Articles

Adjuvant radiotherapy for rectal cancer: a systematic overview of 8507 patients from 22 randomised trials

*Colorectal Cancer Collaborative Group**

Summary

Background At least 28 randomised, controlled trials have compared outcomes of surgery for rectal cancer combined with preoperative or postoperative radiotherapy with those of surgery alone. We have done a collaborative meta-analysis of these results to give a more balanced view of the total evidence and to increase statistical precision.

Methods We centrally checked and analysed individual patient data from 22 randomised comparisons between preoperative (6350 patients in 14 trials) or postoperative (2157 in eight trials) radiotherapy and no radiotherapy for rectal cancer.

Findings Overall survival was only marginally better in patients who were allocated to radiotherapy than in those allocated to surgery alone (62% *vs* 63% died; p = 0·06). Rates of apparently curative resection were not improved by preoperative radiotherapy (85% radiotherapy *vs* 86% control). Yearly risk of local recurrence was 46% (SE 6) lower in those who had preoperative radiotherapy than in those who had surgery alone (p=0·00001), and 37% (10) lower in those who had postoperative treatment than those who had surgery alone (p=0·002). Fewer patients who had preoperative radiotherapy died from rectal cancer than did those who had surgery alone (45% *vs* 50%, respectively, p=0·0003), but early (≤1 year after treatment) deaths from other causes increased (8% *vs* 4% died, p<0·0001).

Interpretation Preoperative radiotherapy (at biologically effective doses ≥30 Gy) reduces risk of local recurrence and death from rectal cancer. If safety can be improved without compromising effectiveness, then overall survival would be moderately improved by use of preoperative radiotherapy, especially for young, high risk patients. Postoperative radiotherapy also reduces local recurrence, but short preoperative radiation schedules seem to be at least as effective as longer schedules.

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Introduction

Despite apparently curative surgery, rectal cancer recurs locally in up to 25% of patients. Radiotherapy might reduce risk of local recurrence and improve survival rates. At least 28 randomised trials have compared patients with rectal cancer who had adjuvant preoperative or postoperative radiotherapy with those who had surgery alone. We have done an overview (meta-analysis) of their findings to give a more accurate and balanced account. Because a larger number of patients is analysed in a systematic overview, random errors are smaller than in individual trials. Additionally, a review of all related trials avoids potentially misleading selective emphasis on more (or less) promising results, which can arise solely by chance, especially since not all results are published, and those that are tend to have more striking results.

Methods

Trials

We identified trials and checked data according to the procedures described by the Early Breast Cancer Trialists' Collaborative Group.[1] We included trials if they were unconfounded, correctly randomised comparisons between either preoperative or postoperative radiotherapy and no radiotherapy for rectal cancer, and had started before Jan 1, 1987. Trials of radiotherapy for colon cancer were not eligible. To be correctly randomised, trials had to have used treatment allocation methods that precluded foreknowledge of the allocated treatment. To be unconfounded the treatment regimens had to differ only in that one included radiotherapy (either preoperatively or postoperatively) whereas the other did not. Age, sex, site of cancer (colon/rectum), Dukes' stage, and allocated treatment were sought for each patient randomised (including those who entered later into trials begun before 1987). Dates of randomisation, surgery, and first recurrence were recorded, and site of first recurrence (local/distant) and last known vital status were also obtained. Causes of death were recorded only for those who died without recorded recurrence. Data were checked for completeness and internal consistency and were amended through correspondence with the investigators. As a final check, this report has been circulated to all members of the collaborative group, and revised in accordance with their comments.

Figure 1 shows details of the 19 trials of preoperative radiotherapy[2–21] and the nine of postoperative radiotherapy[22–30] that were identified. Trials are identified by the year in which randomisation began and the study name. The UK MRC1[3] study of medium dose versus low-dose versus no radiotherapy is split into two parts by radiotherapy dose and thus control patients in this study appear in two subtotals and count twice in the total. In trials in which entry criteria but not treatments

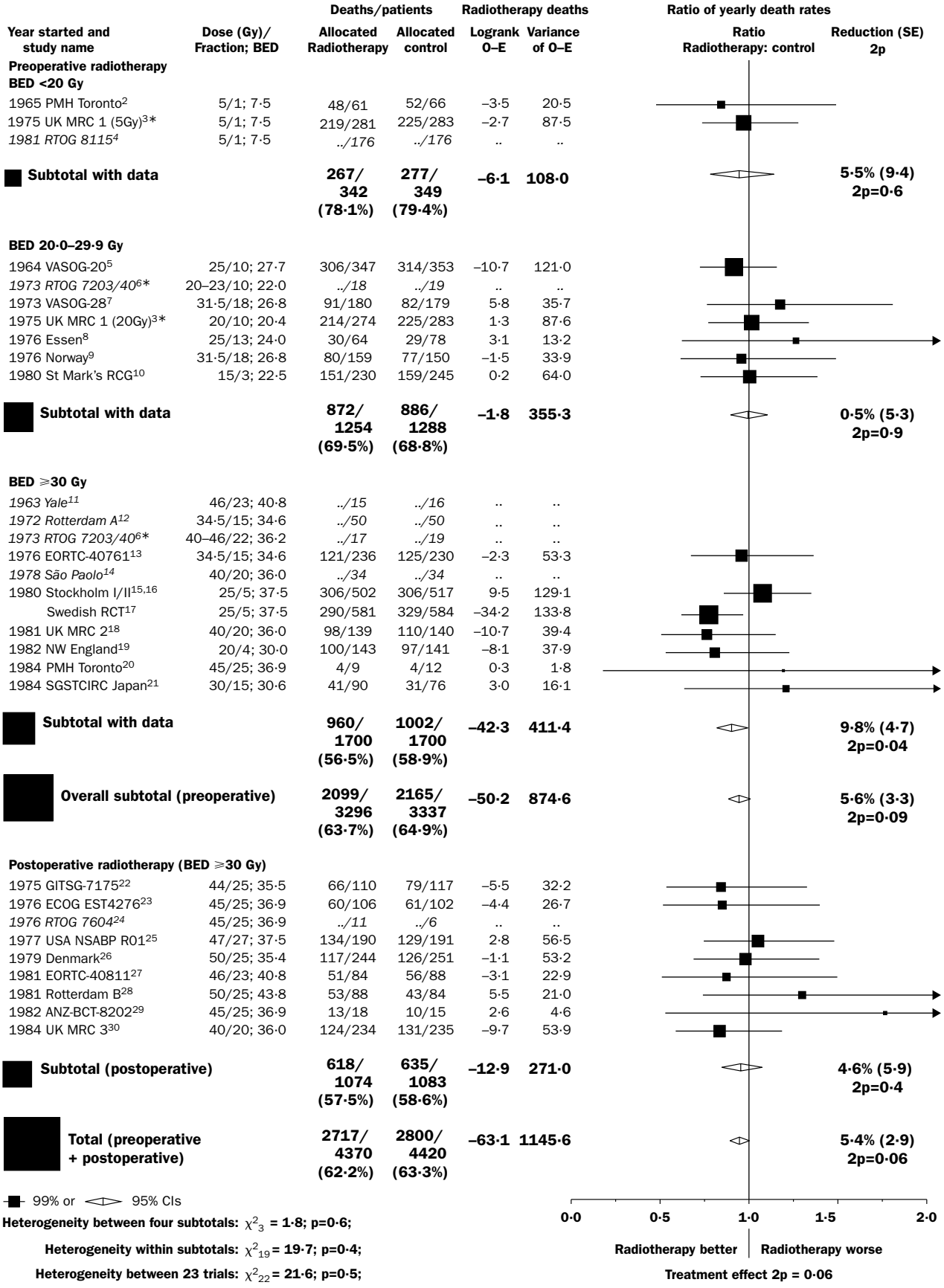


Figure 1: **Mortality rates for patients with rectal cancer treated with surgery and preoperative, postoperative, or no radiotherapy**
Seven trials with no data do not contribute to subtotals or to the overall total (allocated radiotherapy, 321; allocated control, 320). BED=biologically effective dose. O=observed. E=expected. *The UK MRC1 and RTOG 72–03/COG 72–40 studies are split into two parts by radiotherapy dose, and thus control patients in these studies are counted twice. MRC1 patients appear in two subtotals and count twice in the total.

were modified (eg, Stockholm II[16] excluded patients older than 80 years whereas Stockholm I[15] did not), the two trials were treated as one. Hence, the Swedish Rectal Cancer Trial,[17] which started in 1987, is included because it is essentially a continuation of the Stockholm II trial, which began before our cutoff of Jan 1, 1987 (and because outcome of patients in the Stockholm part of the Swedish Rectal Cancer Trial has been reported both in the Stockholm II study[16] report and in the Swedish Rectal Cancer Trial[17] report).

