Adjuvant Preoperative Radiotherapy for Locally Advanced Rectal Carcinoma

Results of a Prospective, Randomized Trial

P. J. Marsh, F.R.C.S.,* R. D. James, M.R.C.P., F.R.C.R.,†
P. F. Schofield, M.D., F.R.C.S.*

*From the Departments of *Surgery and †Radiotherapy, Christie Hospital National Health Service Trust, Withington, Manchester, United Kingdom*
(On behalf of the Northwest Region Rectal Cancer Group, Manchester, United Kingdom)

PURPOSE: A prospective, randomized clinical trial was conducted by the Northwest Rectal Cancer Group to study the effects of preoperative radiotherapy given one week before surgery in locally advanced (tethered or fixed) rectal carcinoma. METHODS: A total of 284 patients were entered into the trial between 1982 and 1986; 141 were allocated to receive surgical treatment alone, and 143 were allocated to receive preoperative radiotherapy. A 10 × 10 × 10 cm volume in the posterior pelvis, centered on the tumor, was irradiated at a dose of 20 Gy, divided into four daily fractions of 5 Gy each. RESULTS: No differences were observed in any of the clinicopathologic variables in the two arms of the trial; there were no striking down-staging effects in the irradiated tumors. After a minimum follow-up period of 96 months, the overall and cancer-related mortality rates were similar in both arms of the study ($P = 0.21$ and $P = 0.09$, respectively). There was a highly significant reduction in local recurrences in the irradiated group (12.8 percent x-ray therapy *vs.* 36.5 percent surgery; $P = 0.0001$). The majority of local recurrences after preoperative radiotherapy occurred inside the radiotherapy field (10 cases; 7 percent), with only six cases (5 percent) outside the field. No significant difference was observed in the rates of distant metastasis between the two treatment groups ($P = 0.73$). CONCLUSIONS: Although there is no statistically significant survival benefit in the whole series, there is a survival benefit for the subset of patients considered by the surgeon to have undergone a curative operation. We recommend that this form of adjuvant therapy should be offered to all patients with locally advanced rectal cancer who are to undergo radical surgery. [Key words: Rectal carcinoma; Preoperative radiotherapy]

Marsh PJ, James RD, Schofield PF. Adjuvant preoperative radiotherapy for locally advanced rectal carcinoma: results of a prospective, randomized trail. Dis Colon Rectum 1994; 37:1205-1214.

P. J. Marsh was supported by The Christie Hospital Endowment Fund.
Address reprint requests to Professor Schofield: Department of Surgery, Christie Hospital National Health Service Trust, Wilmslow Road, Withington, Manchester M20 9BX, United Kingdom.

Rectal carcinoma is one of the most common human malignancies, with an incidence of 12,000 per annum in the United Kingdom and 45,000 per annum in the United States.[1, 2] The five-year survival rate following surgery is between 40 and 55 percent,[3] but local recurrence rates after surgical treatment of rectal carcinoma vary widely between 4 and 50 percent.[4–12] Some years ago it was pointed out that the survival after colorectal surgery could be reported at widely different levels for the same cohort of patients, depending on inclusion criteria.[13] The importance of surgical technique to produce a low recurrence rate has been emphasized.[4, 5] Although this is undoubtedly true, there are other factors that are known to affect local recurrence, such as the surgeon's opinion as to the completeness of excision,[14] the pathologic stage of disease,[15] and the height of the tumor above the anal verge.[15] Further, figures can be modified by whether local recurrence associated with widespread recurrence is included or whether the reported local recurrence rate includes only those patients with isolated recurrence. Last, the level of recurrence reported depends on the completeness and adequacy of follow-up.

Preoperative radiotherapy has the advantage over postoperative irradiation in that it is applied to undisturbed, normally oxygenated tissue, is less likely to involve such structures as the small bowel in the irradiated field, and is more cost-effective. There have been a number of prospective, randomized, controlled trials of adjuvant preoperative radiotherapy for rectal carcinoma reported in the literature (Table 1).[16–29] The combined evidence from these trials suggests that adjuvant preoperative radiotherapy does not improve the overall survival at five years.[30] How-

Table 1.
Prospective Randomized Trials of Preoperative Radiotherapy *vs.* Surgery-only for Rectal Carcinoma

Trial	Radiotherapy	Field	NSD	No. of Patients	Local Recurrence	5-year survival
Stockholm[17]*	25 Gy in 5 fractions over 5–7 days	Pelvis to L2 opposed A-P pair	1423	849	$P < 0.01$	Not significant ($P < 0.05$ for curative resections)
MRC II†	40 Gy in 20 fractions over 28 days	Pelvis 18 × 15 cm opposed A-P pair	1362	274	$P = 0.04$ (Metastasis $P = 0.02$)	Not significant ($P = 0.09$ overall)
EORTC II[23, 24]†	34.5 Gy in 15 fractions over 19 days	Pelvis to L2 opposed A-P pair	1303	466	$P = 0.023$	Not significant ($P = 0.08$ for curative resections)
Present study*	20 Gy in 4 fractions over 4 days	Posterior pelvis 3 field rotational wedge	1231	284	$P = 0.0001$	Not significant ($P = 0.03$ for curative resections)
Norway[25]†	31.5 Gy in 18 fractions over 14–21 days	Pelvis to L2 opposed A-P pair	1178	309	Not significant ($P < 0.01$ for recurrence free interval)	Not significant
VASAG II[26]†	31.5 Gy in 18 fractions over 24 days	Pelvis to L2 opposed A-P pair	1110	361	Not significant	Not significant
ICRF[22]*	15 Gy in 3 fractions over 5 days	Pelvis to L5 opposed A-P pair	965	478	$P < 0.05$	Not significant
VASAG I[27, 28]†	20 Gy in 10 fractions over 12–14 days (+5 Gy boost for APR)	Pelvis 20 × 20 cm opposed A-P pair	876	700	Not significant ($P < 0.05$ for APR)	Not significant ($P < 0.02$ for APR)
MRC I[19, 20]†	20 Gy in 10 fractions over 12–14 days	Pelvis 15 × 18 cm opposed A-P pair	876	824	Not significant	Not significant
Toronto[29]*	5 Gy in 1 fraction on day of surgery	Pelvis 15 × 18 cm opposed A-P pair	500	125	Not presented	Not significant ($P = 0.014$ for Dukes C tumors)
MRC I[19, 20]*	5 Gy in 1 fraction the day before surgery	Pelvis 15 × 18 cm opposed A-P pair	500	824	Not significant	Not significant

