Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial

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Summary

Background **Preoperative or postoperative radiotherapy reduces the risk of local recurrence in patients with operable rectal cancer. However, improvements in surgery and histopathological assessment mean that the role of radiotherapy needs to be reassessed. We compared short-course preoperative radiotherapy versus initial surgery with selective postoperative chemoradiotherapy.**

Methods **We undertook a randomised trial in 80 centres in four countries. 1350 patients with operable adenocarcinoma of the rectum were randomly assigned, by a minimisation procedure, to short-course preoperative radiotherapy (25 Gy in five fractions; n=674) or to initial surgery with selective postoperative chemoradiotherapy (45 Gy in 25 fractions with concurrent 5-fluorouracil) restricted to patients with involvement of the circumferential resection margin (n=676). The primary outcome measure was local recurrence. Analysis was by intention to treat. This study is registered, number ISRCTN 28785842.**

Findings **At the time of analysis, which included all participants, 330 patients had died (157 preoperative radiotherapy group *vs* 173 selective postoperative chemoradiotherapy), and median follow-up of surviving patients was 4 years. 99 patients had developed local recurrence (27 preoperative radiotherapy *vs* 72 selective postoperative chemoradiotherapy). We noted a reduction of 61% in the relative risk of local recurrence for patients receiving preoperative radiotherapy (hazard ratio [HR] 0·39, 95% CI 0·27–0·58, p<0·0001), and an absolute difference at 3 years of 6·2% (95% CI 5·3–7·1) (4·4% preoperative radiotherapy *vs* 10·6% selective postoperative chemoradiotherapy). We recorded a relative improvement in disease-free survival of 24% for patients receiving preoperative radiotherapy (HR 0·76, 95% CI 0·62–0·94, p=0·013), and an absolute difference at 3 years of 6·0% (95% CI 5·3–6·8) (77·5% *vs* 71·5%). Overall survival did not differ between the groups (HR 0·91, 95% CI 0·73–1·13, p=0·40).**

Interpretation **Taken with results from other randomised trials, our findings provide convincing and consistent evidence that short-course preoperative radiotherapy is an effective treatment for patients with operable rectal cancer.**

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Introduction

Loco-regional recurrence after resection of rectal cancer is difficult to treat and is associated with severe debilitating symptoms. The prognosis after a local recurrence is poor, with a median survival of 12–18 months.[1,2]

Randomised controlled trials published before 1998 showed a high rate of local recurrence after surgery alone[3–14] and a reduction in local recurrence with radiotherapy used either preoperatively[3–9] or postoperatively.[10–14] Of these trials, the Swedish rectal cancer trial[7] was the largest (1168 patients) and showed that the addition of a 1-week (short) course of pelvic radiation (25 Gy in five fractions) before surgery resulted in a statistically significant reduction in local recurrence rate and improvement in overall survival compared with surgery alone (at 5 years: local recurrence 11% *vs* 27%, overall survival 58% *vs* 48%).

Chemotherapy can also be added to radiotherapy; the use of postoperative concurrent chemoradiotherapy reduced local recurrence rates[14,15] and improved survival.[15,16] The consensus statement by the US National Institutes for Health in 1990[17] recommended postoperative chemoradiotherapy as standard treatment in the USA for all patients with completely resected stage II or III rectal cancer.

Nevertheless, pelvic radiotherapy is associated with an increased risk of late complications, including a substantial increase in bowel frequency and incontinence[18,19] and delayed healing of the perineal wound when an abdominoperineal excision is done.[20] Therefore, targeting radiotherapy to patients considered at high risk of local recurrence is an attractive option, especially if the number of such patients can be kept to a minimum.

Specialist colorectal surgeons in individual centres reported improvements in surgical technique, using careful sharp dissection of the mesorectal tissues (total mesorectal excision), with 5-year local recurrence rates of less than 10%.[21,22] Thus, at the end of the 1990s, two questions remained: did preoperative radiotherapy add anything to total mesorectal excision, and could

improved methods be found to identify the few patients at high risk postoperatively (rather than postoperative chemo-radiotherapy for all patients with stage II or III disease)?

Adam and colleagues[23] described the histopathological assessment of the circumferential resection margin and showed that involvement of this margin (defined as microscopic tumour present 1 mm or less from the radial margin) was associated with a high risk of local recurrence and poor survival. This method of assessment offered much appeal since it could identify a few patients at high risk of failure who might benefit from selective postoperative chemoradiotherapy.

This trial was therefore designed to compare the use of routine short-course preoperative radiotherapy with initial surgery and selective postoperative chemo-radiotherapy reserved for patients who had involvement of the circumferential resection margin.

