to determine the highest possible dose that can be safely administered.

A first undesirable consequence of adjuvant preoperative radiotherapy might be the increased number of amputations of the rectum; one could, at first sight, believe that this was the case in our series, since 81% of the patients underwent an abdominoperineal resection (Table 2).

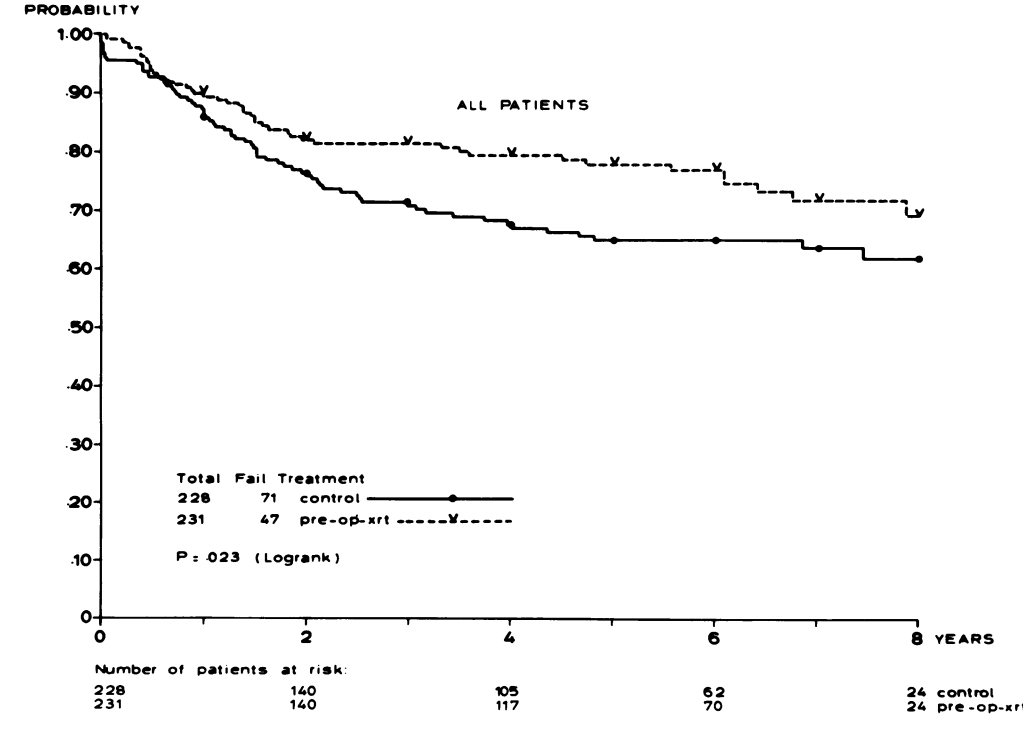

FIG. 4. Time to local progression for all eligible patients according to treatment group.