NSD = nominal standard dose (Ellis, 1967),[16] a calculation to account for the wide variation in daily fraction size; APR = abdominoperineal resection; Not significant = $P > 0.05$.
* = Immediate surgery.
† = Delayed surgery.
MRC II data, personal communication (1993).

ever, higher dose regimes do have a significant beneficial effect on local disease control; namely the Stockholm, European Organization for Research and Treatment of Cancer (EORTC) II, Medical Research Council (MRC) II, Imperial Cancer Research Fund (ICRF), and Norwegian trials.[17, 22–25] Only the second MRC trial has found a significant reduction in the rate of distant metastasis following preoperative radiotherapy (MRC, personal communication). There is also evidence from the Stockholm, EORTC II, and ICRF trials to suggest that preoperative radiotherapy increases perioperative surgical and medical morbidity.[17, 22–24]

Caution should be exercised, however, when comparing the data from these different sources, because each trial has different patient selection criteria, different radiotherapy schedules and fields, and different end points. The extent of the radiotherapy field is of

particular importance when defining local recurrence. Published trials have, in general, used very large radiotherapy fields, equivalent in size to standard surgical procedures, most commonly using parallel, opposed anteroposterior fields to irradiate the pelvis, pelvic side walls and brim, and regional lymph nodes to the level of the origin of the inferior mesenteric artery (*i.e.*, analogous to a radical surgical resection). A local recurrence after radiotherapy may be inside or outside the radiotherapy field. Recurrence outside the field requires an increase in the size of the field, and recurrence inside the field requires an increase in the total dose. We report here on the results of a prospective, randomized trial of adjuvant preoperative radiotherapy for rectal carcinoma.[31]

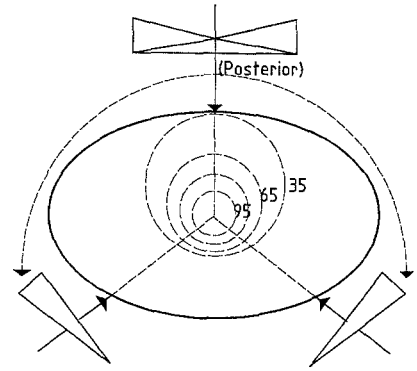

Figure 1. 4 MeV wedge-filter rotation field for rectal carcinoma produces a cylinder of radiation approximately 10 × 10 cm. Figures refer to absorbed doses relative to the tumor, which is designated 100 percent. Anterior pelvis and inguinal nodes are not irradiated.

MATERIALS AND METHODS

Patients

The Northwest of England Rectal Cancer Trial is a prospective, multicenter randomized study designed to evaluate preoperative radiotherapy in patients with locally advanced (*i.e.*, tethered or fixed), but operable, carcinomas of the true rectum (within 13 cm of the anal verge). The patients were accepted as locally advanced after examination under an anesthetic by PFS. Recruitment into the trial was between 1982 and 1986, and patients were randomized within hospitals to receive either surgery alone or adjuvant preoperative radiotherapy before surgical treatment. A total of 284 patients were recruited; 141 were randomized to surgery alone, and 143 were to receive adjuvant radiotherapy 1 week before surgical resection. Surgery was performed at the referral hospital, and radiotherapy was administered at the regional radiotherapy center (Christie Hospital National Health Service Trust).

Radiotherapy

Patients were treated in the prone position using a rotational three-field wedge technique delivered by an isocentric 4 MeV linear accelerator (Fig. 1). A dose of 20 Gy, in four daily fractions, was administered to a 10 × 10 × 10 cm cylindrical volume in the posterior pelvis (nominal standard dose = 1,231).[16] The radiotherapy field included the mesorectal lymph nodes but not the pelvic brim, pelvic side walls, anterior pelvis, inguinal lymph nodes, or para-aortic lymph nodes. All patients had their tumors localized by computed tomography (CT) planning, the results of which were stored on magnetic disc for correlation with sites of any subsequent disease recurrence.

Surgery

Surgery was performed at the referral hospital within a week of completing high-dose radiotherapy. The operating surgeon recorded a "curative" resection if the carcinoma was removed with neither spillage nor perforation, and there was no macroscopic evidence of residual local disease or distant metastases. The degree of local invasion present at operation was also noted. Pathologic information on the resected tumor was recorded prospectively by pathologists from the referral hospital on a standard form for each of the 284 patients. Lymph nodes were sampled and assessed in the normal way, as was the presence of venous invasion.

Patient Follow-Up

Patients have been subject to regular clinical review and carcinoembryonic antigen measurement. The fate and status of all patients are known. Local recurrence was diagnosed by clinical examination, supplemented by histology and CT. Patients with elevated carcinoembryonic antigen or clinical suggestion of recurrence also underwent CT scanning. By comparing these CT films with those taken at the time of radiotherapy planning, it was possible to accurately localize any disease recurrence; in particular, it has been possible to define the site of any given local recurrence in relation to the radiotherapy field.