Methods

Study design and patients

The Medical Research Council (MRC) CR07 and National Cancer Institute of Canada (NCIC) Clinical Trials Group C016 trial was a multicentre, randomised controlled trial comparing preoperative radiotherapy with selective postoperative chemoradiotherapy. Between March 16, 1998, and Aug 5, 2005, eligible patients were recruited from 80 centres in four countries (69 UK, nine Canada, one South Africa, and one New Zealand). The protocol was approved in the UK by the Multicentre Research Ethics Committee for Scotland. Local ethics approval was obtained at all participating institutions, and written and informed consent was obtained from all patients. The MRC Clinical Trials Unit coordinated the trial, and an independent trial steering committee oversaw the trial. Confidential interim analyses were reviewed approximately every year during the recruitment period by an independent data monitoring committee.

Eligible patients had histologically confirmed adenocarcinoma of the rectum (defined as the distal tumour less than 15 cm from the anal verge measured by rigid sigmoidoscopy) with no evidence of metastases (identified by liver ultrasound or CT scan and chest radiograph). The primary tumour had to be deemed resectable (defined as not fixed to the pelvis and that complete excision was feasible). If operability could not be established by digital examination, examination under anaesthetic, supplemented when appropriate by pelvic CT or MRI scanning or by endoluminal ultrasound, was recommended. Patients had to be regarded as sufficiently fit to receive all treatments (an upper age limit was not defined), and those with previous or present malignant disease that was likely to interfere with protocol comparisons were regarded as ineligible.

Eligible consenting patients were randomly assigned to treatment groups by the MRC Clinical Trials Unit by a minimisation procedure, with stratification for surgeon, distance of distal tumour extent from the anal verge, and WHO performance status. Patients were assigned to either a preoperative radiotherapy regimen of 25 Gy in five consecutive daily fractions followed by surgery (recommended to take place within 7 days of the last fraction of radiotherapy), or to a selected post-operative chemoradiotherapy regimen of initial surgery with selective postoperative concurrent chemo-radiotherapy of 45 Gy in 25 fractions with concurrent 5-fluorouracil (either continuous infusion 200 mg/m² per day or weekly bolus 5-fluorouracil 300 mg/m² and leucovorin 20 mg/m²) for patients with involvement of the circumferential resection margin (≤1 mm).

Procedures

Surgeons were encouraged to use total mesorectal excision, although it was not mandated in the trial protocol. This approach was already in clinical use in the UK at the time that the trial was launched. No formal training or accreditation programme was used for surgeons participating in the trial. At the time of trial design, a validated audit method to assess whether total mesorectal excision was done, or to assess the quality of the surgical specimen, did not exist. However, a simple grading system of the resected macroscopic surgical specimen was prospectively assessed as part of the trial and the results are presented in an accompanying article.[24]

The radiotherapy target volume was defined as the sacral promontory superiorly, 3–5 cm below the inferior tumour extent, 2–3 cm anterior to the sacral promontory, 1 cm posterior to the anterior sacrum, and 1 cm lateral to the most lateral aspect of the bony true pelvis. Whenever possible, the anal canal was to be spared in patients with mid and upper rectal cancer. The perineal scar was to be included postoperatively in patients with tumours less than 5 cm from the anal verge.

Adjuvant chemotherapy could be given with either a monthly (5-fluorouracil 370–425 mg/m² on days 1–5 every 28 days) or weekly (5-fluorouracil 370–425mg/m² once per week) schedule combined with 20 mg/m² leucovorin with each 5-fluorouracil administration. Centres were required to state their local policy for the use of adjuvant chemotherapy according to circumferential resection margin and lymph node status, which was to be applied to both treatment groups. If both postoperative chemoradiotherapy and adjuvant chemotherapy were required, postoperative chemoradiotherapy was to be given first.

After randomisation, follow-up forms were required at 3, 6, 9, and 12 months, and then every 6 months to 3 years and yearly thereafter. Patient-reported quality of life was collected with the validated questionnaires SF36,[25] and EORTC (European Organisation for Research and Treatment of Cancer) quality-of-life questionnaire CR-38,[26] which were administered at baseline (before randomisation) and at the same timepoints as the clinical data, up to 36 months.

Outcome measures

The primary outcome measure was local recurrence, irrespective of any occurrence of distant metastases. The time to local recurrence was defined as the time from randomisation to a confirmed local recurrence. Confirmed local recurrence was defined as intraluminal tumour confirmed by a biopsy sample, positive imaging, or equivocal pelvic imaging with a raised serum carcino-embryonic antigen without distant metastases. Patients without a confirmed local recurrence were censored at the time of last follow-up.

Secondary outcome measures were overall survival, disease-free survival, local-recurrence-free survival, time to appearance of distant metastases, postoperative morbidity, quality of life, and long-term complications.

Overall survival was defined as the time from randomisation to death from any cause, with survivors being censored at the time of last follow-up. Disease-free survival was defined as the time from randomisation to confirmed local recurrence, distant metastases, or death due to disease or treatment, whichever occurred first. Patients who were alive and disease free (or died of a non-rectal-cancer cause with no evidence of disease) were censored at the time of last follow-up.

