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Papers

Long-term Results of a Randomised Trial of Short-course Low-dose Adjuvant Pre-operative Radiotherapy for Rectal Cancer: Reduction in Local Treatment Failure

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A prospective randomised multicentre trial compared pre-operative radiotherapy followed by surgery with surgery alone for rectal cancer ≤12 cm from the anal verge. Of 468 patients (mean age 67 years, range 31–94, 273 males) who met the entry criteria, 228 were randomised to radiotherapy (3 × 5 Gy over 5 days within 2 days of operation) followed by surgery, and 239 to surgery alone. Randomisation was unknown in 1 patient. Follow-up to death or 5 years was achieved in 454 (97%) patients. 31 (7%) of the 468 patients died within 30 days of operation (radiotherapy and surgery 21 [9%], surgery alone 10 [4%]; $P < 0.05$). Cardiovascular and thromboembolic complications were more common after radiotherapy and surgery (30, 13%) than after surgery alone (8, 3%; $P < 0.005$). Of the 280 patients who had curative surgery, 52% of those who had radiotherapy and surgery and 56% of those who had surgery alone survived 5 years ($P = 0.88$). 395 patients attended outpatients clinics at least once. Local treatment failure was identified during follow-up in 82 patients [31/185 (17%) radiotherapy and surgery; 51/210 (24%) surgery alone; $P < 0.05$]. It occurred in 33 of the 258 patients who had a curative resection and attended outpatients [radiotherapy and surgery, 11/120 (9%), surgery alone, 22/138 (16%); $P = 0.08$]. Long-term survival was unaffected, but long-term local recurrence was reduced by the addition of low-dose radiotherapy to surgery. Peri-operative mortality was, however, increased.

Key words: randomised trial, rectal cancer, pre-operative radiotherapy, local treatment failure
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INTRODUCTION

RADIOTHERAPY HAS been used in many forms as an adjunct to curative surgery in an attempt to improve the results of treatment of rectal cancer [1]. Metastatic disease is the major cause of cancer-related death after curative resection [2]. In our experience, local treatment failure without metastases is uncommon [3, 4] and rarely curable. While it was found in one series that approximately 15% of patients develop local recurrence [5], a large autopsy study showed local recurrence without dissemination to be present in only 8% of all patients dying from large bowel cancer [6]. These observations would explain the failure of adjuvant radiotherapy to reduce mortality. Nevertheless, local recurrence causes morbidity, and is often responsible for the patient's main suffering. While surgery has been claimed to reduce local recurrence rates to a minimum of as little as 2% [7], the general experience has been that the rate with surgery alone is much greater [5, 8–10].

A number of trials have examined the role of pre-operative radiotherapy. Most were not randomised. Of the few randomised trials, only three have examined local treatment failure [11–13]. These have used dose/fractionation regimes, sometimes lasting up to 3 weeks, pre-operatively. The present trial was designed to see the effect of a short course of radiotherapy, completed within a week, on local treatment failure and survival.

PATIENTS AND METHOD

Study design

The study was carried out in 15 hospitals with 27 surgeons, 19 radiotherapists and 19 pathologists participating. Patients who met the entry criteria were, after informed consent, randomised (via sealed envelopes) to radiotherapy followed by surgery or to surgery alone in blocks within each hospital. The study opened in 1980 and closed to admission of patients in 1984.

Entry criteria

Patients were entered and randomised if they were fit for surgery and had a resectable (in the opinion of the surgeon)

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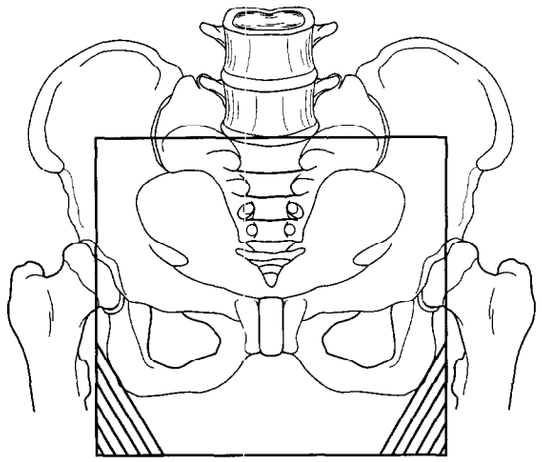

Figure 1. Diagram of radiotherapy field.

biopsy-proven adenocarcinoma with the lower border less than or equal to 12 cm from the anal verge on rigid sigmoidoscopy. There was no upper age limit. Patients with familial adenomatous polyposis and ulcerative colitis were excluded.

Before treatment, the mobility of the tumour, its height above the anal verge and the number of quadrants involved were recorded.