For each individual trial, the total radiotherapy dose, the number of fractions in which it was delivered, the biologically effective dose, the numbers of patients dying, and the numbers randomly allocated to each treatment group are reported. Data were available for 8507 individuals, 6350 patients from 13 preoperative radiotherapy studies, and 2157 from eight postoperative studies (figure 1). In this report, the total number of patients is 8790 since the 283 controls in the three-group MRC1[3] study are counted twice. Cause of death and site of recurrence (local/distant) were not available for the two VASOG trials[5,7] or the ECOG trial,[23] and site of recurrence was missing for the PMH Toronto[2] trial. No data were provided on 605 patients in five preoperative studies[4,6,11,12,14] or for 17 patients in one small postoperative study.[24] Crude mortality data could be extracted from publications for three of these studies, but are not used in the present overview because no quality assessment was possible. Because these studies were small, their inclusion or exclusion would not much affect our results. Thus, this overview includes almost complete data for 92% of patients from known studies of preoperative radiotherapy, and 99% of all data from known studies of postoperative treatment.

Statistical methods

The main statistical methods for combining information from different trials have been described elsewhere.[1] Analyses are by allocated treatment (ie, intention to treat). Crude unstratified totals are provided for descriptive purposes, but cause-specific mortality (total, rectal cancer, non-rectal cancer) and first recurrence site (any, isolated local) were analysed with log rank methods. Within each trial, the number of events observed in the group allocated one treatment was compared with the log rank expected number (on the basis of exposure to risk in each treatment group in that trial). The difference between these (observed–expected) and its variance provide the log rank test in that one trial. The values of observed minus expected from several trials are then added together to get an appropriately stratified overview of the results. The separate variances are likewise summed to give an overall variance. The odds ratio and its standard error are calculated from these two totals.[1]

Curative surgery is defined as resection of rectal cancer with no metastases detected, and no residual tumour (as judged by surgeon). Mortality was categorised as deaths from non-rectal cancer causes after curative surgery and before any recurrence was reported (non-rectal cancer), and other deaths (rectal cancer). To avoid bias, log rank subtraction was used in analysis of these data.[31] These methods assume that at any particular time after randomisation the all-cause mortality rate is equal to the rectal cancer mortality rate plus the non-rectal cancer mortality rate. The mortality rate for all causes is known, for non-rectal cancer, it is estimated from deaths before recurrence, and for rectal cancer it is obtained by subtraction. These methods assume that all deaths without recurrence are not due to rectal cancer, but do not assume that all deaths after recurrence are due to rectal cancer.

For log rank analysis of all-cause mortality, observed minus expected and its variance are calculated ignoring recurrences. To prevent delays in recurrence from biasing analyses of cause-specific mortality, the log rank analysis of non-rectal cancer mortality covers only the period before recurrence (ie, it is censored at first recurrence), and is therefore unbiased. Finally, unbiased log rank analysis of rectal cancer mortality is obtained indirectly by subtracting the log rank analysis for non-rectal cancer mortality from the log rank analysis for all-cause mortality (ie, the two observed values are subtracted from each other, the two expected values are subtracted from each other, and the two variances are subtracted from each other). Some comparisons are shown as survival curves, but others use odds ratios (or, equivalently, risk ratios—a risk ratio of 0·9 implies a risk reduction of 10%). A persistent 10% reduction in the annual risk of death would, when about half the patients have died, produce a survival difference of about 4% (eg, 46% rather than 50% dead).[1] Likewise, a persistent 5% risk reduction would eventually produce a difference in absolute risk of about 2%.[1]

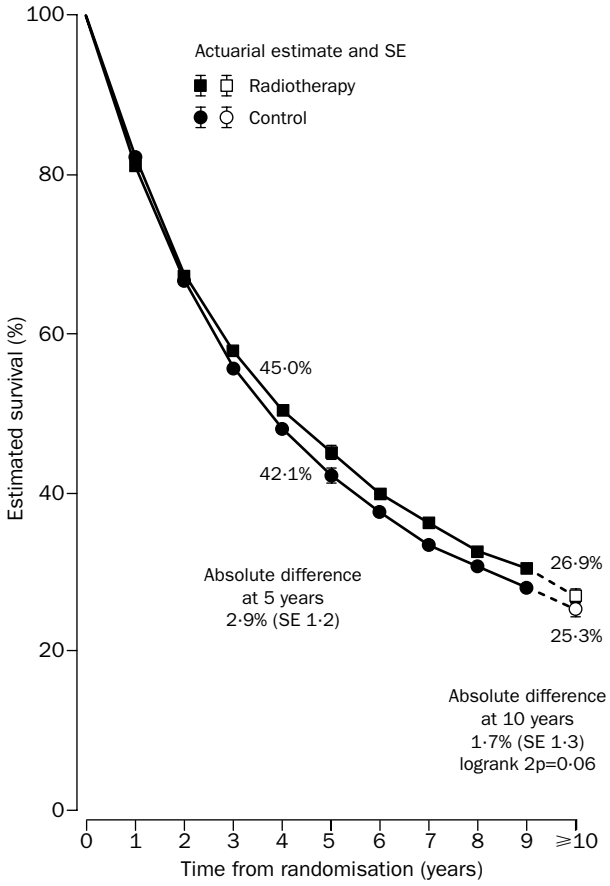
Radiotherapy: biologically effective dose

Effects of irradiation in terms of local tumour control, and acute and late damage of healthy tissues, are dependent not only on total dose, but also on the dose delivered in each fraction and the total treatment time. Since the total dose, the fraction dose, and thus the total treatment time varied greatly between the trials, we used biologically effective dose rather than total physical dose to compare different regimens. Biologically effective dose was calculated according to the time-corrected linear quadratic model of radiation effect,[32] which is probably the best available model.[33] In this model, biologically effective dose $=n\times d(1+[d\div\alpha/\beta])-\gamma/\alpha\times(T-T_k)$, in which n=number of fractions, d=dose (Gy) per fraction, α/β=common linear-quadratic quotient (10 Gy), γ/α=repair rate (0·6 Gy per day), T=total treatment time (days), and T_k=proliferation delay (7 days). The choice of coefficients reflects acute effects. For example, 45–50 Gy given in 2 Gy doses over 5 weeks would correspond to a biologically effective dose of 40–44 Gy, which might well be needed to eradicate microscopic disease.[34] However, in these trials, the biologically effective dose varied between 7·5 Gy and 37·5 Gy in the preoperative trials and between 35·4 Gy and 43·8 Gy in the postoperative trials. Arbitrarily, we decided to split the preoperative trials into three groups of dose: less than 20 Gy, from 20 Gy to 29·9 Gy, and 30 Gy or more; postoperative trials all used doses of greater than 30 Gy.

Results

Overall survival

Overall survival was only marginally better in patients allocated radiotherapy than those allocated none (figure 2), with 45·0 versus 42·1% alive at 5 years, and 26·9% *vs* 25·3% alive at 10 years. Overall, the yearly death rate was 5·4% (SE 2·9, 95% CI 0–11%) lower in patients who had radiotherapy than in those who had none (figure 1); the reductions did not differ significantly between patients who had preoperative radiotherapy and those who had postoperative radiotherapy (5·6%, SE 3·3; and 4·6%, 5·9, respectively; p=0·9). No significant heterogeneity was seen between



Deaths/1000 person-years and absolute difference in yearly mortality/1000

	Years 0–4	Years 5–9	Years ⩾10
Radiotherapy	2275/13·5	343/3·4	99/0·7
Control	2404/13·4	319/3·1	77/0·6
Difference	11·1 (SE 5·1)	2·2 (SE 8·0)	19·6 (SE 19·4)

Figure 2: **Probability of survival at 5 and 10 years for patients with rectal cancer treated with surgery and preoperative, postoperative, or no radiotherapy**

the four subtotals for the preoperative and postoperative trials (p=0·6) or between the 23 separate mortality results (p=0·5). Significantly fewer patients died in the group who had preoperative radiotherapy at higher doses than in controls (56·5% *vs* 58·9% died; p=0·04). However, a test for trend between biologically effective dose and treatment effect in preoperative radiotherapy studies was not significant. Results from only one individual study (the Swedish Rectal Cancer Trial[17]) showed a significant survival benefit from radiotherapy (the Stockholm data used in this meta-analysis show a less statistically extreme difference than the published data[16] since two-thirds of patients in the Stockholm II trial were also reported in the Swedish National Study but are only counted once, with the national study data, in these analyses).

Curative resection

In studies of preoperative radiotherapy, patients were randomly allocated to treatment or control before the outcome of surgery was known, and hence, some patients were subsequently shown to have unresectable or metastatic disease or did not receive any surgical intervention because of death before surgery, unfitness for surgery, or unrecorded reason. The high early mortality seen in figure 2 is in part explained by inclusion of non-curatively resected patients.

Figure 3 shows the disease status of patients who had preoperative radiotherapy or surgery alone. 483 of 3296 (15%) patients who had radiotherapy and 468 of 3337 (14%) controls did not have curative resection—most frequently because of metastatic disease (usually discovered at laparotomy) followed by locally unresectable tumours. The number of patients who had metastatic disease seemed unrelated to treatment allocation (figure 3), with 7·8% (257 of 3296) of preoperative radiotherapy patients and 7·5% (250 of 3337) of surgery only patients having metastases (p=0·6). Similarly, the proportion with locally unresectable disease was close in both treatment groups: 4·1% (134 of 3296) *vs* 4·8% (159 of 3337) (p=0·2). More patients allocated radiotherapy did not have curative resection for other reasons than those allocated no radiotherapy (2·8% *vs* 1·8%; p=0·005), mainly because there were more early deaths in the radiotherapy group than controls. However, inadequate detail was available for any meaningful subanalyses of these different outcomes by treatment allocation.