Statistical Analysis

Statistical comparison of clinicopathologic variables was made using the chi-squared test. The minimum period of follow-up for all 284 patients is 96 months. Survival curves were constructed using the life-table method.[32] For local recurrence-free and metastasis-free survival, patients dying without either local recurrence or distant metastasis were treated as censored observations at the time of death, and cumulative proportions were calculated for those at risk. The overall survival curve includes all deaths from the date of randomization; deaths from intercurrent disease are, however excluded from the rectal cancer-related mortality curve. The survival curves were compared by log-rank analysis.[33] The subset of patients who underwent curative surgery were also analyzed independently, and survival curves were constructed as detailed above.

RESULTS

Clinicopathologic Variables

As reported by James *et al.*,[31, 34] the clinicopathologic variables are equally distributed in the two arms of the trial. No morphologic differences or downstaging effects could be demonstrated in the 143 irradiated cases, as compared with the 141 nonirradiated controls. Jones *et al.*,[35] however, demonstrated a significant decrease in the aneuploid cell population in the irradiated group.

Radiotherapy

Ninety-six percent of patients received 20 Gy in four daily fractions of 5 Gy. There were only six protocol violations in the 143 irradiated patients; two received less than 20 Gy (5 and 11 Gy), and four received in excess of 20 Gy (25–35 Gy). These cases are all considered evaluable for survival and recurrence.

Surgery

Twenty-five tumors (9 percent) were found to be inoperable at laparotomy because of either extensive local or metastatic disease, and these have been excluded from the analysis of local recurrence rates. One hundred forty-three (50 percent) patients underwent a curative resection (48.3 percent x-ray therapy (XRT) *vs.* 53.2 percent surgery), and 95 (33 percent) received a palliative operation (34.3 percent XRT *vs.* 32.6 percent surgery). The remaining 20 (8 percent) cases were either not classified or were of indeterminate classification. There was no significant difference in this assessment of surgery between the two arms of the trial.

Survival

Seven years after the close of the trial, the minimum period of follow-up was 96 months. The outcome for all patients in the trial is shown in Table 2, and the survival curves are shown in Figure 2. The overall mortality is 69.5 percent for patients allocated to surgery alone and 69.9 percent for patients allocated to preoperative radiotherapy. There were a total of 18 deaths from intercurrent disease during this period of follow-up, 13 in the irradiated group, and 5 in the control group. Therefore, the rectal cancer-related mortality rate is 66.0 percent following surgery alone and 60.8 percent following preoperative radiotherapy and surgery. There is no significant difference in either overall survival or cancer-related mortality between the two treatment groups ($P = 0.21$ and $P = 0.09$, respectively, with 1 degree of freedom). Subset analysis of the patients who underwent curative surgery alone (Table 3 and Fig. 3), reveals an overall mortality of 53.3 percent for patients allocated to surgery alone and 44.9 percent for patients allocated to preoperative radiotherapy. This is a significant reduction in mortality ($P = 0.033$, with 1 degree of freedom).

Local Recurrence

Local recurrence was defined as any local tumor detected at follow-up and included patients with known residual disease at operation as well as those with local disease as part of widespread recurrence. The local recurrence-free survival curve is shown in Figure 4. The local recurrence rate for the whole series in this study is 12.8 percent following preoper-

Table 2.
Patient Outcome in NWRCT

	Surgery Alone (%)	XRT + Surgery (%)	Log-rank *P* Value
Alive	43 (30.5)	43 (30.1)	—
Inoperable	15 (10.6)	10 (7.0)	—
Local recurrences	46 (36.5)	17 (12.8)	0.0001
Distant metastases	50 (35.5)	61 (42.7)	0.73
Cancer-related deaths	93 (66.0)	87 (60.8)	0.09
All deaths	98 (69.5)	100 (69.9)	0.21

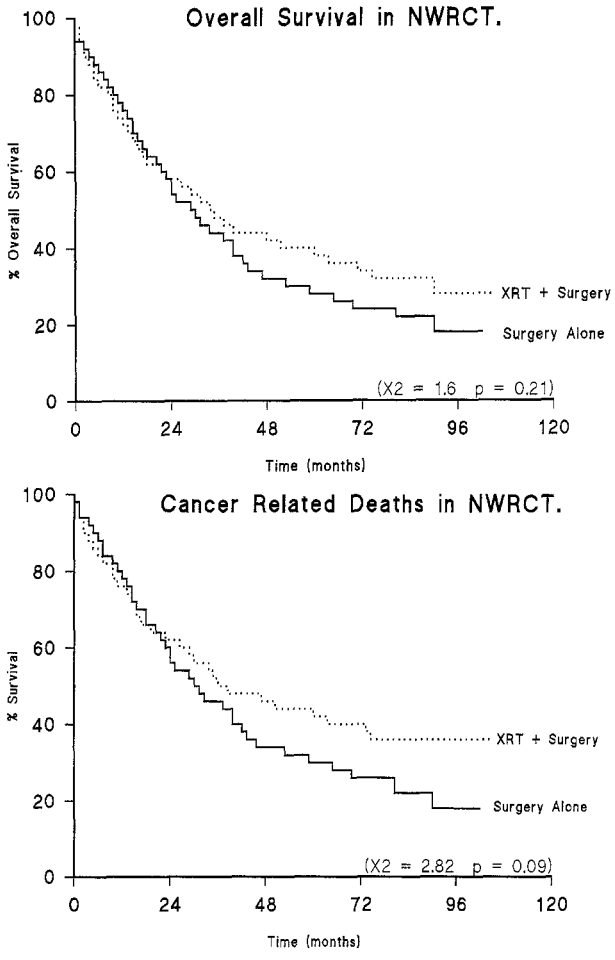

Figure 2. Overall and cancer-related survival curves for all patients in NWRCT.