In this paper we report the primary outcome measure (local recurrence) and related secondary outcome measures (disease-free and overall survival), and put these results into context. Although quality of life is an important consideration when comparing treatments for rectal cancer, the analyses, presentation, and interpretation of quality-of-life data are complex. Initial analyses have been recently presented[27] and a separate paper is in preparation.

Statistical analysis

At the start of the trial, the standard of care in most of the UK was considered to be preoperative radiotherapy. This trial was therefore initially designed to establish whether selective postoperative chemoradiotherapy would be no worse than preoperative radiotherapy. The local recurrence rate for preoperative radiotherapy was estimated as approximately 10% at 2 years. To show non-inferiority and reliably exclude a difference of less than 5% at 2 years with selective postoperative chemoradiotherapy, 1800 patients were required (two-sided log-rank test, $\alpha=0\cdot05$, power=90%). In 2001, and on the basis of the evidence of a lower than expected local-recurrence rate in a large randomised trial,[28] the sample size was revised to exclude a difference of more than 2·5% in the local-recurrence rate at 2 years, assuming a 2-year local-recurrence rate of 2·5% with preoperative radiotherapy, which required 1350 patients (one-sided log-rank test, $\alpha=0\cdot05$, power=90%).

However, by 2006, most UK clinicians were using selective postoperative chemoradiotherapy, and therefore we took a decision to analyse the results in terms of superiority of preoperative radiotherapy over selective postoperative chemoradiotherapy. The 1350 patients were sufficient to reliably detect a 2·5% improvement in the local-recurrence rate at 2 years with preoperative radiotherapy, from 5% with selective postoperative chemoradiotherapy to 2·5% with preoperative radiotherapy (two-sided log-rank test, $\alpha=0\cdot05$, power=80%).

All analyses were by intention to treat. We compared proportions with the χ^2 test, and ordered categorical variables by the Mann-Whitney test. Survival curves of local-recurrence-free interval, disease-free survival, and overall survival were calculated by the Kaplan-Meier method and compared with a two-sided log-rank test. Potential differences between preoperative radiotherapy and selective postoperative chemoradiotherapy across subgroups were compared by a test for interaction for groups with two levels and a test for trend for groups with three or more levels. All hazard ratios (HRs) have been calculated in relation to the preoperative radiotherapy group to show the hazard associated with this treatment compared with selective postoperative chemoradiotherapy.

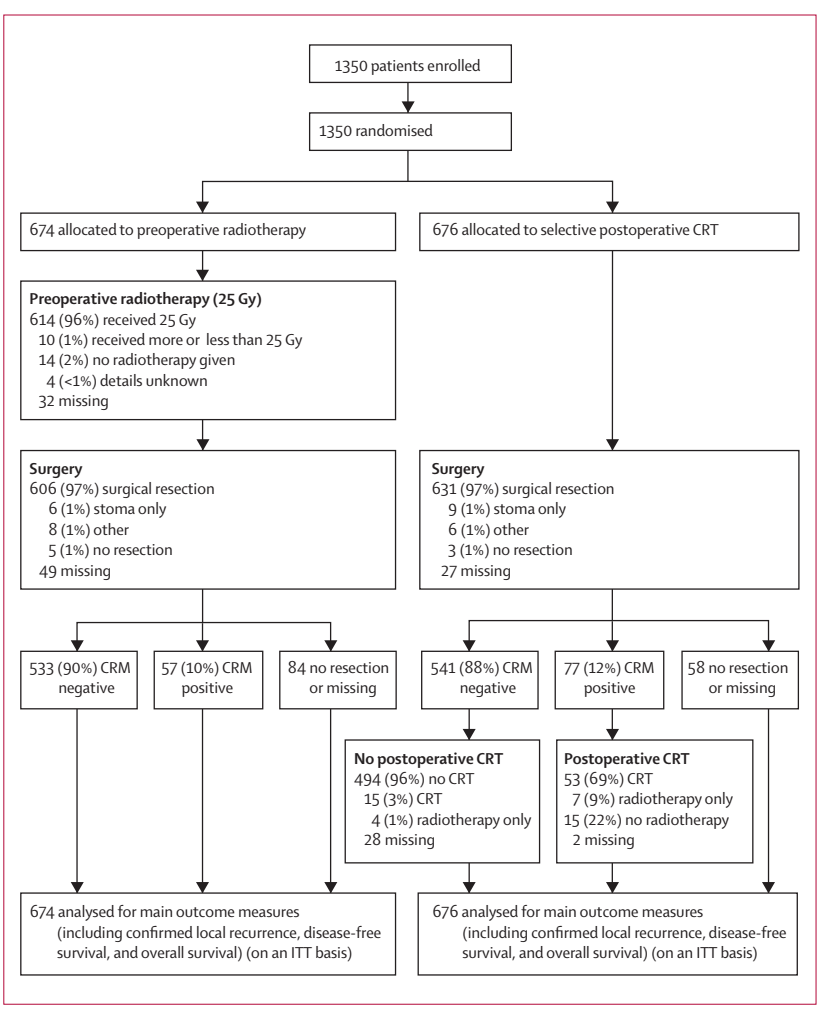

Figure 1: **Trial profile**
CRT=chemoradiotherapy. CRM=circumferential resection margin. ITT=intention to treat.