Mortality by stage

The mortality reductions for Dukes' stage A, B, and C disease, were not significant either individually or cumulatively (figure 3). However, these stage-specific analyses are potentially biased by stage migration in the radiotherapy group, since radiotherapy before surgery can conceal local spread. Thus, patients in the preoperative radiotherapy group were less likely to have positive nodes at pathological examination than were controls (32% [915 of 2813] *vs* 38% [1096 of 2869] node positive; p<0·0001). More patients who had had preoperative radiotherapy had Dukes' stage A or B disease (ie, node-negative), and uncertain nodal involvement, or apparently benign disease (figure 3). This downstaging by preoperative radiotherapy would be expected to introduce some bias against radiotherapy in stage-stratified analyses because patients with stage C disease and few positive nodes would be more likely to be downstaged to node-negative than patients with a larger number of affected nodes (and hence a greater risk of recurrence), leaving a remnant of especially high-risk node-positive patients in the radiotherapy group. Paradoxically, the apparently node-negative radiotherapy group would also be adversely affected because of inclusion of patients downstaged from node-positive to node-negative who tend to have worse outlook than genuinely node-negative patients. This bias is sometimes called the Will Rogers' phenomenom;[35] the magnitude of which can be assessed by noting that the stage-stratified total in figure 3 suggests a slightly smaller benefit than the unstratified, and hence unbiased, subtotal in figure 1 for the preoperative radiotherapy trials. But, because preoperative radiotherapy changes stage C into stage B rather than unresectable to resectable disease, analyses that are restricted just to operable patients are not appreciably biased and some such analyses are presented below.

Recurrence

The absolute risks of any recurrence and isolated local recurrence at 5 years were significantly lower in patients who had preoperative radiotherapy than those who did not (any recurrence, 45·9% *vs* 52·9%, p<0·00001;

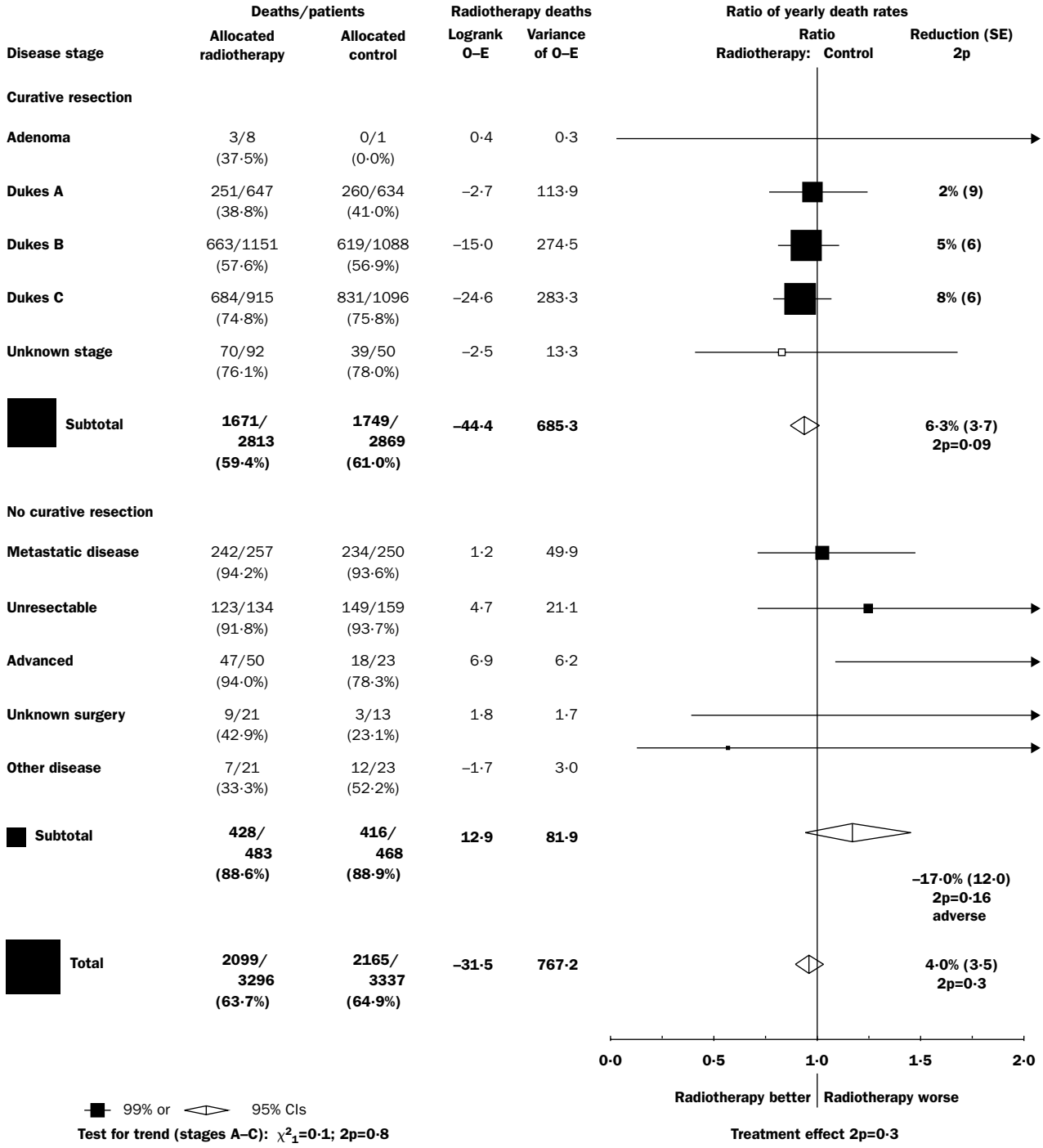
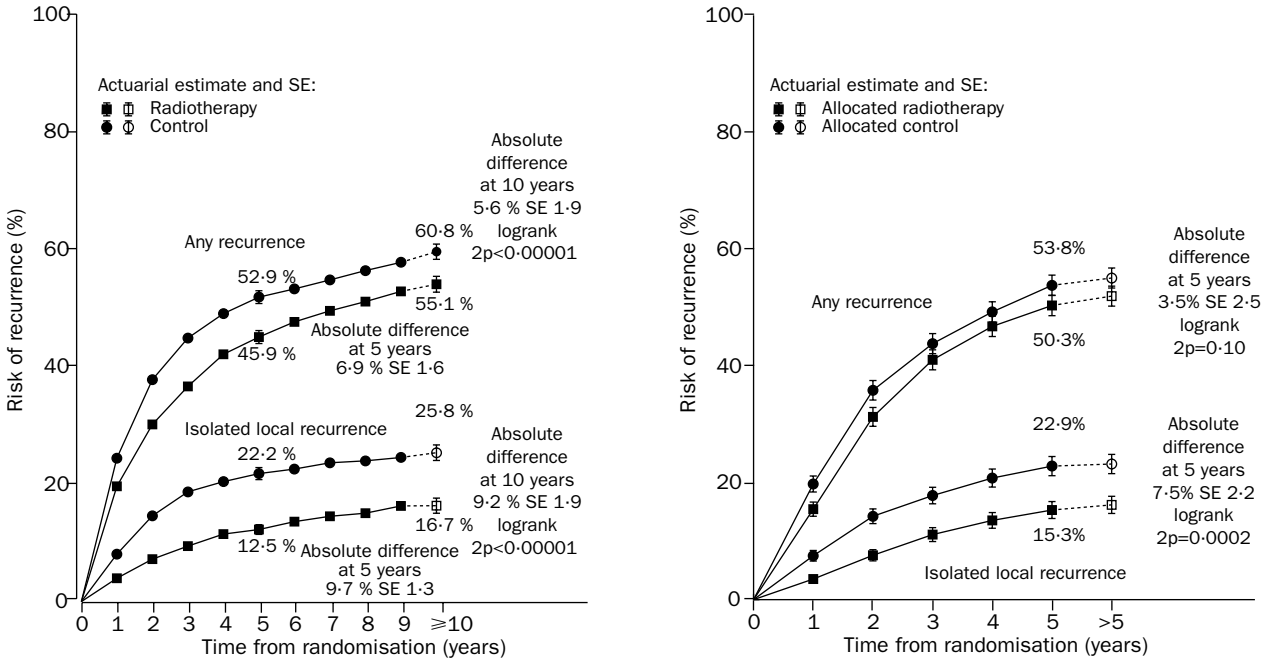


Figure 3: **Mortality by disease stage for patients in trials of preoperative radiotherapy versus no radiotherapy**
O=observed. E=expected.

isolated local recurrence, 12·5% *vs* 22·2%, p<0·00001) and at 10 years were 55·1% versus 60·8% (p<0·00001) for any recurrence, and 16·7% versus 25·8% (p<0·00001) for isolated local recurrence (figure 4). Although no reduction in risk of any recurrence was apparent in patients who had postoperative radiotherapy at 5 years (50·3% radiotherapy *vs* 53·8% control, p=0·10); the risk of isolated local recurrence at 5 years was significantly lower in this group than in controls (15·3% *vs* 22·9%, p=0·0002). Few recurrences were recorded after 5 years in the postoperative radiotherapy studies. The 37% (SE 10) proportional reduction in the yearly odds of local recurrence was not significantly less than the 46% (6) reduction in isolated local recurrence seen, overall, in studies of preoperative radiotherapy (figure 5).