Table 3.
Patient Outcome Following Curative Surgery in NWRCT

	Surgery Alone (%)	XRT + Surgery (%)	Log-rank *P* Value
Number of patients	75 (52.4)	68 (47.6)	—
Local recurrences	29 (38.6)	8 (11.8)	0.0001
Distant metastases	21 (28.0)	28 (41.2)	0.695
All deaths	40 (53.3)	31 (45.6)	0.0334

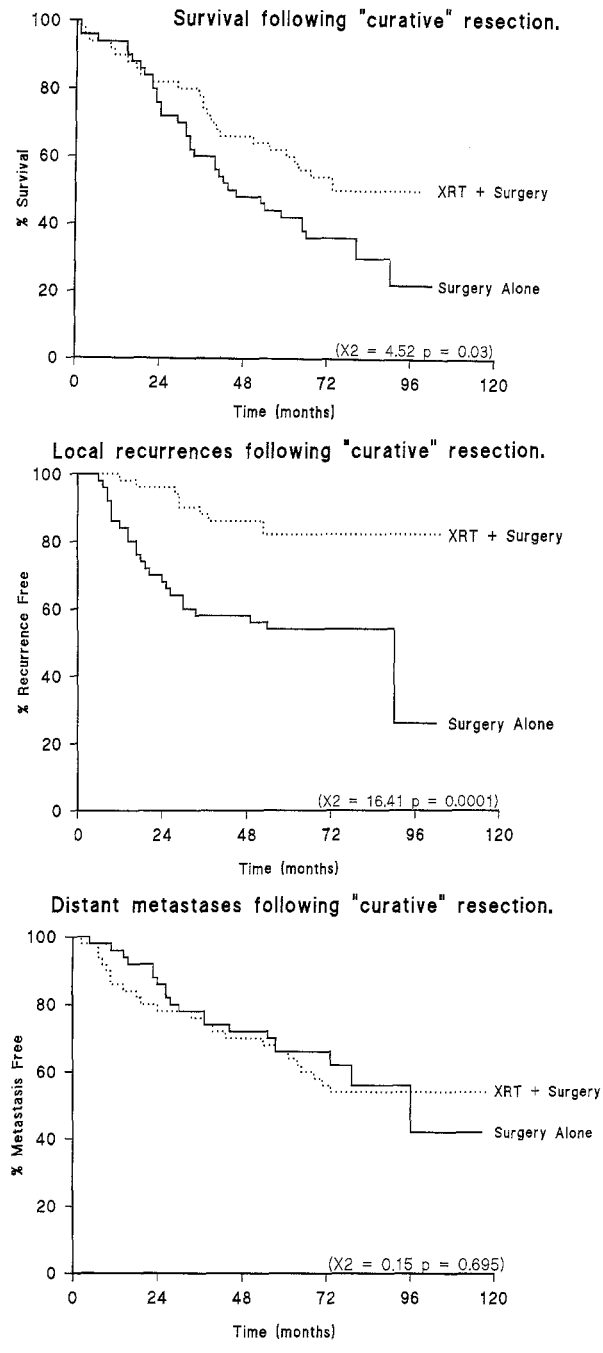

Figure 3. Overall survival, local recurrence-free, and metastasis-free survival curves for patients undergoing curative surgery in NWRCT.

ative radiotherapy, as compared with 36.5 percent (46 patients) after surgery alone (Table 2). This is a highly significant difference ($P = 0.0001$, with 1 degree of freedom). Of the 17 local recurrences in the irradiated group, 12 patients (9 percent) had local and disseminated recurrence and 5 (4 percent) had local recurrence alone. Fifteen of these patients have died of rectal carcinomatosis, but two remain alive at 96 months with advanced local disease (Table 4). One of these 17 patients received inadequate radiotherapy according to the protocol; the remaining 16 local recurrences comprise 6 that occurred outside the radiotherapy field, and 10 that occurred inside the field (*i.e.*, true recurrences). Further details of these patients are shown in Table 4.

There were 46 local recurrences following surgery alone; 30 patients (24 percent) had local and disseminated recurrence, and 16 (13 percent) had local recurrence alone. Forty-four of these patients (96 percent) have died of rectal carcinomatosis, but two remain alive following excision of the recurrence.

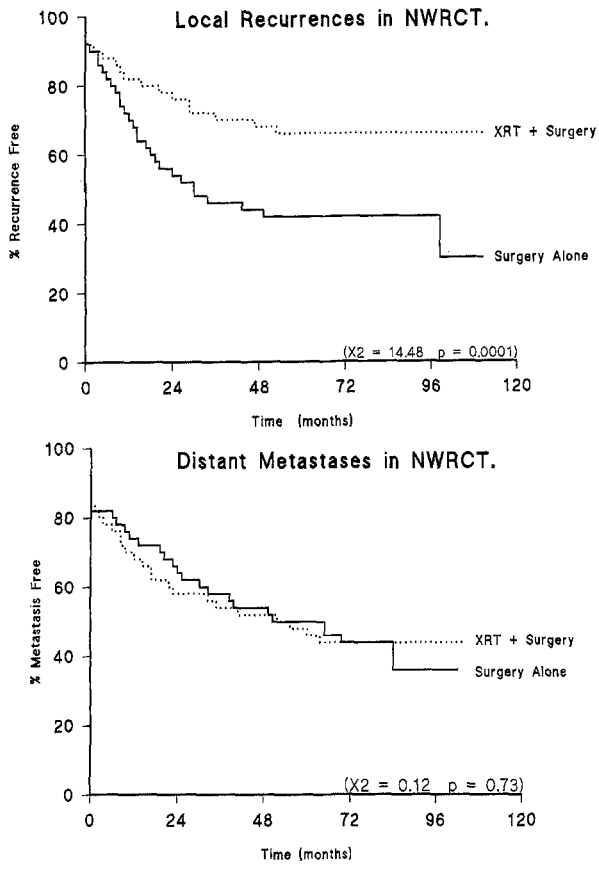

Figure 4. Local recurrence-free and metastasis-free survival curves for all patients in NWRCT.