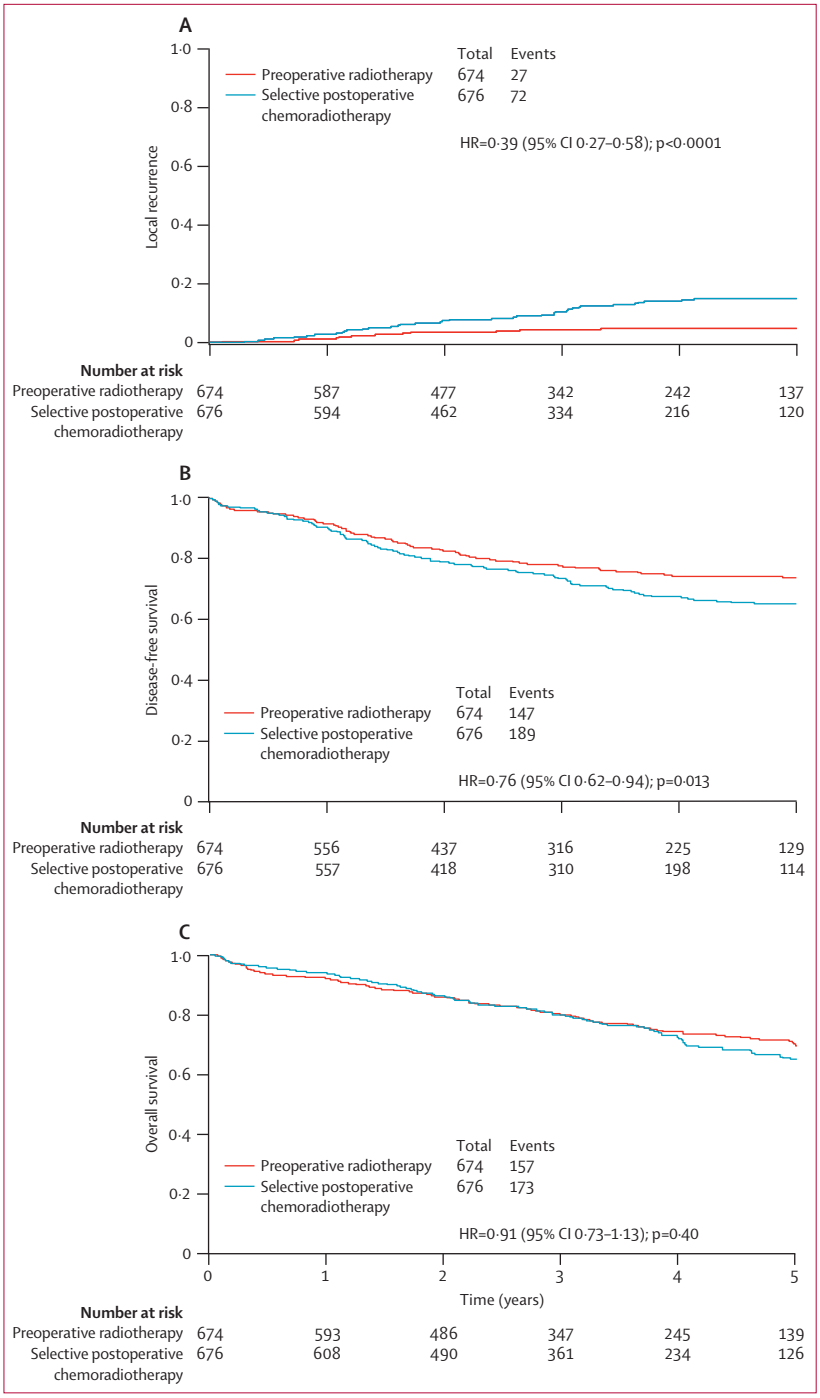

Figure 2: **Proportion of patients with a confirmed local recurrence (A), disease-free survival (B), and overall survival (C)**

Quotation of landmark values, such as the median, directly from the Kaplan-Meier plots can be very misleading, since the curves might randomly converge or separate at the crucial timepoint. We have therefore used the result from the preoperative radiotherapy group and applied the HR for the whole curve to provide an estimate of the values for the selective postoperative chemoradiotherapy group. This method assumes proportional hazards but is more accurate than reading off the curve.[29]

This study is registered, number ISRCTN 28785842.

Role of the funding source

The sponsor of the study had no role in the design and conduct of the trial, or in the analysis of the data. The corresponding author had full access to the data and had final responsibility for the decision to submit for publication.