There was, however, significant (p=0·002) heterogeneity between the results of the 12 trials of preoperative radiotherapy which was entirely explained by the highly significant trend (p<0·0001) towards greater efficacy of preoperative radiotherapy with higher biologically effective dose. Large, highly significant reductions were seen in four studies of preoperative radiotherapy (Stockholm I[15] & II,[16] Swedish rectal cancer



Recurrences/1000 person-years and absolute difference in annual recurrence/1000

	Years 0–4	Years 5–9	Years ⩾10		Years 0–4	Years 5+
Radiotherapy	1122/7·9	78/2·0	9/0·2	Radiotherapy	500/3·3	35/1·1
Control	1327/7·5	59/1·7	9/0·2	Control	545/3·2	25/0·9
Difference	34·1 (SE 6·4)	6·1 (SE 6·3)	7·5 (SE 19·5)	Difference	18·9 (SE 10·0)	5·1 (SE 7·8)

Isolated recurrences/1000 person-years and absolute difference in annual recurrence/1000

	Years 0–4	Years 5–9	Years ⩾10		Years 0–4	Years 5+
Radiotherapy	213/7·2	21/1·7	0/0·2	Radiotherapy	106/3·0	8/0·8
Control	399/6·8	17/1·6	0/0·1	Control	170/2·9	3/0·7
Difference	28·6 (SE 3·5)	1·2 (SE 3·7)		Difference	22·7 (SE 5·6)	6·1 (SE 4·5)

Figure 4: **Risk of any recurrence, and of isolated local recurrence of disease in patients who underwent apparently curative surgery**

Left: 13 studies of preoperative radiotherapy versus no radiotherapy. Right: Seven trials of postoperative radiotherapy versus no radiotherapy.

trial,[17] UK MRC2,[18] and Northwest England[19]), all of which used biologically effective doses of at least 30 Gy. No significant reductions were seen in the studies using intermediate biologically effective doses (20·0–29·9 Gy), although there were trends towards fewer recurrences in several of these studies. Studies of preoperative radiotherapy that used low (<20 Gy) biologically effective doses had no significant benefit, although data on local recurrence were not available from two of these studies and so the apparent absence of effectiveness at low biologically effective doses is attributable to just one study (UK MRC1[3]). Studies in which high (⩾30 Gy) biologically effective doses were used showed a halving of risk of local recurrence (57% [SE 7], p<0·0001; figure 5), which was significantly (p=0·01) larger than the 37% (SE 10) reduction in the postoperative studies. Although only two (UK MRC3[3] and NSABP R-01[25]) of the eight studies of postoperative therapy showed a significant reduction in local recurrences, there was no significant heterogeneity (p=0·3) between individual study results, as might be expected in view of the similar radiotherapy schedules used. Because of the apparent ineffectiveness of low biologically effective doses seen in trials of preoperative radiotherapy, investigation of any treatment differences within subgroups has been restricted to studies that used a dose of 30 Gy or more. To increase statistical sensitivity, we used isolated local recurrence as the primary endpoint for investigation of subgroup effects because of its large and significant treatment effect. Table 1 shows isolated local recurrences by treatment group according to Dukes' stage, age, sex, and treatment schedule for trials of preoperative radiotherapy at a biologically effective dose of 30 Gy or more, and for trials of postoperative radiotherapy.

The proportional reduction in risk of local recurrence did not differ in patients at various stages of disease in trials of preoperative radiotherapy. These stage-stratified analyses would be expected to reduce the apparent benefits from preoperative radiotherapy within each stage group.[35] However, this potential bias seems unimportant in these data since the overall stage-stratified analysis risk reduction of 56% is almost identical to the unstratified analysis risk reduction of 57% (figure 5). The reductions in local recurrences at different ages, and between men and women were almost identical. A lesser effect in patients aged 75 years or older than in younger patients was attributed to small numbers, as a test for trend provided no support for any diminishing effectiveness of radiotherapy with increasing age (p=0·8). In longer preoperative schedule trials, the treatment effect was smaller (not significantly) than in those with short schedules.

In postoperative radiotherapy trials, there were fewer local recurrences, and the overall effect was smaller and less significant than in trials of preoperative radiotherapy

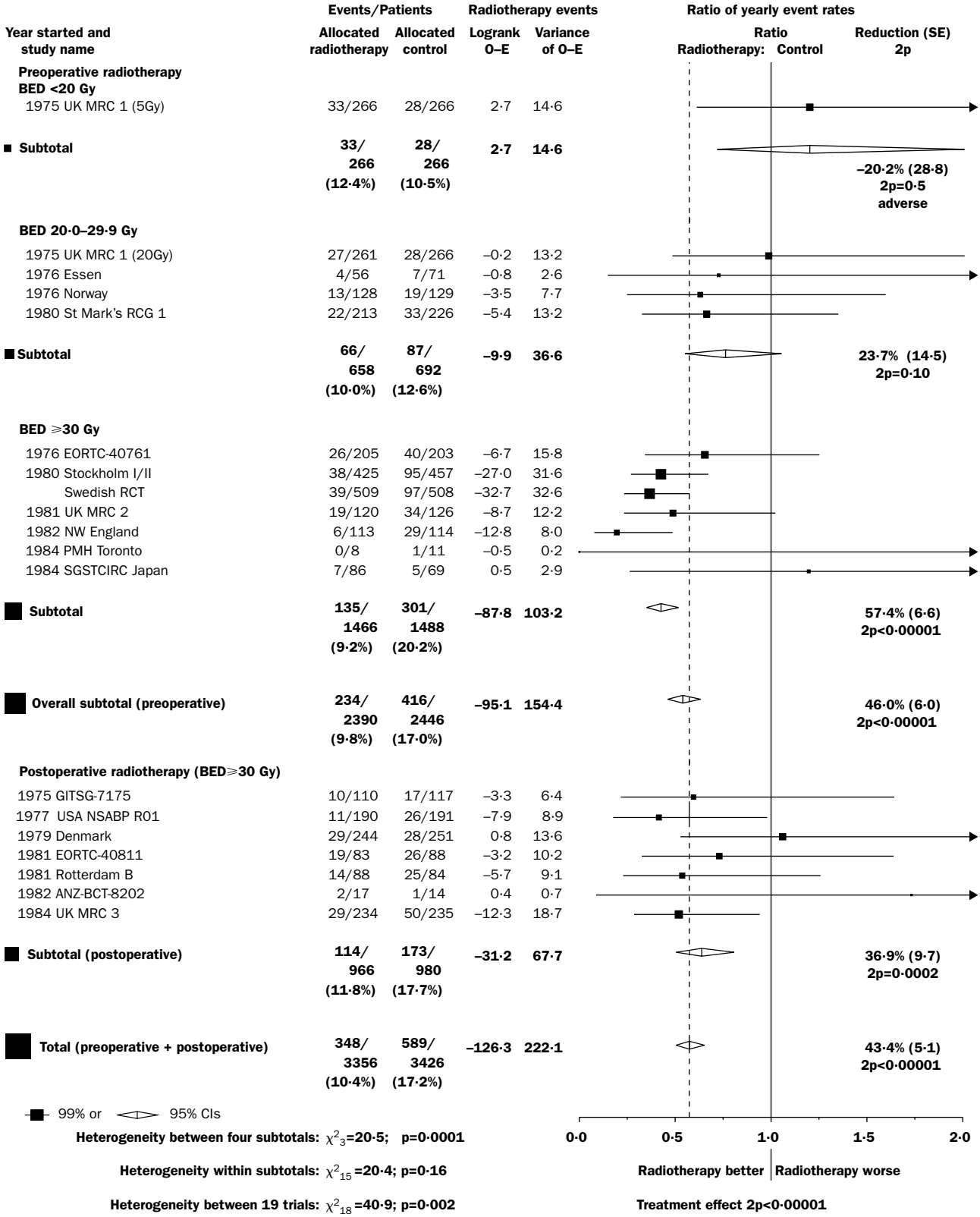


Figure 5: **Effect of radiotherapy on risk of isolated local recurrence for patients in 11 studies of preoperative radiotherapy and patients in seven studies of postoperative radiotherapy**
BED=biologically effective dose. O=observed. E=expected. *Study is split into two parts by radiotherapy dose, and thus control patients appear twice.

that used high biologically effective doses. Consequently, the subgroup analyses of local recurrence are statistically less reliable. Nevertheless, no evidence for any selective benefit of postoperative radiotherapy was seen in the subgroups. The risk reduction seemed larger for women than men (47%, SE 14; and 29%, 13,

	Preoperative radiotherapy			Postoperative radiotherapy		
	Recurrence*			Recurrence*		
	Radiotherapy	Control	Odds reduction (SE)	Radiotherapy	Control	Odds reduction (SE)
Dukes' stage						
Stage A	14/400	38/367	64% (18)	0/4	0/1	
Stage B	55/564	108/544	53% (11)	44/424	59/427	31% (17)
Stage C	60/464	152/556	58% (10)	70/532	114/542	41% (12)
Age group (years)						
<55	32/226	56/240	50% (16)	31/195	41/227	22% (22)
55–64	26/372	63/394	60% (14)	27/350	54/317	60% (15)
65–74	54/616	137/612	63% (9)	46/341	56/340	18% (19)
75+	23/250	45/242	49% (18)	10/74	22/95	49% (28)
Sex						
Men	77/914	170/892	58% (9)	71/568	97/572	29% (13)
Women	58/552	131/596	55% (10)	43/392	76/407	47% (14)
Radiotherapy schedule						
Short (≤5 days)	83/1047	221/1079	64% (7)	..	..	..
Long (>5 days)	52/419	80/409	39% (14)	114/966	173/980	37% (10)

*Number of patients with recurrence/total number of patients in group.