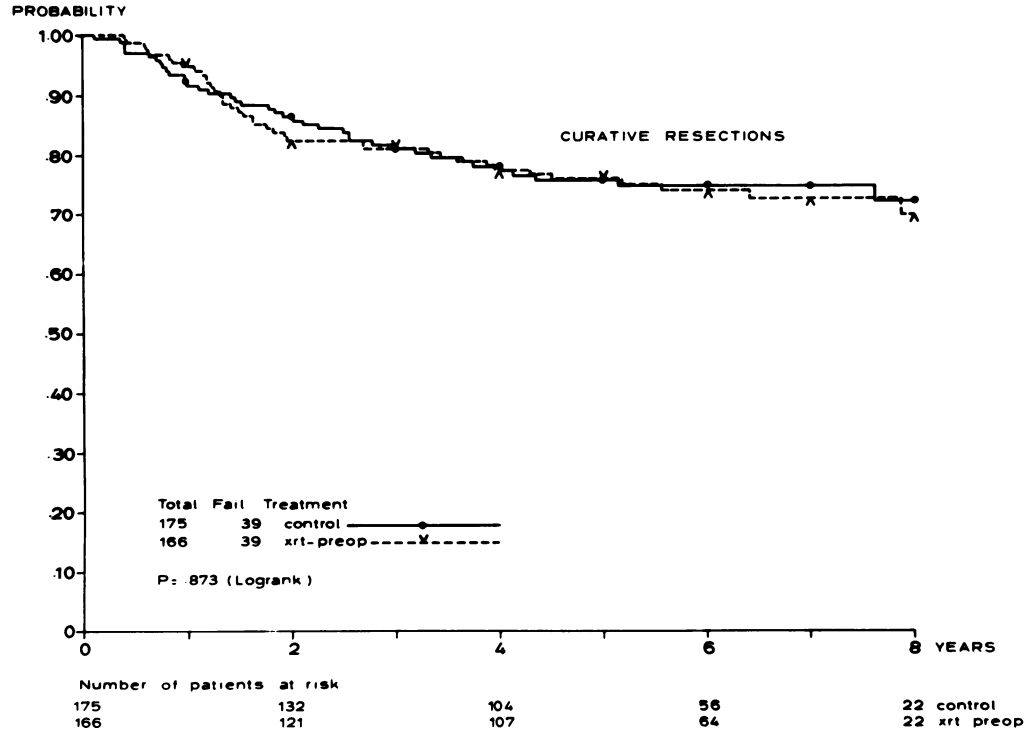

FIG. 5. Time to distant metastases for eligible patients operated on with a curative aim according to treatment group.

Nevertheless, radiotherapy does not appear to be the factor that explains this high percentage of amputations of the rectum; the distribution of surgical procedure is roughly the same for the group treated with preoperative radiotherapy as it is for the control group. Moreover, one should remember that this study was conducted between 1976 and 1981. During that period, the criteria of an abdominoperineal amputation depended, in most institutions, on the possibility of touching the tumor with the fingertip while performing rectal palpation, and 90% of the tumors in our series are located within the last 10 cm of the rectum (Table 2). Thus, it seems that radiotherapy does not constitute a contraindication to a low anterior resection or to the Babcock technique, since 18% of our patients were treated according to these surgical procedures, without increased operative complications occurring in the irradiated group.

TABLE 6. *Site of First Distant Recurrence by Treatment Group After Resection with a Curative Aim*

	Surgery	Radiotherapy + Surgery	Total (%)
Liver	29	28	57 (73%)
Lung	5	7	12 (15%)
Bone	2	3	5 (6%)
Brain	1	1	2 (3%)
Peritoneal seeding	2	—	2 (3%)
Total	39	39	78 (100%)

The tolerance and the side effects of radiation therapy appear very acceptable if contraindication criteria are carefully checked; these, as we demonstrated in an earlier work[14] depend principally on the age of the patient, the vascular perturbations due to atherosclerosis, and a history of thromboembolic diseases. It must be emphasized that many of the complications observed were seen in patients for whom the protocol had been violated by administering radiation to patients older than 70 years of age. In a previous work,[11] we summed up the side effects to radiotherapy: a slight increase in the duration of hospitalization and of wound-healing, more frequent urinary complications, infectious episodes, and diarrhea after the operation. With the dose of 34.5 Gy used in our trial, there was no increase in postoperative mortality.

Noncompliance with the assigned treatment was low in our clinical trial: less than 7% of all randomized cases did not follow the assigned treatment. In some cases, this resulted from the patient's refusal to comply with the treatment, but in a few instances, patients in generally poor condition were mistakenly entered in the trial.

The number of patients in whom curative resection was impossible may seem high (96 out of 466, Table 1). However, one should remember that at the time of this clinical trial, liver ultrasonography was not as reliable and as widely available as it is today, which may explain the presence of 57 nondiagnosed hepatic metastases found at the time of surgical intervention. In addition, over half of the patients had a T3 or T4 tumor, explaining the re-