Results

1350 patients were recruited and randomised (674 preoperative radiotherapy group, 676 selective postoperative chemoradiotherapy group). The median number of patients per centre was six (IQR two to 17), although 814 (60%) were treated in 12 centres that contributed 30 or more patients. Figure 1 shows the trial profile. Six patients did not meet the eligibility criteria: two in the preoperative radiotherapy group (not cancer, unfit) and four in the selective postoperative chemoradiotherapy group (unfit, metastases present [two patients], previous malignancy), but these patients have been included in all analyses. Table 1 shows the baseline characteristics of patients.

628 patients (98% of the 642 patients with available data) received preoperative radiotherapy (figure 1). 14 (2%) patients did not receive any radiotherapy, because of other disease being present (n=5), problems with radiotherapy administration (3), patient choice (1), patient death (1), and unknown reasons (4). The median time from the end of radiotherapy to surgery was 4 days (IQR 3–6), and 524 (91% of the 578 patients with available surgery and radiotherapy data) had their surgery within 7 days of radiotherapy.

The median time from randomisation to surgery was 27 days (IQR 21–33) in the preoperative radiotherapy group and 19 days (IQR 12–26) in the selective postoperative chemoradiotherapy group. Surgical resection was done in 1237 patients (97% of the 1274 patients with data available; figure 1), and 1143 (92%) of these resections were recorded as total mesorectal excision by the operating surgeon. In patients who had an anterior resection, the clinical anastomotic leak rates at 1 month were similar in both groups (preoperative radiotherapy: 9% [95% CI 6–12], selective postoperative chemoradiotherapy: 7% [4–9]). However, in patients who had an abdominoperineal excision, more of those in the preoperative than in the selective postoperative group were reported as having a non-healing perineum (70/202 [35%] *vs* 44/202 [22%]). Longer-term follow-up (in patients with an abdominoperineal excision) at 12 and 24 months showed that rates of small bowel obstruction, perineal wound failure to heal, and lumbar or sacral neuropathy did not differ between the two treatment groups (data not shown). The 30-day postoperative mortality rate was 2%

(95% CI 1–3) in both groups. Of the 792 patients who had an anterior resection, 317 (83%) in the preoperative radiotherapy group and 318 (78%) in the selective postoperative chemoradiotherapy group were reported as having a defunctioning stoma.

The rate of circumferential resection margin involvement (table 1) and the proportion of patients with pathological stage III disease did not differ between the two groups (p=0·12 and p=0·29, respectively). However, we noted some evidence of a small downstaging effect on T stage (p=0·0001) in the preoperative radiotherapy group, since there were 9% more patients with stage I disease and 6% fewer with stage II disease than in the selective postoperative chemoradiotherapy group.

Of the 646 patients allocated to receive selective postoperative chemoradiotherapy and who had a resection, 77 (12%) had involvement of the circumferential resection margin. Of these 77 patients, 53 (69%) received chemoradiotherapy, seven (9%) received radiotherapy only, 15 (19%) had no radiotherapy, and two had no treatment data. Only one of the 53 patients who received chemoradiotherapy had any interruptions to their treatment as a result of toxic effects from treatment. The median time from surgery to start of chemoradiotherapy was 57 days (IQR 43–72). Of those who had a negative circumferential resection margin, 494 (91%) had no radiotherapy, 15 (3%) received chemoradiotherapy, and four (1%) received radiotherapy only. Treatment data were not available for the remaining 28 (6%) patients.

Adjuvant chemotherapy was given to 235 of 585 (40%) patients in the preoperative radiotherapy group and 274 of 609 (45%) in the selective postoperative chemoradiotherapy group. 138 (27%) received the monthly regimen (64/235 [27%] in the preoperative radiotherapy group, 74/274 [27%] in the selective postoperative chemoradiotherapy group), and 320 (63%) received the weekly regimen (144/235 [62%] *vs* 176/274 [64%]). The remaining 51 (10%) patients received a variety of other adjuvant regimens. Adjuvant chemotherapy was given to 28 (18%) and 37 (18%) of patients with stage II disease, and 201 (84%) and 232 (87%) of those with stage III disease in the preoperative radiotherapy and selective postoperative chemoradiotherapy groups, respectively.

Table 2 and figure 2 show the results for local recurrence, disease-free survival, and overall survival. 99 patients (27 preoperative radiotherapy group *vs* 72 selective postoperative chemoradiotherapy group) developed a confirmed local recurrence. It was the only reported site of recurrence in 54 patients (13 *vs* 41), and occurred before (one *vs* 11), concurrently with (ten *vs* eight), or after (three *vs* 12) distant metastases in the remaining patients. Comparison of the Kaplan-Meier curves (figure 2A) gives an HR of 0·39 (95% CI 0·27–0·58; p<0·0001), indicating a 61% relative reduction in the risk of recurrence with preoperative radiotherapy.