Table 1: **Effect of preoperative radiotherapy, at biologically effective dose ⩾30 Gy, and of postoperative radiotherapy, on risk of isolated local recurrence by Dukes' stage, age, sex and radiotherapy schedule for curatively resected patients**

respectively) but the CIs for each estimate were wide, and the difference in treatment effect between sexes was not significant (p=0·2). This trend was not apparent in preoperative radiotherapy trials, suggesting that it is probably due to chance.

Cause-specific mortality

Of 1085 patients who died without recorded recurrence, 900 (83%) died from causes other than rectal cancer; the remaining 185 deaths (17%) were from unknown causes. These were generally later deaths and, in these analyses, are included with deaths from non-rectal cancer causes (as are the 245 deaths without recorded recurrence in the three studies without any cause of death information). 1990 of 4370 (46%) patients who had radiotherapy died from rectal cancer compared with 2197 of 4420 (50%) controls, which is an 11·8% (SE 3·2) proportional reduction in the risk of rectal cancer death (p = 0·0003) (figure 6). The largest effect was seen in studies of preoperative radiotherapy that used biologically effective doses of 30 Gy or more (overall reduction in deaths was 22% [SE 5]; p=0·00002). Few, if any, benefits were seen in studies of preoperative radiotherapy that used lower biologically effective doses.

Patients who had postoperative radiotherapy had a 9% (7) lower risk of death from rectal cancer than controls (p=0·2). This reduction was not significantly less than the 22% (5) reduction seen in studies of preoperative radiotherapy at higher biologically effective doses. The reduction in deaths from rectal cancer in patients who had radiotherapy was partly counterbalanced by an increase in deaths from other causes. Overall, the risk of death from non-rectal cancer was 15% (6) higher in patients who had radiotherapy (figure 7) than those who did not: 19% [727 of 3873] versus 15% [603 of 3945] died; p=0·02. Most patients who died from non-rectal cancer were in preoperative radiotherapy trials—602 (21%) of the 2813 patients from the preoperative radiotherapy group who had been curatively resected died from non-rectal cancer causes compared with 500 (17%) of 2868 controls. The 15% (7) increase in risk in the preoperative radiotherapy studies combined was significant (p = 0·02).

The Stockholm[15,16] study had the largest number of deaths from non-rectal causes and the largest apparent excess risk, but there was no significant evidence of heterogeneity between the 23 individual trial results (p=0·8). However, in six of the seven studies that used preoperative radiotherapy at biologically effective doses of 30 Gy or more, there were more non-rectal cancer deaths in the radiotherapy group than in controls. When the results were combined, the number of deaths from non-rectal causes was significantly greater with radiotherapy than control (37% [12]; p=0·001). There was also a non-significant 12% (SE 14) trend towards more non-rectal cancer deaths in postoperative radiotherapy studies, which all used biologically effective doses of 30 Gy or more (125 radiotherapy [12%] *vs* 103 controls [10%]). A test for interaction (ie, greater treatment hazard in the trials of preoperative radiotherapy ⩾30 Gy than in postoperative trials) showed no significant difference in risk in the preoperative studies (p=0·2).

Figure 8 shows life-table estimates of the risk of death from non-rectal cancer causes and from rectal cancer in the six studies of preoperative radiotherapy at biologically effective doses of 30 Gy or more. Almost all excess mortality occurred in the first year after randomisation (123 [8%] radiotherapy *vs* 54 [4%] control deaths; p<0·0001). The excess of non-rectal cancer deaths was seen not only in the immediate postoperative period with 52 (4%) radiotherapy deaths versus 28 (2%) control deaths occurring within 30 days after surgery (p = 0·008), but also in months 2–3 (27 *vs* 7; p=0·0005), 4–6 (21 *vs* 7; p=0·007), and 6–12 (23 *vs* 12; p=0·006) after surgery. After the first year, there was no excess, with 137 (9%) versus 124 (8%) non-rectal cancer deaths (p=0·4). The excess of non-cancer deaths in the first year was mainly due to an increase in deaths attributed to vascular (52 *vs* 19; p = 0·0001), and infective causes (29 *vs* 9; p = 0·001). Of the other deaths, ten versus three (p=0·05) were from surgical complications, 12 versus 11 (p=0·8) from other specified causes, and 20 versus 12 (p=0·14) from unknown causes.

Survival by subgroups

Table 2 shows mortality in patients of different ages and stages who had curative resection in trials of high dose preoperative radiotherapy. The proportional reductions in deaths from rectal cancer did not differ significantly with age (p=0·4) or stage (p=0·7). The proportional increases in non-rectal cancer mortality also did not differ with age (p=0·7) or stage (p=0·4). The p values for effect of treatment on these other endpoints are less extreme than those for local recurrence, and so investigation of any difference in treatment effect within

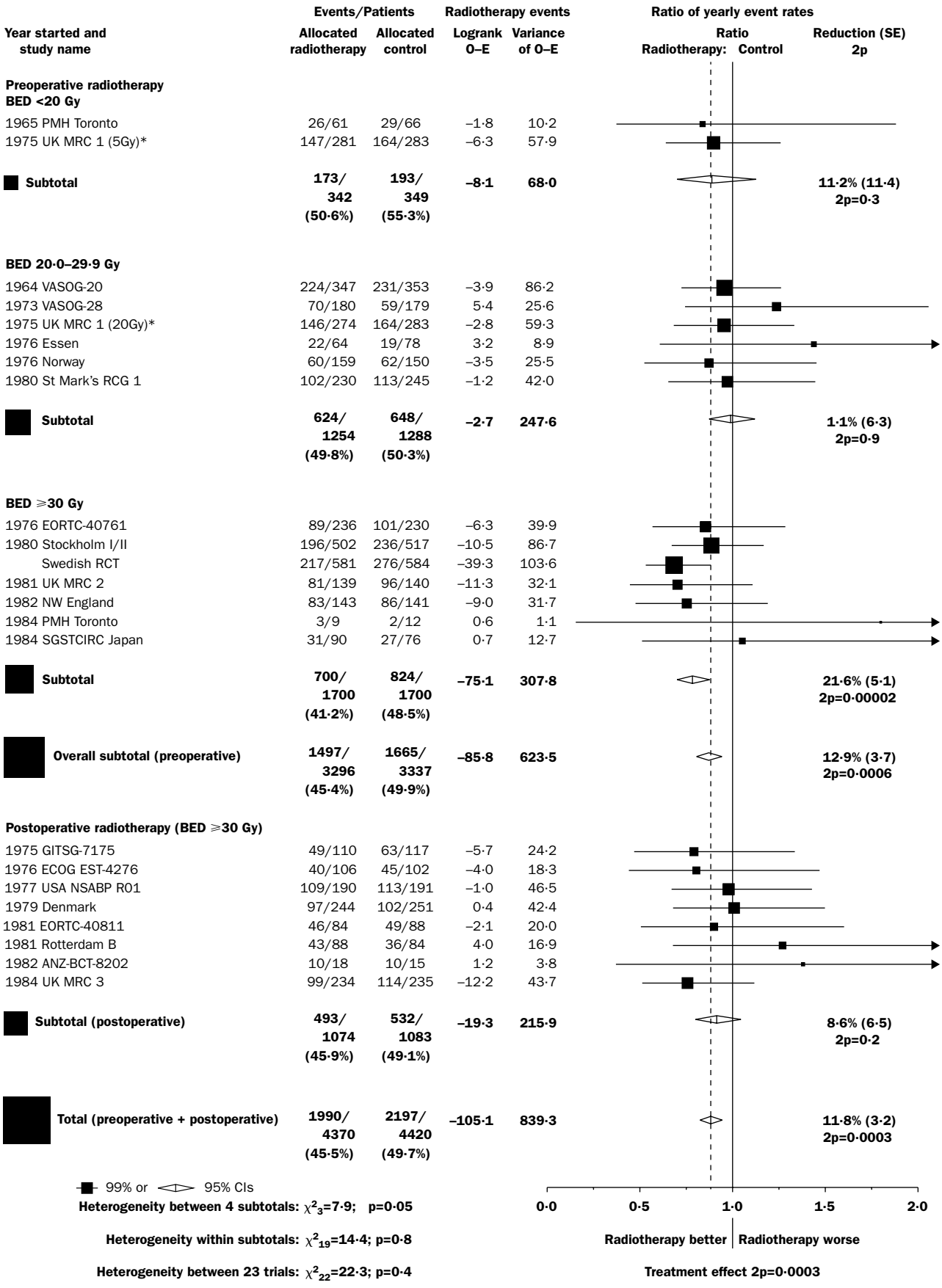


Figure 6: **Mortality rates for patients who died from rectal cancer by biologically effective dose**
BED=biologically effective dose. O=observed. E=expected. *Study is split into two parts by radiotherapy dose, and thus, control patients appear twice.