Radiotherapy

Radiotherapy was given to a dose of 15 Gy (midplane) in three 5-Gy fractions from a megavoltage source on alternate days over 5–7 days (extra day allowed over weekends), with the third fraction no more than 48 h prior to surgery. Each treatment was by a pair of parallel opposed fields, anterior and posterior, and extended from the lumbosacral junction to the perineum and 1.5 cm lateral to the pelvic side walls (Figure 1).

Surgery

Surgery was carried out within 2 days of completion of radiotherapy in those patients randomised to receive it. In patients randomised to surgery alone, operation was performed on the first available list. At operation, the surgeon recorded the local and distant extent of the disease. A statement was made as to whether local clearance had been achieved and whether the operation was curative or palliative.

Pathology

The operative specimens were pinned out prior to fixation and the size of the tumour determined. After fixation, the number of involved and uninvolved lymph nodes in the mesorectum was recorded. Dukes' stage and histological grade were determined. The pathologist decided whether the resection was locally complete or not.

Follow-up

Patients were followed up at 3-monthly intervals for the first year and then at 6-monthly intervals until death or for at least 5 years. Recurrence of disease was determined clinically and by carcinoembryonic antigen measurement at each visit. Radiological imaging techniques were used where clinically indicated. It was a protocol requirement to biopsy suspected recurrent disease wherever possible.

Statistical analysis

Survival in the treatment groups was calculated from date of randomisation. The association between categorical variables was evaluated by the χ^2 test on contingency tables or Fisher's exact probability test when appropriate. Intergroup differences in data were tested by the Student's *t*-test. Survival and disease recurrence rates were calculated using the Kaplan–Meier method [14] and comparison between the curves assessed by the log-rank test [15, 16]. The stratified log-rank test [16], with Dukes' stage defining the strata, was used to detect if an imbalance in Dukes' stage affected the treatment outcome.

RESULTS

478 patients were entered and randomised. There were 10 protocol violations (Table 1). These were excluded from further analysis. Of the 468 patients (mean age 67 years, range 31–94, 273 males), all had adenocarcinoma of the rectum with the lower border at or within 12 cm of the anal verge, 228 were randomised to radiotherapy and surgery and 239 to surgery alone. For 1 patient, the randomisation group was unknown. There were no important differences between the two groups in sex (60 versus 56% male), age at operation [69 (range 31–94) versus 69 (range 36–93) years median] or duration of symptoms [4 (range 1–60) versus 3 (range 1–60) months]. Mortality, morbidity and survival were calculated using the 468 patients as the denominator.

Of the 228 patients randomised to receive radiotherapy, 23 did not complete the course in the prescribed period because of logistical reasons in 12 cases, unfitness for radiotherapy in 6, previous pelvic radiotherapy in 1, refusal of radiotherapy in 2 and 2 patients were deemed inoperable. One patient died of a myocardial infarct prior to surgery after completing radiotherapy.

There was no difference in the extent of disease found at operation or the type of operation performed in the two groups (Table 2).

The in-hospital 30-day mortality was significantly higher in those patients who received radiotherapy. They also had significantly more cardiovascular and thromboembolic complications. Thromboembolic prophylaxis was given to 23 (10%) patients in each group. There was no difference in the rate of anastomotic leakage after anterior resection or perineal breakdown after total rectal excision in the two groups (Table 3).

Table 1. Protocol violations

	No. of patients
Radiotherapy and surgery	2
Villous adenoma	1
Adenocarcinoma above 12 cm	1
Surgery alone	6
Lymphoma	1
Melanoma	1
Diverticular disease	1
Basaloid carcinoma	1
Adenocarcinoma above 12 cm	2
Treatment group unknown	2
Familial polyposis and previous total colectomy and ileorectal anastomosis	1
Adenocarcinoma above 12 cm	1
Total	10

Table 2. Type of operation

	Treatment group	
	Radiotherapy and surgery (*n*)	Surgery alone (*n*)
No operation	6	1
Laparotomy alone	2	5
Colostomy alone	2	2
Total rectal excision	82	93
Anterior resection	123	117
Local excision	5	1
Hartmann's	8	19
Operation unknown	0	1

The pathological stages of the tumours were similar in both groups, with a total of Dukes' A = 26%, B = 31%, C1 = 38% and C2 = 5% (Table 4). There was no difference in the distribution of histological grading in the two groups.

Follow-up

73 patients never attended outpatients. 46 (10%) of the 468 patients who met the entry criteria died in hospital prior to discharge. Two of these deaths occurred prior to surgery and 31 (7%) within 30 days of surgery. A further 13 patients died before discharge, but after 30 days. 14 patients died after discharge, but within 4 months without attending outpatients. Of the remaining 13 patients, 12 have died, and 1 left the country and was lost to follow up. This last patient had residual disease at operation and has probably died. The remaining 395 patients attended outpatients at least once (median 8 times, range 1–22). Local recurrence rates were calculated using these 395 patients as the denominator.