	Preoperative radiotherapy (n=674)	Selective postoperative chemoradiotherapy (n=676)
Before treatment		
Median age (range [years])	65 (38–87)	65 (36–87)
Sex		
Men	499 (74%)	482 (71%)
Women	175 (26%)	194 (29%)
WHO performance status		
0	535 (79%)	534 (79%)
1	134 (20%)	135 (20%)
2	4 (<1%)	7 (1%)
3	1 (<1%)	0
Distance of distal tumour extent from anal verge (cm)		
>10–15	95 (14%)	112 (17%)
>5–10	345 (52%)	337 (50%)
0–5	229 (34%)	217 (33%)
Missing	5	10
Type of surgery		
Anterior resection	383 (61%)	409 (63%)
Abdominoperineal excision	202 (32%)	202 (31%)
Hartmann's	21 (3%)	20 (3%)
Other	14 (2%)	15 (2%)
None	5 (1%)	3 (1%)
Missing	49	27
After treatment		
Patients with a known resection	620	646
Operative mortality		
30 day	12 (2%)	15 (2%)
60 day	17 (3%)	20 (3%)
Clinical anastomotic leak (anterior resection only)		
Yes	32 (9%)	26 (7%)
No	338 (91%)	370 (93%)
Missing	13	13
Circumferential resection margin*		
Involved	57 (10%)	77 (12%)
Not involved	533 (89%)	541 (88%)
Missing	30	28
Number of lymph nodes†		
≥10	340 (57%)	426 (68%)
<10	257 (43%)	202 (32%)
Missing	23	18
TNM stage‡		
I	183 (31%)	140 (22%)
II	169 (28%)	215 (34%)
III	239 (40%)	269 (43%)
IV	5 (1%)	5 (1%)
Missing	24	17

Data are number (%), unless otherwise indicated. *p=0·12. †p<0·0001. ‡p=0·034.

Table 1: **Clinical, surgical, and histopathological details**

This finding translates to an absolute difference in the 3-year local-recurrence rate of 6·2% (95% CI 5·3–7·1) (4·4% in the preoperative radiotherapy group *vs* 10·6% in the selective postoperative chemoradiotherapy group).

	Preoperative radiotherapy (n=674)	Selective postoperative chemoradiotherapy (n=676)	HR (95% CI)
Disease-related events			
Local recurrence criteria			
Intraluminal tumour			
Positive biopsy	2	23	..
No biopsy	0	2	..
Not intraluminal tumour			
Positive imaging	15	25	..
Positive biopsy	4	18	..
Eq imaging, CEA+ve, M0	3	2	..
Missing data	3	2	..
Local recurrence (total)	27 (4%)	72 (11%)	..
Distant metastases	128 (19%)	139 (21%)	..
Disease-related death	89 (13%)	102 (15%)	..
Kaplan-Meier results*			
Local recurrence	..	..	0·39 (0·27–0·58); p<0·0001
2 year	3·4%	8·3%	..
3 year	4·4%	10·6%	..
5 year	4·7%	11·5%	..
Disease-free survival	..	..	0·76 (0·62–0·94); p=0·013
2 year	82·5%	77·6%	..
3 year	77·5%	71·5%	..
5 year	73·6%	66·7%	..
Overall survival	..	..	0·91 (0·73–1·13); p=0·40
2 year	86·1%	84·8%	..
3 year	80·3%	78·6%	..
5 year	70·3%	67·9%	..
Effects in subgroups			
3-year local recurrence by CRM involvement†			
Involved (positive)	13·8%	20·7%	0·64 (0·25–1·64)
Not involved (negative)	3·3%	8·9%	0·36 (0·23–0·57)
3-year local recurrence by tumour position (cm)‡			
>10–15	1·2%	6·2%	0·19 (0·07–0·47)
>5–10	5·0%	9·8%	0·50 (0·28–0·90)
0–5	4·8%	10·4%	0·45 (0·23–0·88)
3-year local recurrence by TNM stage§			
I	1·9%	2·8%	0·68 (0·16–2·81)
II	1·9%	6·4%	0·29 (0·12–0·67)
III	7·4%	15·4%	0·46 (0·28–0·76)

Eq imaging, CEA+ve, M0=equivocal imaging, abnormal carcino-embryonic antigen, and no metastases. CRM=circumferential resection margin. *The proportion of patients surviving in the selective postoperative chemoradiotherapy group has been calculated by applying the HR to the proportion in the preoperative radiotherapy group, to achieve a more reliable overall estimate. †Test for interaction p=0·29. ‡Test for trend p=0·21. §Test for trend p=0·93.

Table 2: **Disease-related events and data for time to event**

147 disease-related events were recorded in the preoperative radiotherapy group and 189 in the selective postoperative chemoradiotherapy group. Comparison of the Kaplan-Meier curves (figure 2B) gives an HR of 0·76 (95% CI 0·62–0·94; p=0·013), indicating a 24% relative reduction in the risk of a disease-related event with preoperative radiotherapy. This finding translates to an absolute difference in 3-year disease-free survival of 6·0% (95% CI 5·3–6·8) (77·5% in the preoperative group *vs* 71·5% in the selective postoperative group).