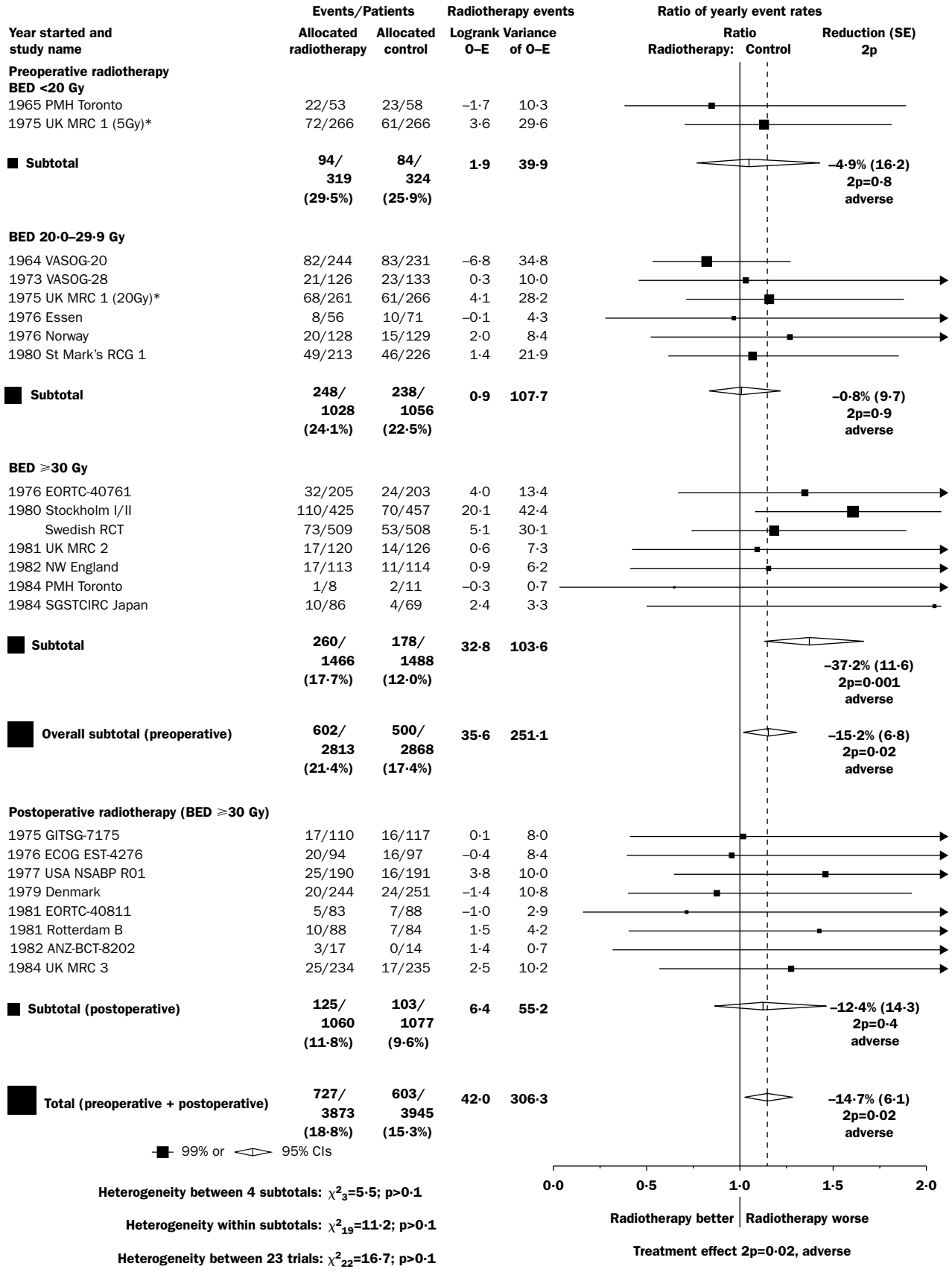
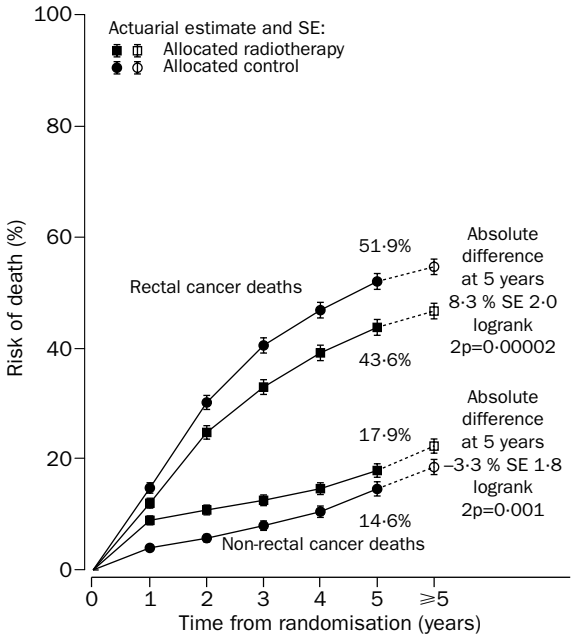


Figure 7: **Mortality rates for curatively resected patients who died from non-rectal cancer causes without recurrence**
BED=biologically effective dose. O=observed. E=expected. *Study is split into two parts by radiotherapy dose, and thus, control patients appear twice.



Rectal cancer deaths/1000 person-years and absolute difference in annual mortality/1000

	Years 0–4	Years ⩾5
Radiotherapy	635/5·2	65/1·2
Control	768/5·0	56/1·0
Difference	30·9 (SE 7·3)	0·2 (SE 10·0)

Non-rectal deaths/1000 person-years and absolute difference in annual mortality/1000

	Years 0–4	Years ⩾5
Radiotherapy	200/4·6	60/1·1
Control	134/4·2	45/0·9
Difference	11·8 (SE 4·1)	4·7 (SE 10·0)

Figure 8: **Life-table estimates of risk of death from non-rectal cancer causes and from rectal cancer from six trials of preoperative radiotherapy (biologically effective dose ⩾30 Gy)**

subgroups is less reliable. However, in view of the absence of any apparent subgroup effects in the more sensitive analyses of local recurrence, any differences in the proportional reductions in rectal cancer deaths or increases in non-rectal cancer deaths between groups are probably also minor. However, because the absolute risk of death from non-rectal cancer causes rises rapidly with age, a similar proportional increase in each age group will result in an absolute excess risk that also rises rapidly with age. This trend can be seen in these data in which the absolute excess of non-rectal cancer deaths increases from 1% (6% *vs* 5% dead) at ages younger than 55 years to 8% (34% *vs* 26% dead) at ages 75 or older. By contrast, the risk of death from rectal cancer was not much affected by age and so absolute reductions in risk of rectal cancer death are similar at different ages. The net effect of similar absolute treatment benefit at different ages but a rapidly increasing excess risk of death from other causes is that for younger patients the improvement in survival from rectal cancer with preoperative radiotherapy outweighs the small excess risk of death from other causes, and hence all-cause mortality is significantly better with preoperative radiotherapy for patients aged younger than 55 years. However, for patients older than 75 years, the larger excess risks of non-rectal cancer death, with the radiotherapy regimens tested, outweigh the improvement in cancer survival and hence all-cause mortality is worse with preoperative radiotherapy—albeit not significantly so. This trend of decreasing treatment benefit of preoperative radiotherapy on overall mortality with increasing age is significant ($p = 0·02$) and does seem plausible, even in view of the number of subgroup investigations that have been undertaken.

For Dukes' stage, the opposite pattern is seen. The proportional increases in non-rectal cancer deaths and the proportional reductions in rectal cancer deaths with preoperative radiotherapy again did not differ across subgroups. But, the risk of rectal cancer death was much higher for patients with stage C disease than for those with stage A. So, absolute improvements in rectal cancer survival are larger for patients with stage C (12%, 54% *vs* 66% dead) than for those with stage A (5%, 12% *vs* 17% dead). As the net increase in risk of death from other causes averages 6%, independent of stage, net improvements in all-cause survival are substantial for patients with stage C with no apparent benefit, and possibly harm, for those with stage A. This trend of greater overall survival benefit with higher-risk stage is again significant (p=0·02).