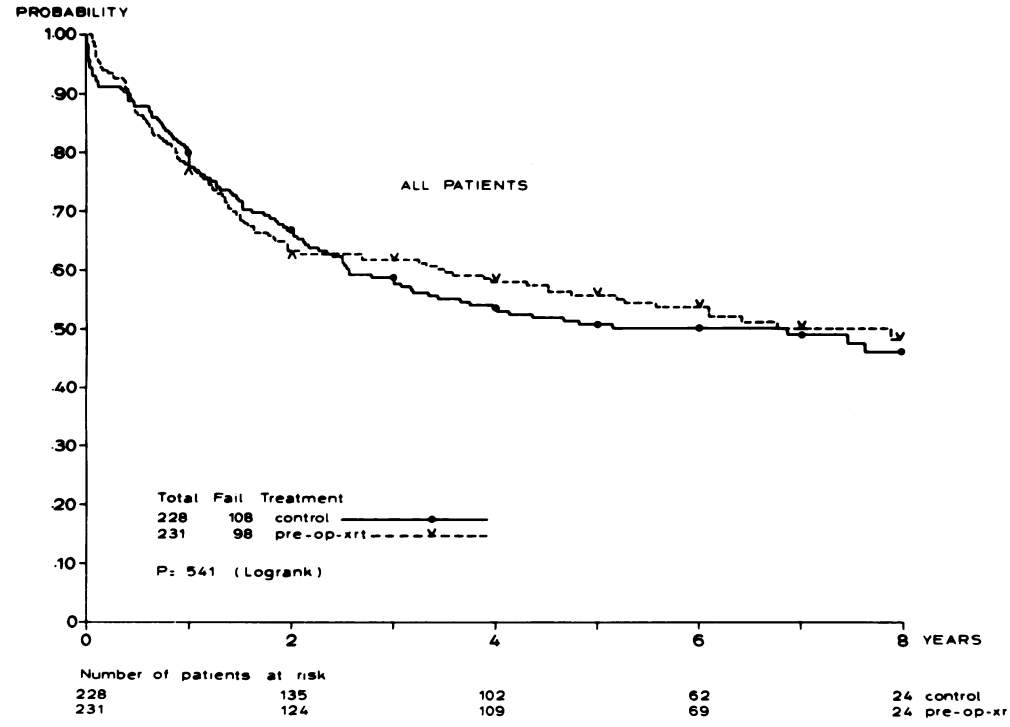

FIG. 6. Time to progression for all eligible patients according to treatment group.

sidual tissues found after surgery in 37 patients. This relatively high number of palliatively treated cases is evenly distributed between the two treatment groups.

A common criticism of preoperative radiotherapy is its uselessness in patients with Dukes' A tumors. However, this argument stands on thin ice: it has been shown that more than 7% of Dukes' A tumors may develop local recurrences.[19] In our series, three deaths of six of the Dukes' A patients were clearly attributable to malignant disease.

We have not observed any striking down-staging effects caused by the administration of preoperative radiotherapy. The percentage of Dukes' C tumors was about the same for both groups (Table 2). However, five tumors were completely sterilized by the administration of radiation before surgical resection.

The difference in life expectancy between the group of patients treated with preoperative radiation and the control group is 10% at 5 years for patients operated on with a curative aim (Fig. 2), and 2.6% for all patients (Fig. 3). Even if these results are not statistically significant, they do not discount that preoperative radiotherapy benefits those patients in whom a curative resection could be performed. These results are clearly better than those obtained by the Medical Research Council (United Kingdom) with doses of 20 Gy and 5 Gy.[4] They also seem more favorable than those of Higgins et al., who did not observe any difference in survival between a group treated with 31.5 Gy before surgery and the control group.[7] Survival curves consistently show a slight advantage for the group treated with preoperative radiotherapy if subgroups are looked at (*e.g.*, in terms of tumor localization in the rectum, Dukes' classification, or T classification). This advantage is particularly striking for patients younger than 55 years of age, but the dangers of multiple comparisons when analyzing subgroups are so great that this observation is, at best, worth anecdotal mention. In addition, the age distribution is not well-balanced between the two treatment groups (38 patients younger than 55 years of age in the control group *vs.* 65 in the combined modality group), which casts further doubts on this result.

Preoperative radiotherapy has a clear effect on local control of the disease (Figs. 3 and 4). Of the 341 patients operated on with a curative aim, approximately 25 (*i.e.*, approximately 50%) appear to have been spared a local recurrence of the disease, and thus the pelvic pains that are known to be intolerable (Table 5). In terms of death after disease recurrence, radiotherapy seems to have been beneficial for approximately 20 patients (Table 4).

Preoperative radiotherapy has no effect whatsoever on the development of distant metastases (Fig. 5), justifying attempts at combined adjuvant approaches, including chemotherapy.[6]

Conclusion

Preoperative radiation for cancer of the rectum has secondary effects and toxicities that are tolerable and acceptable. It increases operative morbidity slightly, but not operative mortality. The incidence of local recurrences is twice as high for the control group as for the group re-

ceiving adjuvant radiotherapy, and this observed benefit is highly statistically significant. After curative resection, the survival rates at 5 years are 59% and 69% in the control group and in the radiotherapy group, respectively. Hence, a benefit in terms of life expectancy cannot be discounted, even though the observed difference is not statistically significant. Clinical trials would have to involve larger numbers of patients to demonstrate such small, yet clinically worthwhile, benefit on survival.[20]

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