330 patients died (157 in the preoperative group, 173 in the selective postoperative group), and the median follow-up for surviving patients is 4 years. Comparison of the Kaplan-Meier curves (figure 2C) gives an HR of 0·91 (95% CI 0·73–1·13; p=0·40), indicating no significant difference between treatment groups.

A few variables were explored (involvement of circumferential resection margin, distance of tumour from anal verge, and TNM stage; table 2) to investigate any variation of the treatment effect across subgroups on rates of local recurrence. We detected no evidence of any interactions across any of the variables, although we acknowledge that the power to detect any interactions is low because of the small number of events.

Discussion

This trial was designed to compare the rates of local recurrence with two adjuvant radiotherapy regimens in patients with resectable rectal cancer. Results show that both local control and disease-free survival are improved by preoperative radiotherapy compared with selective postoperative chemoradiotherapy. The significant improvement in 3-year disease-free survival seems to be predominantly attributable to the reduction in local recurrence, although we noted a small non-significant reduction in both the number of patients with distant metastases and with deaths related to rectal cancer. At present there is no clear evidence of a difference in overall survival, although there are fairly few deaths so far, and any difference might be diluted by the large proportion (42%) of non-cancer deaths.

Trials undertaken before the introduction of total mesorectal excision strongly lent support to the preoperative radiotherapy regimen. Similarly, the selective postoperative chemoradiotherapy regimen was supported by studies showing a low rate of local recurrence after surgery and a highly selective approach to postoperative chemoradiotherapy, allowing most patients to avoid radiotherapy.

Although total mesorectal excision was not mandated within the trial design, surgeons considered that it had been achieved in 93% of patients who underwent resection. No formal surgical training programme was used for centres participating in the trial. However, the overall negativity rate for circumferential resection margin was 89%, which compares favourably with the Dutch trial in which 77% of patients in the intention-to-treat analysis had tumour-free margins without tumour spillage.[28] Quirke and colleagues[24] present the assessment of the surgical resection plane achieved and its correlation with outcome in the accompanying paper; they show that 86% of surgical specimens were done in the mesorectal or intramesorectal plane. The fairly high rate (32%) of abdominoperineal

excisions is not unexpected since a third of patients had a tumour less than 5 cm from the anal verge. We therefore believe that the outcome data from this trial are likely to represent that observed in routine clinical practice.

Most patients with stage III disease in this trial received adjuvant chemotherapy in keeping with standard practice in many countries, including the USA, with no real difference in its use between treatment groups. Importantly, the proportion of patients with pathologically assessed stage III disease was the same in both groups, showing that no observed downstaging effect of preoperative radiotherapy had occurred in terms of nodal status. Thus patients could be logically selected for postoperative adjuvant chemotherapy, which contrasts with the uncertainties surrounding selection for this treatment for patients who have undergone preoperative chemoradiotherapy and in whom substantial change in the histopathological stage might have occurred.

A Cochrane meta-analysis[30] identified four phase III trials[3,6,7,31] undertaken before the introduction of total mesorectal excision that used short-course preoperative 25 Gy radiotherapy. Three trials[3,6,7] compared short-course preoperative radiotherapy followed by surgery with surgery alone, although 316 of the 557 patients in the Stockholm II trial were also included in the Swedish Rectal Trial. The pooled data of the remaining two trials[6,7] show a highly consistent and significant reduction in the rate of local recurrence with the use of preoperative radiotherapy (HR 0·46, 95% CI 0·38–0·56; figure 3). A similar benefit is also seen in the Uppsala trial[31] that compared short-course preoperative radiotherapy with surgery followed by postoperative split-course radiotherapy for patients with Dukes B and C histology. The Cochrane meta-analysis identified CR07 and the Dutch colorectal cancer group trial,[28] which used short-course preoperative radiotherapy and total mesorectal excision (although only data from the Dutch trial were available at that time). Both trials assessed short-course preoperative radiotherapy with a highly selective postoperative radiotherapy regimen. The CR07 trial used postoperative concurrent chemoradiotherapy, whereas the Dutch trial used radiotherapy alone in the selective postoperative group. The combined data from the CR07 trial and the Dutch trial (the two largest adjuvant radiotherapy trials, totalling 3211 patients) show a highly significant reduction in the rate of local recurrence with the use of preoperative radiotherapy (HR 0·38, 95% CI 0·29–0·49) when combined with total mesorectal excision (figure 3).

Very clear evidence now suggests that preoperative radiotherapy produces the same proportional reduction in the rate of local recurrence when combined with total mesorectal excision as that seen in previous studies undertaken before such excision. The preoperative radiotherapy regimen is also a very cost-effective way to deliver treatment, since it uses only five fractions of radiation. Furthermore, evidence from the 13-year follow-up from the Swedish rectal cancer trial,[32] and data from three meta-analyses,[30,33,34] lend support to the view that preoperative radiotherapy prevents a proportion of patients from developing local recurrence rather than merely delaying the event.