Subset analysis of the 143 patients receiving curative surgery confirms highly significant reduction in local recurrences in the irradiated patients (Table 3 and Fig. 3); the local recurrence rate is 11.8 percent (8 patients) following preoperative radiotherapy, as compared with 38.6 percent (29 patients) after surgery alone ($P = 0.0001$, with 1 degree of freedom). Of the eight local recurrences in the irradiated patients operated on for cure, five (7 percent) had local and disseminated recurrence and three (4 percent) had local recurrence alone. These recurrences following radiotherapy were located outside the radiotherapy field in five instances and inside the field in three (Table 4). The 29 cases of local recurrence following curative surgery alone comprise 15 (20 percent) that were part of a generalized disease recurrence, and 14 (18.6 percent) that were local recurrences in isolation. All of these patients have died of rectal carcinomatosis.

Metastatic Recurrence

There was no significant difference in the rate of disseminated disease in the two arms of the trial (Table 2 and Fig. 4); 35.5 percent of patients allocated to surgery and 42.7 percent of patients allocated to radiotherapy developed metastatic disease ($P = 0.73$, with 1 degree of freedom). Similarly, there was no difference in the rates of metastatic recurrence in patients undergoing curative surgery (41.2 percent XRT *vs.* 28.0 percent surgery; $P = 0.695$) (Table 3 and Fig. 3).

DISCUSSION

This study of the effects of preoperative adjuvant radiotherapy on survival and local recurrence in rectal carcinoma has been performed on a group of operable, locally advanced (tethered or fixed) rectal carcinomas. There is no difference in the distribution of the clinicopathologic variables between the two arms of the trial, and no striking down-staging effects have been observed in the irradiated patients.[31, 34] The latter is not surprising, because surgery was performed within a week of completing high-dose radiotherapy, too short a time for any morphologic changes to become apparent.

In this study only 50 percent of patients underwent a curative resection, highlighting the difference between this and other similar studies (Table 1). In the Stockholm trial 80 percent of patients had a curative resection,[17] in the EORTC II trial 78 percent,[24] in the Norwegian study 92 percent,[25] and in the ICRF trial 76 percent.[22] In the control arms of these trials the local recurrence rates were 23 percent, 25 percent, 21 percent, and 24 percent, respectively, and the metastasis rates were 28 percent, 22 percent, 21 percent but were not reported for the ICRF study. However in the series reported here, the control arm local recurrence rate was 36.5 percent, and the metastasis rate was 35.5 percent (Table 2). The second MRC trial of preoperative radiotherapy in operable, locally advanced rectal tumors is the most directly comparable with the present study; the MRC trial had a curative operation rate of 44 percent and control local recurrence and metastasis rates of 46 percent and 48 percent, respectively (Medical Research Council, personal communication). This highlights the problems inherent in comparing trials that have different patient selection and exclusion criteria; it also emphasizes that in this study the patient population had particularly advanced disease.

The rates of local recurrence after surgery alone in this study, both in the series as a whole and in the subset undergoing curative surgery (36.5 percent and

Table 4.
Local Recurrences Following Radiotherapy

	Age/Sex	Primary	Operation	Recurrence	Metastasis	Outcome
			Outside radiotherapy field			
1	73 years Male	3 cm tethered—C Well	Palliative APR	10 months—pelvic side wall	10 months—liver and chest	Died 18 months—carcinomatosis
2	59 years Male	12 cm tethered—C Poor	Curative AR	22 months—pelvic and inguinal nodes	9 months—retroperitoneal nodes	Died 23 months—carcinomatosis
3	73 years Female	5 cm tethered—C Moderate	Curative APR	26 months—perineum and pre—sacral	39 months—groin nodes	Alive
4	69 years Male	3 cm fixed—C Poor	Curative APR	54 months—pelvic brim	54 months—liver—bony pelvis	Died 55 months—carcinomatosis
5	73 years Female	6 cm tethered—C Moderate	Curative APR	25 months—presacral and through pyriformis	23 months—sacrum	Died 30 months—carcinomatosis
6	71 years Male	5 cm tethered—C Moderate	Curative APR	96 months—pelvic side wall and through pyriformis	Nil	Alive
			Inside radiotherapy field			
1	72 years Male	3 cm tethered—C Moderate	Curative APR	28 months—anastomosis	Nil	Died 36 months—local disease
2	58 years Male	5 cm tethered—C Moderate	Palliative APR	20 months—pelvis	16 months—liver	Died 33 months—carcinomatosis
3	67 years Male	10 cm tethered—C Moderate	Curative APR	28 months—pelvis	Nil	Died 30 months—local disease
4	61 years Female	6 cm fixed—C	Palliative APR	0 months—residual tumor in pelvis	0 months—liver	Died 9 months—carcinomatosis
5	74 years Male	4 cm fixed—C Moderate	Palliative APR	9 months—pelvis	4 months—liver	Died 15 months—carcinomatosis
6	64 years Male	10 cm tethered—C Moderate	Palliative APR	7 months—presacral	11 months—liver	Died 12 months—carcinomatosis
7	73 years Male	3 cm tethered—A Moderate	Curative APR	36 months—pelvis	63 months—liver	Died 64 months—carcinomatosis
8	76 years Male	9 cm tethered—C Poor	Palliative APR	21 months—retrovesical	Nil	Died 27 months—local disease
9	74 years Male	6 cm tethered—B Moderate	Palliative APR	3 months—presacral—liver	0 months	Died 15 months—carcinomatosis
10	48 years Male	8 cm fixed—C Moderate	Palliative APR	0 months—residual tumor in pelvis	3 months—liver and chest	Died 4 months—carcinomatosis