Discussion

In this systematic review of data from 8507 patients in 22 trials of adjuvant radiotherapy for rectal cancer, radiotherapy both before and after surgery substantially reduced the risk of local recurrence in apparently curatively resected patients and moderately reduced deaths from rectal cancer. The largest reductions were in studies of preoperative radiotherapy with biologically effective doses of 30 Gy or more; no significant reductions were recorded in studies of radiotherapy schedules with low biologically effective doses. Data were not sufficiently detailed to ascertain whether the reduced death rate from rectal cancer was achieved through better local control, or by reducing the risk of metastasis from incompletely excised tumour. However, because there were fewer distant recurrences as first

Age group (years)	Numbers randomised		Deaths from:					
			Rectal cancer		Other cause		Any cause	
	Radiotherapy	Control	Radiotherapy	Control	Radiotherapy	Control	Radiotherapy	Control
<55	226	240	71 (31%)	115 (48%)	14 (6%)	11 (5%)	85 (38%)	126 (53%)
55–64	372	394	143 (38%)	156 (40%)	33 (9%)	24 (6%)	176 (47%)	180 (46%)
65–74	616	612	199 (32%)	265 (43%)	127 (21%)	79 (13%)	326 (53%)	344 (56%)
75+	250	242	80 (32%)	96 (40%)	86 (34%)	64 (26%)	166 (66%)	160 (66%)
Dukes' stage								
Stage A	400	367	48 (12%)	62 (17%)	90 (22%)	52 (14%)	138 (34%)	114 (31%)
Stage B	564	544	175 (31%)	196 (36%)	98 (17%)	73 (13%)	273 (48%)	269 (49%)
Stage C	464	555	251 (54%)	364 (66%)	66 (14%)	49 (9%)	317 (68%)	413 (74%)

Values are number (%).

Table 2: **Effect of preoperative radiotherapy, at biologically effective dose ⩾30 Gy, on death from rectal cancer, on death from other cause, and overall mortality by age and stage in patients who have been curatively resected**

event with radiotherapy, when more would be expected artefactually,[36] the reduced death rate could partly be accounted for by a reduction in metastatic spread from residual tumour cells. However, since data on second recurrences were not sought, or generally recorded, the effect of local radiotherapy on distant recurrence could not be investigated thoroughly.

The radiotherapy regimens used substantially increased risk of death from causes unrelated to rectal cancer (one death per 21 patients treated [95%CI 15–32]). The risk was greatest in trials of preoperative radiotherapy that used high biologically effective doses. However, there were also more deaths from causes unrelated to rectal cancer with postoperative radiotherapy than with control (non-significant). The greater number of deaths due to non-cancer causes seen in studies of preoperative radiotherapy was not explained solely by a higher perioperative (<30 days after surgery) mortality, since deaths from non-cancer causes were higher throughout the first year after surgery. Most of the increase was in deaths from vascular or infective causes.

The proportional increase in the risk of non-cancer death did not differ between subgroups of patients, or between studies, but the absolute increase was notably greater for older patients who had a higher background risk. Similarly, reductions in recurrence and death from rectal cancer with radiotherapy were similar in different subgroups of patients, but the absolute benefits were larger for patients with Dukes' stage C disease because of their higher risk of death from rectal cancer. Consequently, the benefits clearly outweighed the risks for younger patients who had positive nodes whereas the risks outweighed the benefits for older patients with negative nodes.

Because the increased risk of death from other causes largely counterbalanced the reduction in mortality from rectal cancer, there was no clear benefit of radiotherapy in respect of overall survival. Although this review is the most reliable available assessment of the net effects of preoperative and postoperative radiotherapy on recurrence and cause-specific mortality, it would be unsafe to conclude that radiotherapy does not improve overall survival—the number of patients was not large enough to detect reliably differences in long-term survival of just a few percent. Further, the radiotherapy regimens used in these old studies were not optimum. The biologically effective dose used in many preoperative studies was inadequate, and those with adequate biologically effective doses generally used parallel-field techniques, which irradiate larger volumes of healthy tissue, and hence are more toxic than three-field or four-field methods. In the Swedish national study,[17] radiotherapy was delivered more safely without compromising efficacy and hence the benefits outweighed the risks and a significant overall survival benefit was recorded. This finding suggests that preoperative radiotherapy at an appropriately high biologically effective dose can be delivered safely enough to achieve overall survival benefit especially for patients at high risk of recurrence.

Finally, what are the implications of these results for current practice? Although the overall reductions with preoperative and postoperative radiotherapy did not differ significantly, the benefits seen with preoperative treatment at high biologically effective doses were significantly greater than those with postoperative radiotherapy—even though lower biologically effective doses were used than those in postoperative studies (range 30·0–37·5 Gy *vs* 35·4–43·8 Gy). The greater efficacy of preoperative compared with postoperative radiotherapy is lent support by a direct randomised comparison.[38] Moreover, a 1–week preoperative radiotherapy schedule is more convenient than the 5–week or 6–week schedules usually used for postoperative radiotherapy—although the convenience needs to be balanced against the potential for greater toxic effects[39] (late morbidity could be assessed by longer follow-up of patients in these trials). A disadvantage of preoperative radiotherapy is that no pathological data are available to help guide its use. However, preoperative ultrasound can usually differentiate between stage A and B tumours.[40] Other prognostic variables, such as involvement of the lateral resection margins, seem to be better predictors of local recurrence than Dukes' stage[41] and so selective use of postoperative radiotherapy based on more efficient predictors of local recurrence could be a more cost-effective strategy than indiscriminate use of preoperative radiotherapy. The present UK MRC CR-07 trial compares these two policies.

Large reductions in local and distant recurrence are reported with total mesorectal excision.[42] Total mesorectal excision was rarely used at the time these studies were undertaken, but results of a European study[43] have shown that similar proportional reductions in local recurrence can be achieved with radiotherapy before total mesorectal excision as before traditional surgery, although the absolute reductions in local recurrence with radiotherapy are reduced. Although no survival benefit was seen with radiotherapy before total mesorectal excision, this meta-analysis suggests that any reduction in local recurrence with radiotherapy should result in some survival benefit. Even if no survival benefit was achievable with radiotherapy before total mesorectal excision, uncontrolled local recurrence can have a devastating effect on a patient's quality of life and so improved local control with radiotherapy might be a sufficient benefit to justify its use.

Another change in practice since most of these studies were undertaken is adoption of systemic chemotherapy, especially for patients with node-positive disease, and combined chemoradiotherapy has been recommended as the treatment of choice for those with Dukes' stage B and C rectal cancer.[44] Few studies in this systematic review used chemotherapy, however, and so no comparisons of the effectiveness of radiotherapy in the presence and absence of chemotherapy were possible. A series of striking and consistent findings have been reported with the use of continuous infusional fluorouracil in conjunction with radiotherapy in rectal and other cancers.[45] However, the NSABP R-02 study[46] has reported similar results with radiotherapy added to bolus fluorouracil to those seen in this review. If fluorouracil and radiotherapy do act synergistically, then even greater benefits from radiotherapy could be achieved. This possibility is being investigated by researchers in the EORTC 22921 study. Results from this systematic review suggest that further improvements in survival are achievable, but that they will be of only moderate size and thus large-scale participation in well designed, randomised trials is needed to reliably detect, or refute, any further benefits.

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References

1 Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy: 133 randomised trials involving 31 000 recurrences and 24 000 deaths among 75 000 women. *Lancet* 1992; **339:** 1–15, 71–85.

2 Rider WD, Palmer JA, Mahoney LJ, et al. Preoperative irradiation in operable cancer of the rectum: report of the Toronto trial. *Can J Surg* 1977; **20:** 335–38.

3 MRC Working Party—second report. The evaluation of low dose preoperative X-ray therapy in the management of operable rectal cancer. *Br J Surg* 1984; **71:** 21–25.

4 Sause WT, Martz KL, Noyes D, et al. RTOG 81–15 ECOG 83–23 evaluation of preoperative radiation therapy in operable rectal carcinoma. *Int J Rad Oncol Biol Phys* 1990; **19:** 179.

5 Higgins GA, Conn JH, Jordan PH, et al. Preoperative radiotherapy for colorectal cancer. *Ann Surg* 1975; **181:** 624–31.

6 Radiation Therapy Oncology Group. Pre-operative irradiation in potentially curable adenocarcinoma of the rectum, report by T J Thompson, RTOG Statistical Centre, June, 1997.

7 Higgins GA, Humphrey EW, Dwight RW. Preoperative radiation and surgery for cancer of the rectum: Veterans' Administration Surgical Oncology Group Trial II. *Cancer* 1986; **58:** 352–59.

8 Niebel W, Schulz U, Ried M, et al. Five-year results of a prospective randomised study: experience with combined radiotherapy and surgery for primary rectal carcinoma. *Recent Results Cancer Res* 1988; **110:** 111–13.

9 Dahl O, Horn A, Morild I, et al. Low dose preoperative radiation postpones recurrences in operable rectal cancer: results of a randomised multicenter trial in Western Norway. *Cancer* 1990; **66:** 2286–94.

10 Goldberg PA, Nicholls RJ, Porter NH, et al. Long-term results of a randomised trial of short-course low-dose adjuvant preoperative radiotherapy for rectal cancer: reduction in local treatment failure. *Eur J Cancer* 1994; **30:** 1602–06.

11 Kligerman MM. Preoperative radiation therapy in rectal cancer. *Cancer* 1975; **36:** 691–95.

12 Boulis-Wassif S, Langenhorst BL, Hop WCJ. The contribution of pre-operative radiotherapy in the management of borderline rectal cancer. In: Jones, Salmon (eds), *Adjuvant Therapy of Cancer* 1979, II: 613–20.