The follow-up to 5 years or death was complete in 454 (97%) of the 468 patients. Of these, 307 are known to have died. 14 (3%) patients were lost to follow up. These patients were censored after their last follow-up visit for the life table analysis.

Survival

The 5-year actuarial survival of all 468 patients was similar in the two groups (radiotherapy and surgery 38.8%, surgery alone 40.3%, log-rank test $\chi^2 = 0.01$, $P = 0.92$). 280 patients (146 radiotherapy and surgery, 134 surgery alone) were assessed by both the surgeon and pathologist as having had a curative resection. There was no statistical difference in the 5-year survival of those treated by curative operation having radiotherapy and surgery (52%) compared with surgery alone (56%)

Table 4. Number of patients by stage where information available, n = 449

Dukes' stage	Radiotherapy and surgery	Surgery alone
A	55	62
B	69	69
C1	84	88
C2	9	13

(log-rank test $\chi^2 = 0.02$, $P = 0.88$; Figure 2). Adjusting for Dukes' stage, the effect remained non-significant (adjusted log-rank $\chi^2 = 0.00$, $P = 0.9$). There was no statistical difference in the survival of palliative cases in the two treatment groups.

Recurrence

Of the 395 outpatient attenders (258 curative and 137 palliative, as assessed by the surgeon and pathologists), recurrent disease occurred in 156 patients. Of these, the first appearance of recurrence was local only in 56, distant only in 74 and both local and distant in 26 patients. Therefore, 82 of the 395 patients developed local treatment failure. There was a significant difference in the incidence of local recurrence in the two groups [radiotherapy and surgery 31/185, 17%, surgery alone 51/210, 24% (5-year actuarial), log-rank test $\chi^2 = 4.37$, $P = 0.04$; Figure 3]. When adjusted for Dukes' stage, the effect remained of borderline significance (adjusted log-rank $\chi^2 = 3.65$, $P = 0.056$).

Recurrent disease was recorded in 70 of the 258 patients who

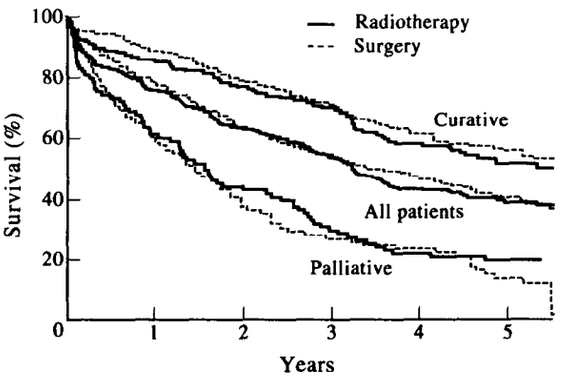

Figure 2. Five-year survival—all patients and after curative resection.

Table 3. Mortality and morbidity

	Radiotherapy and surgery *n* (%)	Surgery alone *n* (%)	*P*
n	228	239	
In-hospital mortality	27 (12)	16 (7)	0.056
30-day mortality	21 (9)	10 (4)	<0.05
Cardiovascular and thromboembolic complications	30 (13)	8 (3)	<0.001
Anastomotic leak (anterior resection)	18/122 (15)	15/117 (13)	ns
Perineal breakdown (total rectal excision)	21/82 (26)	20/93 (22)	ns

ns, non-significant.

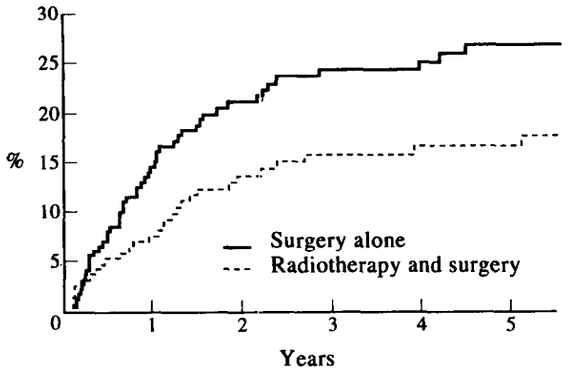

Figure 3. Local treatment failure—all outpatient attenders.

had a curative resection and attended outpatients at least once. The recurrence was local only in 23 patients, distant only in 37 and both local and distant in 10. Thus, 33 patients developed local treatment failure, 11/120 (9%) after radiotherapy and surgery and 22/138 (16%) after surgery alone (5-year actuarial log-rank $\chi^2 = 3.59$, $P = 0.08$; Figure 4). After adjustment for Dukes' stage, the treatment effect remained of borderline significance (adjusted log-rank $\chi^2 = 3.04$, $P = 0.08$).

There were no differences in the incidence or timing of distant recurrences in the two treatment groups (data not shown).