APR = abdominoperineal resection; AR = anterior resection. Times in months refer to the time from surgery. Localization of recurrences was made by comparing the pretreatment CT planning films with those taken at the time of recurrence.

38.6 percent, respectively), are much higher than many would consider acceptable. Phillips *et al.*[10] reported a local recurrence rate of 15 percent following curative resection for rectal carcinoma, Dixon and colleagues[11] reported 6.4 percent and 14 percent (for anterior and abdominoperineal resections, respectively), and MacFarlane *et al.*[5] reported 4 percent for patients undergoing curative procedures. However, these series were all treated at a single center, were all operated on by a single surgeon, and were not confined to tethered and fixed tumors. By comparison, the Northwest Rectal Cancer Trial was a multicenter study with the surgery being performed at various hospitals throughout the Northwest Region by any of a number of surgeons (see Acknowledgments). As demonstrated by McArdle and Hole,[36] this can result in wide variations in the rates of curative resection, overall postoperative mortality and morbidity, local recurrence, and overall survival. The local recurrence rate in their study varied from 0 to 21 percent for

patients undergoing apparently curative surgery. In addition, it should be stressed that our study is concerned with a series of particularly advanced tumors and that the local recurrence rates reported include both local recurrence as part of a generalized disease recurrence as well as local recurrence in isolation.

Despite the above considerations, our results show a highly significant reduction in the rate of local tumor recurrence following preoperative adjuvant radiotherapy (12.8 percent after XRT *vs.* 36.5 percent after surgery; $P = 0.0001$) (Table 2). In common with all other prospective trials of preoperative radiotherapy, we have failed to demonstrate any benefit to overall survival in the whole group of patients, as distinct from the curative resection group (Fig. 2). A large meta-analysis of adjuvant therapy for colorectal cancer reported by Buyse *et al.*[30] calculates no survival advantage when all preoperative adjuvant radiotherapy cohorts are examined (odds ratio = 0.91; 95 percent CI = 0.79–1.06); this is compatible with a reduction in the risk of death by as much as 21 percent or an increase in the risk of 6 percent. Similarly, we have not shown any effect of radiotherapy, either beneficial or detrimental, on the rate of metastatic spread (Fig. 4). It is this disseminated disease that causes the high mortality of rectal carcinoma and justifies attempts at combined adjuvant approaches, including chemotherapy.[37] The reduction in local recurrences after radiotherapy is, however, of great significance, because the symptoms caused by locally recurrent rectal cancer result in considerable morbidity and are often refractory to conventional treatment.[6–8, 10, 12]

Analysis of the subset of patients who underwent a curative procedure, however, does show a significant reduction in mortality in the irradiated patients (45.6 percent XRT *vs.* 53.3 percent surgery; $P = 0.033$), as well as a reduction in local recurrences (11.8 percent XRT *vs.* 38.6 percent surgery; $P = 0.0001$) (Table 3 and Fig. 3). This effect of preoperative radiotherapy on the survival of patients undergoing curative surgery is similar to that reported by the Stockholm Rectal Cancer Study Group.[17] Subset analysis does not show any effect of radiotherapy on the rate of metastatic spread (41.2 percent XRT *vs.* 28 percent surgery; $P = 0.695$).

The Northwest Rectal Cancer Trial used a radiotherapy schedule that gave a nominal standard dose of 1,231 (Ellis, 1967),[16] which was comparable to the higher dose regimes in Table 1 (Stockholm, EORTC II, MRC II, VASAG II, and Norwegian studies).[17, 19, 20, 23–27] The rotational three-field wedge technique delivers radiation to a 10 × 10 × 10 cm cylindrical volume in the posterior pelvis, encompassing the tumor and including the mesorectal lymph nodes but not the pelvic brim, pelvic side walls, anterior pelvis, inguinal, or para-aortic lymph nodes (Fig. 1). Previous studies of moderate-dose to high-dose preoperative irradiation have almost exclusively used an extremely large field extending up to the level of the second lumbar vertebral body, to include the superior hemorrhoidal lymphatic system to the level of the origin of the inferior mesenteric artery. None of these studies, however, describes the exact sites of local recurrence in relation to the radiotherapy field. Because all patients receiving radiotherapy in this trial had CT planning before treatment, it has been possible to accurately define the location of any recurrences. The 17 (12.8 percent) recorded local recurrences in the irradiated patients included one case that received only 11 Gy. The remaining 16 local recurrences were sited inside the field (*i.e.*, true recurrences) in ten instances and outside the field in six (Table 4). All of the latter were Dukes C tumors, and hence spread to the regional lymph nodes had occurred by the time of surgery. The ten cases recurring inside the radiotherapy field included a preponderance of palliative operations on tethered or fixed Dukes C tumors (8 cases) (Table 4). This local recurrence rate following radiotherapy compares favorably with rates of 21 percent in the Stockholm study,[17] 15 percent in the EORTC II trial,[24] 15 percent in the Norwegian study,[25] 16 percent in the ICRF trial,[22] and 36 percent in MRC II (Medical Research Council, personal communication), the only trials to demonstrate significant benefits for preoperative radiotherapy on local recurrence rates. We can conclude, therefore, that the radiotherapy field arrangement and dose regime used in this study results in improved local control, as compared with previous trials using more extensive radiotherapy fields.