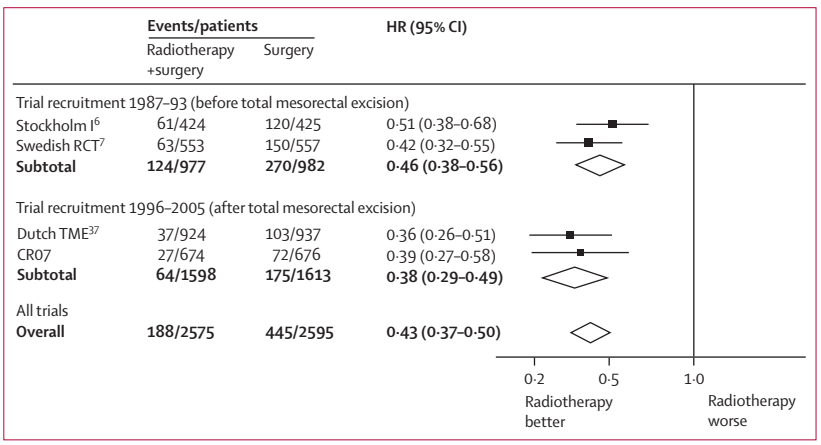

Figure 3: **Summary of reduction in risk of local recurrence in phase III trials that have assessed short-course preoperative radiotherapy with 5 Gy per fraction**

However, clear evidence also suggests that long-term surgically-related morbidity is increased by both preoperative and postoperative radiotherapy. Previous studies have reported sexual dysfunction,[33] long-term impairment of bowel function and incontinence,[18,19,34] a significant delay in healing of the perineal wound after abdominoperineal excision,[20] and an increased risk of second malignancy with the use of adjuvant radiotherapy.[35] Furthermore, loss of fertility in men and premenopausal women inevitably occurs. The main measure of the long-term effect of treatment in this trial was the use of prospective quality-of-life questionnaires. The initial results have been presented[27] and suggest that sexual functioning seemed to be most affected, mainly as a result of surgery, with worse sexual functioning after an abdominoperineal excision. However, sexual functioning was further reduced in patients who had an anterior resection after preoperative radiotherapy. Detailed analysis will be presented elsewhere.

The risk of late toxic effects emphasises the need to identify patients in whom the benefit (prevention of incurable local recurrence) is balanced against the long-term side-effects related to the radiotherapy. Unfortunately, none of the phase III trials of radiotherapy had sufficient power or a priori planned interaction analyses to adequately address this issue. The interaction analyses in this trial showed no evidence of a difference in the benefit from preoperative radiotherapy when distance from the anal verge and TNM stage were considered, although the absolute difference in local recurrence is greatest for patients with stage III disease.

Two recent phase III trials[36,37] have shown a significant reduction in local recurrence with the use of preoperative

concurrent chemoradiotherapy with 5-fluorouracil and leucovorin compared with long-course radiotherapy alone. A further trial[38] has shown a significant reduction in both local recurrence and late toxic effects in favour of preoperative chemoradiotherapy compared with post-operative chemoradiotherapy. This finding has affected the US policy of postoperative chemoradiotherapy, with a shift to the use of preoperative chemoradiotherapy in selected patients. These results suggest that a direct comparison of short-course preoperative radiotherapy and preoperative chemoradiotherapy is needed. One small Polish trial used this design with results showing no evidence of a difference in the rates of sphincter preserving surgery[39] (the primary outcome measure) or local recurrence,[40] although it was not statistically powered to address local recurrence. An Australian trial[41] has reported initial quality-of-life data, but outcome data are still awaited.

At the time that this trial was recruiting, evidence for the use of pelvic MRI to accurately assess stage of rectal cancer was insufficient. (The results of the multicentre MERCURY study[42,43] were published after the trial closed to recruitment.) Pelvic MRI and CT scans were used in the preoperative staging in 556 (41%) and 812 (60%) of the patients in this trial, respectively, and examination under anaesthetic in 548 (41%). These factors suggest that there is scope for future studies that incorporate MRI staging and compare preoperative radiotherapy and chemoradiotherapy in a defined population of patients whose margin of excision is not at risk.

Contributors

All the authors were members of the trial management group, participated in the discussion and interpretation of data, and in writing of the paper. DS-M was the chief investigator, chair of the trial management group, and participated in the design of the trial. RS originally conceived the idea for the trial, participated in its design, and advised on the surgical aspects. JM participated in the design and advised on the surgical aspects of the trial. RG and SK advised on the radiotherapy aspects of the trial. PQ participated in the design and advised on the pathological aspects of the trial. JC and CdM were responsible for the involvement of the National Cancer Institute of Canada. RJS was the lead Clinical Trials Unit investigator for the trial, and participated in the design and data analysis. GG was the project leader for the trial up until 2005. LCT was the trial statistician and was responsible for the data analysis of the trial. MP was the programme leader for colorectal cancer trials in the Medical Research Council Clinical Trials Unit, and participated in the design and data analysis of the trial.

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Conflict of interest statement

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