13 Gerard A, Buyse M, Nordlinger B, et al. Preoperative radiotherapy as adjuvant treatment in rectal cancer: final results of a randomised study of the European Organisation for Research and Treatment of Cancer (EORTC). *Ann Surg* 1988; **208:** 606–14.

14 Reis Neto JA, Quichi FA, Reis JA. A comparison of non-operative versus preoperative radiotherapy in rectal carcinoma: a 10–year randomised trial. *Dis Colon Rectum* 1989; **32:** 702–10.

15 Cedermark B, Johansson H, Rutqvist LE, Wilking N. The Stockholm I trial of pre-operative short-term radiotherapy in operable rectal cancer: a prospective randomised controlled trial. *Cancer* 1995; **75:** 2269–75.

16 Stockholm Colorectal Cancer Study Group. A randomised study on pre-operative radiotherapy in rectal carcinoma. *Ann Surg Oncol* 1996; **3:** 423–30.

17 Swedish Rectal Cancer Trial. Improved survival with pre-operative radiotherapy in resectable rectal cancer. *N Engl J Med* 1997; **336:** 980–87.

18 Medical Research Council Rectal Cancer Working Party. Randomised trial of surgery alone versus radiotherapy followed by surgery for potentially operable locally advanced rectal cancer. *Lancet* 1996; **348:** 1605–10.

19 Marsh P, James R, Schofield LPF. Adjuvant pre-operative radiotherapy for locally advanced rectal carcinoma: results of a prospective randomised trial. *Dis Colon Rectum* 1994; **37:** 1205–14.

20 Cummings BJ. Radiation therapy and rectal carcinoma: the Princess Margaret Hospital experience. *Br J Surg* 1985; **72** (suppl)**:** S64–66.

21 Kimura K, Tuchiya S, Masayuki Y, et al. Comparisons of surgical therapy and combined irradiation in rectal cancer: first report, effect of irradiation on the tumour. *Jpn J Cancer Chemotherapy* 1989; **16:** 3161–72.

22 Thomas PRM, Lindblad AS. Adjuvant postoperative radiotherapy and chemotherapy in rectal carcinoma: a review of the Gastrointestinal Tumour Study Group experience. *Radiother Oncol* 1988; **13:** 245–52.

23 Mansour E, Lefkopoulou M, Johnson R, et al. A comparison of post-operative chemotherapy, radiotherapy or combination therapy in potentially curable rectal carcinoma: an ECOG study EST 4276. *Proc ASCO* 1991; **10:** 154 (A484).

24 Radiation Therapy Oncology Group. The value of postoperative radiation and chemotherapy alone and together as combination therapy with surgery in the treatment of rectal and rectosigmoid carcinoma without known gross or microscopic residual disease. December 1977. RTOG Statistical Office.

25 Fisher N, Wolmark N, Richette H, et al. Postoperative adjuvant chemotherapy or radiation therapy for rectal cancer: results from the NSABP Protocol R-01. *J Natl Cancer Inst* 1988; **80:** 21–29.

26 Balslev I, Pedersen M, Teglbjaerg PS, et al. Postoperative radiotherapy in Dukes' B and C carcinoma of the rectum and rectosigmoid: a randomised multicentre study. *Cancer* 1986; **58:** 22–28.

27 Buyse M. EORTC studies of rectal cancer in NIH Consensus Development Conference, adjuvant therapy for patients with colon and rectum cancer. NIH 1996; 53–55.

28 Treurniet-Donker AD, Van Putten WLJ, Wereldsma JCJ, et al. Postoperative radiation therapy for rectal cancer: an interim analysis of a prospective randomised multicentre trial in the Netherlands. *Cancer* 1991; **67:** 2042–48.

29 Marneghan H, Gray BN, de Zwart J, et al. Adjuvant post-operative radiotherapy in rectal cancer: results from the ANZ bowel cancer trial (Protocol 8202). *Australas Radiol* 1991; **35:** 61–65.

30 Medical Research Council Rectal Cancer Working Party. Randomised trial of surgery alone versus surgery followed by radiotherapy for mobile cancer of the rectum. *Lancet* 1996; **348:** 1610–14.

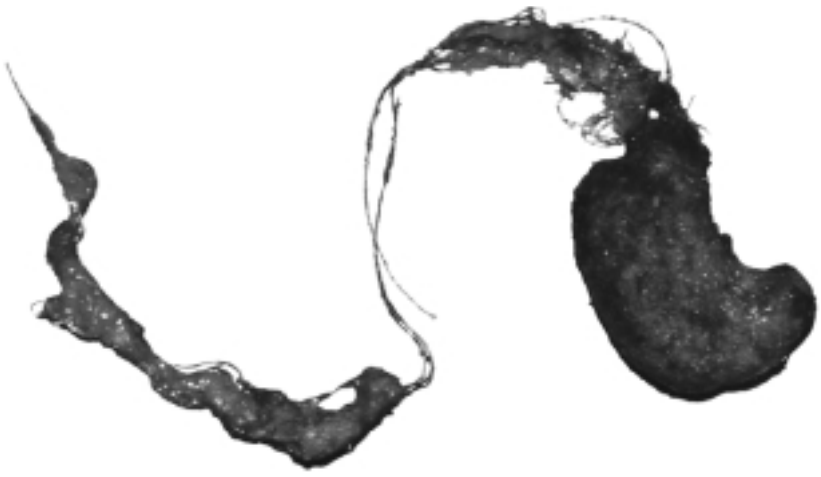
31 Early Breast Cancer Trialists' Collaborative Group. Effects of radiotherapy and surgery in early breast cancer: an overview of the randomised trials. *N Engl J Med* 1995; **333:** 1444–55.

32 Fowler JF. The Linear-quadratic formula and progress in fractionated radiotherapy. *Br J Radiol* 1989; **62:** 679–94.

33 Jones B, Dale RG. Mathematical models of tumour and normal tissue response. *Acta Oncol* 1999; **38:** 883–93.
34 Withers HR, Peters LJ, Taylor JMG. Dose-response relationship for radiation therapy of subclinical disease. *Int J Radiat Oncol Biol Phys* 1995; **31:** 353–59.
35 Feinstein AR, Sosin DM, Wells CK. The Will Rogers' phenomenon: stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *N Engl J Med* 1985; **312:** 1604–08.
36 Gelman R, Gelber R, Henderson IC, et al. Improved methodology for analyzing local and distant recurrence. *J Clin Oncol* 1990; **8:** 548–55.
37 Swedish Rectal Cancer Trial. Initial report from a Swedish multicentre study examining the role of preoperative irradiation in the treatment of patients with resectable rectal carcinoma. *Br J Surg* 1993; **80:** 1333–36
38 Frykholm GJ, Glimelius B, Påhlman L. Pre-operative or post-operative irradiation in adenocarcinoma of the rectum: final treatment results of a randomized trial and an evaluation of late secondary effects. *Dis Colon Rectum* 1993; **36:** 564–72.
39 Holm T, Singnomklao T, Rutqvist LE, Cedermark B. Adjuvant pre-operative radiotherapy in patients with rectal carcinoma. Adverse effects during long-term follow-up of two randomised trials. *Cancer* 1996; **78:** 968–76.
40 Lindmark G, Elvin A, Påhlman L, et al. The value of endosonography in preoperative staging of rectal cancer. *Int J Colorectal Dis* 1992; **7:** 162–66.
41 Quirke P, Durdey P, Dixon MF, Williams NS. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. *Lancet* 1986; **2:** 996–99.
42 Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet* 1986; **1:** 1479–82.
43 Kapiteijn E, Marijnen CAM, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001; **345:** 638–46.
44 NIH Consensus Conference: adjuvant cancer therapy. *JAMA* 1990; **264:** 1444–50.
45 Cancer Guidance Subgroup of the Clinical Outcomes Group. Improving outcomes in colon cancer: The Research Evidence. London: NHS Executive, Department of Health 1997.
46 Wolmark N, Wieand HS, Hyamns DM, et al. Randomized trial of postoperative adjuvant chemotherapy with or without radiotherapy for carcinoma of the rectum. National Surgical Adjuvant Breast and Bowel Project Protocol R-02. *J Natl Cancer Inst* 2000; **92:** 388–96.

Clinical picture: Rapunzel syndrome

Richard T L Couper



A 4-year-old girl of normal intelligence presented with an 18-month history of worsening epigastric pain, partly alleviated by antacids. This pain awakened her at night. Gastric endoscopy showed a large trichobezoar. The bezoar was removed surgically and was cast in the shape of the stomach, extending via strands to further bezoars in the third part of the duodenum and proximal jejunum. She acknowledged hair twisting, pulling, and chewing and was persuaded to desist after surgery. Trichobezoars result from trichotillomania in healthy children and in children with syndromes such as Prader Willi syndrome. They may cause complete small intestinal obstruction and perforation. The constellation of small intestinal obstruction by trichobezoar is known as Rapunzel syndrome, after the German princess in Grimms' fairytales who let her golden hair down from her tower to facilitate a tryst with her lover.

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