Equally important is the fact that distant metastases are not increased by irradiating a small 10 × 10 × 10 cm volume in the posterior pelvis (35.5 percent surgery *vs.* 42.7 percent XRT; $P = 0.73$). The only reported trial to demonstrate a beneficial effect of preoperative radiotherapy on rates of distant metastasis is the second MRC trial (48 percent surgery *vs.* 35 percent XRT; $P = 0.02$) (Medical Research Council, personal communication). The regime used by the MRC study was 40 Gy in 20 fractions over 28 days (nominal

standard dose = 1,362)[16] from two parallel opposed fields 18 × 15 cm.

On the basis of these results, it is the current practice at this institution to treat locally advanced rectal carcinoma with preoperative radiotherapy. Tumors are initially assessed at a joint surgical and radiotherapy examination under anesthetic. Tethered tumors receive 20 Gy in four daily fractions, followed by operation within a week of completion of radiotherapy; more fixed tumors receive 40 to 45 Gy in 20 fractions over 28 days, followed by re-examination under an anesthetic six weeks later to assess operability. Those that are considered operable go on to definitive surgery. The radiotherapy field arrangement and the volume irradiated with this higher dose regime are exactly as described above (Fig. 1) and do not appear to be associated with an increase in small bowel complications.[38–40]

ACKNOWLEDGMENTS

The authors thank R. Swindell, R. Hannon, and M. Dougal of the Department of Medical Statistics for assistance with data retrieval and statistical analysis. Members of the Northwest Region Rectal Cancer Group are as follows: S. Alexander, D. Allen, H. D. Baillie, J. Bancewicz, W. G. T. Bell, M. A. Brennan, T. C. Brightmore, J. Buchanan, K. G. Buckler, D. Cade, A. B. Cassie, J. F. Clegg, M. W. Cooper-Wilson, D. J. Cowley, K. H. Crumplin, M. Davies, R. P. Davies, H. J. Done, J. S. Duthie, M. Duari, P. C. England, L. Forrest, K. M. Fussell, I. E. Gillespie, R. H. Grace, J. Gray, B. D. Hancock, A. W. Hargreaves, R. C. Hartley, A. Higham, N. Hira, E. M. Hoare, J. M. T. Howat, C. S. Humphrey, G. Ingram, M. H. Irving, R. D. James, J. F. Kelly, J. H. Kilshaw, R. D. Kingston, W. R. Lawson, J. B. Laine, H. Leighton-Davies, J. P. Lythgoe, J. Magell, N. MacDonald, I. MacLennan, J. M. Main, N. K. Maybury, R. W. K. Neill, T. C. B. O'Brien, D. G. Ostick, W. G. Paley, K. W. Pearson, S. Rosenberg, P. J. Salem, P. F. Schofield, I. G. Schraibman, J. Seddon, W. S. Sewell, M. Shafiq, J. Skilton, P. A. Sykes, R. S. Todd, D. E. F. Tweedle, P. Wake, and R. J. Williams.

REFERENCES

1. King's Fund Forum. Cancer of the colon and rectum: consensus statement. Br J Surg 1990;77:1063–4.
2. Silverberg E, Boring CE, Squires TS. Cancer statistics. CA Cancer J Clin 1990;40:9–26.
3. Lockhart-Mummery HE, Ritchie JK, Hawley PR. The results of surgical treatment of carcinoma of the rectum at St. Mark's Hospital from 1948–72. Br J Surg 1976;63: 673–7.
4. Heald RJ, Ryall RD. Recurrence and early survival after total mesorectal excision for rectal cancer. Lancet 1986; 1:1479–82.
5. MacFarlane JK, Ryall RD, Heald RJ. Mesorectal excision for rectal cancer. Lancet 1993;341:457–60.
6. Berge T, Ekeland G, Mellner C, Pihl B, Wenckert A. Carcinoma of the colon and rectum in a defined population: an epidemiological, clinical and post-mortem investigation of colorectal carcinoma and coexisting benign polyps in Malmö, Sweden. Acta Chir Scand [Suppl] 1973;438:1–86.
7. Gunderson LL, Sosin H. Areas of failure found at reoperation (second or symptomatic look) following "curative surgery" for adenocarcinoma of the rectum: clinicopathologic correlation and implications for adjuvant therapy. Cancer 1974;34:1278–92.
8. Gunderson LL, Tepper JE, Dosoretz DE, Kopelson G, Hoskins RB, Russell AH. Patterns of failure after treatment of gastrointestinal cancer. Cancer Treat Symp 1983;2:181–97.
9. Phillips RK, Hittinger R, Blesovsky L, Fry JS, Fielding LP. Local recurrence following 'curative' surgery for large bowel cancer: I. The overall picture. Br J Surg 1984;71: 12–6.
10. Phillips RK, Hittinger R, Blesovsky L, Fry JS, Fielding LP. Local recurrence following 'curative' surgery for large bowel cancer: II. The rectum and rectosigmoid. Br J Surg 1984;71:17–20.
11. Dixon AR, Maxwell WA, Thornton Holmes J. Carcinoma of the rectum: a 10-year experience. Br J Surg 1991;78: 308–11.
12. Tagliacozzo S, Accordino M. Pelvic recurrence after surgical treatment of rectal and sigmoid cancer: a prospective clinical trial on 274 patients. Int J Colorectal Dis 1992;7:135–40.
13. Schofield PF, Walsh S, Tweedle DE. Survival after treatment of carcinoma of the rectum. BMJ 1986;293:496–7.
14. Whittaker M, Goligher JC. The prognosis after surgical treatment of carcinoma of the rectum. Br J Surg 1976; 63:384–8.
15. Morson BC, Vaughan EG, Bussey HJ. Pelvic recurrence after excision of rectum for carcinoma. BMJ 1963;2: 13–8.
16. Ellis F. Fractionation in radiotherapy. In: Deeley TJ, Wood CA, eds. Modern trends in radiotherapy. Vol. 1. London: Butterworth, 1967:34–51.
17. Stockholm Rectal Cancer Study Group. Preoperative short-term radiation therapy in operable rectal carcinoma: a prospective randomized trial. Cancer 1990;66: 49–55.
18. Duncan W. Adjuvant radiotherapy in rectal cancer: the MRC trials. Br J Surg [Suppl] 1985;72:59–62.
19. First Report of an MRC Working Party. A trial of pre-