DISCUSSION

Many trials have examined pre-operative radiotherapy as an adjuvant to surgery for rectal cancer. In the late 1970s, two non-randomised studies from Oregon [17] and Montpellier [18] using between 40 and 60 Gy provided evidence of improved survival after radiotherapy, and the Oregon study suggested a reduction in local recurrence. This stimulated a number of randomised trials, none of which have confirmed the improvement in survival [19–23]. Local recurrence has, however, been included as an end-point of three previous studies only [11–13]. For example, the Memorial trial [24], VASOG I [19] and II [20] and MRC I [25] do not give data on local recurrence.

The EORTC trial [12] recruited 466 patients who were randomised to surgery alone or 34.5 Gy in 15 fractions over 19 days followed by surgery a mean of 11 days later. The 5-year survival was similar in both groups (59.1 versus 69.1%, $P = 0.08$) after curative resection. Local recurrence was reduced from 30% in those who received surgery alone to 15% when radiotheapy was added ($P = 0.003$).

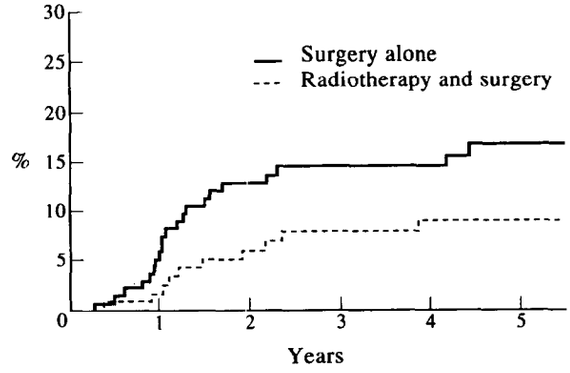

Figure 4. Local treatment failure—curative resection.

Dahl and colleagues [13] reported a trial from western Norway where 309 patients were randomised to surgery alone or 31.5 Gy in 18 fractions over 2–3 weeks, followed by surgery 2–3 weeks later. Five-year survival was similar in the two groups (61 versus 64%), although radiation reduced the local recurrence rate from 21 to 13%, and significantly delayed the appearance of both local and distant recurrence from 13 to 27 months after curative resection.

The Stockholm Rectal Cancer Study Group [11] has reported the early results of a randomised trial of 25 Gy over 5–7 days at a median follow-up of 53 months (range 8–90 months). Local recurrence was less common in those patients who received radiotherapy. The postoperative mortality was higher (8%) in irradiated patients compared to those who had surgery alone (2%, $P < 0.01$).

In the present trial, the local recurrence rate fell from 24% in the control group to 17% in those patients who received radiotherapy. This reduction is similar to the rates of 21 and 15% in all patients in the western Norway study [13], in spite of the larger radiotherapy dose given. It is difficult to compare recurrence rates after curative resection as the definition of curative resection may differ in different studies. This may explain the rates of 16% in the present trial, 21% in the western Norway trial [13] and 30% in the EORTC trial [12] in the groups who had surgery alone, and 9, 14 and 15%, respectively, for radiotherapy with surgery. The local recurrence rate after curative resection in all three studies appears to be halved in those patients who received radiotherapy, irrespective of the dose given.

Two factors might explain why local recurrence is reduced by a reasonably uniform protection of one third to one half in trials with such different dose/fractionation regimes. Firstly, the linear quadratic formula [26] predicts a larger biologically effective dose where larger dose fractions are used. The biologically effective dose in this trial approaches 18 Gy rather than the total dose of 15 Gy that was given. Secondly, there is a direct relationship between the biologically effective dose of radiotherapy given and the logarithm of cell death. At least 99% of all viable tumour cells will be sterilised by 18 Gy, including any remaining after operation. This dose closely approaches the theoretical effectiveness of the higher dose regimes in terms of cell kill and residual viable cells.

The increase in the mortality and morbidity in the group who received radiotherapy is reflected by both the EORTC [12] and western Norway [13] studies, although in neither was the difference statistically significant. The overall mortality in these two trials was lower than the present trial. Perhaps an age factor contributed to this difference. Patients in the EORTC trial were on average 5 years younger than in this trial. The proportion of palliative cases may be another factor. Nearly half the mortality occurred in patients treated palliatively, who comprised approximately only a third of the total. The lower mortality in the Norwegian study may be accounted for by a lower proportion of palliative cases. The large dose fractions given in this trial may contribute to the increased mortality observed [11].

A major cause of mortality and morbidity in the present study was deep vein thrombosis and pulmonary embolism. During the period of the study (1980–1984), thromboembolic prophylactic measures were used in only 10% of patients in both groups. Perhaps their more widespread use today will reduce these complications. The results show that thromboembolic prophylaxis is obligatory with surgery after radiotherapy.

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APPENDIX
The Rectal Cancer Group: Imperial Cancer Research Fund

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