operative radiotherapy in the management of operable rectal cancer. Br J Surg 1982;69:513–9.
20. Second Report of an MRC Working Party. The evaluation of low-dose pre-operative x-ray therapy in the management of operable rectal cancer: results of a randomly controlled trial. Br J Surg 1984;71:21–5.
21. Porter NH, Nicholls RJ. Pre-operative radiotherapy in operable rectal cancer: interim report of a trial carried out by the Rectal Cancer Group. Br J Surg [Suppl] 1985;72:62–4.
22. Goldberg PA, Nicholls RJ, Grimsey JE, Porter NH. Low-dose preoperative radiotherapy for rectal cancer: a prospective randomised trial. Br J Surg [Suppl] 1993;80:21.
23. Gerard A, Berrod J-L, Pene F, *et al.* Interim analysis of a phase III study on pre-operative radiation therapy in resectable rectal carcinoma: trial of the Gastrointestinal Tract Cancer Co-operative Group of the European Organization for Research and Treatment of Cancer (EORTC). Cancer 1985;55:2373–9.
24. Gerard A, Buyse M, Nordlinger B, *et al.* Pre-operative radiation therapy as adjuvant treatment in rectal cancer: final results of a randomized study of the European Organization for Research and Treatment of Cancer (EORTC). Ann Surg 1988;208:606–14.
25. Dahl O, Horn A, Morild I, *et al.* Low-dose pre-operative radiation postpones recurrences in operable rectal cancer: results of a randomized multicenter trial in Western Norway. Cancer 1990;66:2286–94.
26. Higgins GA, Humphrey EW, Dwight RW, Rowsit B, Lee LE, Keehn RJ. Preoperative radiation and surgery for cancer of the rectum: Veterans Administration Surgical Oncology Group Trial II. Cancer 1986;58:352–59.
27. Higgins GA, Conn JH, Jordan PH, Humphrey EW, Rowsit B, Keehn RJ. Preoperative radiotherapy for colorectal cancer. Ann Surg 1975;181:624–31.
28. Rowsit B, Higgins GA, Keehn RJ. Preoperative irradiation for carcinoma of the rectum and rectosigmoid colon: report of a national Veterans Administration randomized study. Cancer 1975;35:1597–602.
29. Rider WD, Palmer JA, Mahoney LJ, Robertson CT. Preoperative irradiation in operable cancer of the rectum: report of the Toronto trial. Can J Surg 1977;20:335–8.
30. Buyse M, Zeleniuch-Jacquotte A, Chalmers TC. Adjuvant therapy of colorectal cancer: why we still don't know. JAMA 1988;259:3571–8.
31. James RD. The northwest of England rectal cancer trial: recent results. Cancer Res 1988;110:104–10.
32. Kaplan E, Meier P. Non-parametric estimation from incomplete observation. J Am Stat Assoc 1958;53:457–63.
33. Peto R, Pike MC, Armitage P, *et al.* Design and analysis of randomized clinical trials requiring prolonged observation of each patient: II. Analysis and examples. Br J Cancer 1977;35:1–39.
34. James RD, Haboubi N, Schofield PF, Mellor M, Salhab N. Prognostic factors in colorectal carcinoma treated by preoperative radiotherapy and immediate surgery. Dis Colon Rectum 1991;34:546–51.
35. Jones DJ, Zaloudik J, James RD, Haboubi N, Moore M, Schofield PF. Predicting recurrence of carcinoma of the rectum after preoperative radiotherapy and surgery. Br J Surg 1989;76:1172–5.
36. McArdle CS, Hole D. Impact of variability among surgeons on postoperative morbidity and mortality and ultimate survival. BMJ 1991;302:1501–5.
37. Krook JE, Moertel CG, Gunderson LL, *et al.* Effective adjuvant therapy for high-risk rectal carcinoma. N Engl J Med 1991;324:709–15.
38. James RD, Schofield PF. Resection of "inoperable" rectal cancer following radiotherapy. Br J Surg 1985;72: 279–81.
39. Dosoretz DE, Gunderson LL, Hedberg S, *et al.* Preoperative irradiation for unresectable rectal and rectosigmoid carcinomas. Cancer 1983;52:814–8.
40. Emami B, Pilepich M, Willett C, Munzenrider JE, Miller HH. Effect of irradiation on resectability of colorectal carcinomas. Int J Radiat Oncol Biol Phys 1982;8: 1295–99.