OLORECTAL CANCER IS A LEADING cause of morbidity and mortality, with about 300,000 new cases and 200,000 deaths in Europe and the United States each year. The 5-year survival rate of patients with rectal cancer undergoing surgery is 50% because of the high risk of local recurrence or of distant metastases even though resection has been considered curative. Therefore, improved survival remains a major issue in the long-term management of resectable rectal cancer.

In 1988, a meta-analysis of 6 randomized controlled trials (RCTs) (n = 2451 patients) failed to show an overall significant effect of preoperative radiotherapy on mortality. It was suggested that new large trials should be performed to answer specific questions, such as the effect of treatment in different stages of the disease and the ideal regimen, and to identify prognostic groups.

In 1990, the National Institutes of Health Consensus Conference on adjuvant therapy for patients with colon and rectal cancer concluded that preoperative radiotherapy was not recommended as a single adjuvant since it did not alter overall survival except in subgroups.

Since then, several large studies have been published. However, the results of published RCTs remain inconsistent and the overall assessment of the treatment effect is difficult to evaluate. The aim of this meta-analysis was to estimate if preoperative radiotherapy prolongs overall and cancer-specific survival compared with surgery alone.

Context The benefit of adjuvant radiotherapy for resectable rectal cancer has been extensively studied, but data on survival are still equivocal despite a reduction in the rate of local recurrence.

Objective To assess the effectiveness of preoperative radiotherapy followed by surgery in the reduction of overall and cancer-related mortality and in the prevention of local recurrence and distant metastases.

Data Sources Computerized bibliographic searches of MEDLINE and CANCERLIT (1970 to December 1999), including non-English sources, were supplemented with hand searches of reference lists. The medical subject headings used were rectal cancer, radiotherapy, surgery, RCT, randomized, and clinical trial.

Study Selection Studies were included if they were randomized controlled trials (RCTs) comparing preoperative radiotherapy plus surgery with surgery alone and if they included patients with resectable histologically proven rectal adenocarcinoma, without metastatic disease. Fourteen RCTs were analyzed.

Data Extraction Data on population, intervention, and outcomes were extracted from each RCT according to the intention-to-treat method by 3 independent observers and combined using the DerSimonian and Laird method.

Data Synthesis Radiotherapy plus surgery compared with surgery alone significantly reduced the 5-year overall mortality rate (odds ratio [OR] 0.84; 95% confidence interval [CI], 0.72-0.98; P = .03), cancer-related mortality rate (OR, 0.71; 95% CI, 0.61-0.82; P < .001), and local recurrence rate (OR, 0.49; 95% CI, 0.38-0.62; P < .001). No reduction was observed in the occurrence of distant metastases (OR, 0.93; 95% CI, 0.73-1.18; P = .54).

Conclusions In patients with resectable rectal cancer, preoperative radiotherapy significantly improved overall and cancer-specific survival compared with surgery alone. The magnitude of the benefit is relatively small and criteria are needed to identify patients most likely to benefit from adjuvant radiotherapy.
METHODS

Selection of Randomized Trials

This meta-analysis was performed according to the criteria recommended by Lau et al.35 The primary sources of the reviewed studies including non-English sources were MEDLINE and CANCERLIT, with the following medical subject headings: rectal cancer, radiotherapy, surgery, RCT, randomized, and clinical trial. The search included literature published through December 1999. The computer search was supplemented with hand searches of reference lists for all available review articles, primary studies, abstracts from meetings, and bibliographies of books.

Studies were included in the meta-analysis if they were RCTs comparing preoperative radiotherapy plus surgery with surgery alone, if they included patients with resectable histologically proven rectal adenocarcinoma and without metastatic disease, and if mortality was assessed as an outcome measure of the effect of the treatment. Among the 196 studies reviewed, 14 RCTs met the inclusion criteria.5-18 Studies were excluded if they combined preoperative and postoperative radiotherapy23; if they did not have a surgery alone group as control20,21; if they were nonrandomized27-30 or if they enrolled randomized nonrandomized patients23,26; if they stopped after accruing only a few patients31; or, if published as a preliminary report19,22,24,32-34 a final article was published subsequently. Since all the trials reported as abstracts36-38 were subsequently published as full articles, this meta-analysis included only peer-reviewed reports.

Review of the Trials

The trials were first reviewed using a list of predefined, pertinent issues that concerned the characteristics of patients and treatments. To assess the methodological quality of RCTs, the 2 domains of blinding and handling withdrawals and dropouts, using the definitions given by Nicolucci et al.39 were used as suggested by Juni and colleagues.40 For each of these 2 domains, RCTs were classed as high or low quality. Each RCT was evaluated and classified by 3 independent investigators (M.G., F.F., C.C.). Discrepancies among reviewers were infrequent (overall interobserver variations <10%) and were solved by discussion.

Statistical Methods

Crude rates of 5-year overall mortality and cancer-related deaths were assessed as measures of the treatment's effect. These data were available in all but 2 RCTs.8,17 A Medical Research Council study (MRC I)39 reported the actuarial probabilities of both 5-year overall and cancer-related mortality in the text. MRC II11 showed crude data for cancer-related mortality, whereas the overall mortality was obtained from a figure. When possible we also analyzed the 5-year rates of local and distant recurrences. The evaluation of therapeutic effectiveness was performed by an intention-to-treat method. When not reported in the trial, the response rate according to intention-to-treat was calculated. The number of patients who discontinued their original irradiation regimen because of adverse effects also was recorded. To combine results from individual trials, we used crude 5-year mortality rates, ie, the proportion of deaths observed in the treatment and control groups, regardless of when these deaths were observed. With these observed proportions of deaths, the odds ratio (OR) was computed for each trial.

We calculated the overall OR among the frequencies of the events in both radiotherapy plus surgery and surgery alone groups, according to the DerSimonian and Laird random-effects model.41 In addition to within-study variance, the random-effects model considers heterogeneity among studies. The 95% confidence interval (CI) of the OR also was calculated. The overall OR was tested for significance using a Mantel-Haenszel χ2 test.32 Moreover, we in turn excluded each study to ensure that no single study would be solely responsible for the significance of any result (so-called robust analysis). All our analyses were computed using a software program. The number needed to treat (NNT) to prevent one death, deriving from the inverse of the risk difference, was also used as a measure of treatment effect.43

We present the random-effect model because we believe that the relevant variation in the treatment effects is a consequence of several intertrial differences. To improve the comparability of the different therapeutic regimens and to assess the relationship between radiation dose and survival benefit, the biological equivalent dose (BED) of the various radiation schedules was estimated.44

In MRC I,8 2 different treatment groups were compared with the same surgery group as the control. We included in the analysis only the most relevant treatment group of this RCT, using effect size estimates calculated from observations on that measure. Therefore, the statistical analysis used only independent estimators of effect size.45

Two different methods were used to explore and explain the diversity among results of different studies: subgroup analyses and meta-regression. A χ2 test for interaction46 or trend47 was used to examine whether the effect of treatment varied significantly between subgroups. To examine the extent to which differences in the study end points could be explained by differences in the therapeutic regimens, characteristics of the patients studied, or study design features, several independent explanatory variables were included in a meta-regression model.48 The dependent variable in the regression analysis was the logarithmic OR of overall mortality in the radiotherapy vs surgery alone group. The statistical analysis was done by weighted multiple linear regression model, where the weights were the inverse of the variance of the treatment effect. The BED was used to characterize each therapeutic regimen. The patient characteristics examined were the proportion of patients with Dukes C stage in the surgery alone group and the proportion of male patients. The average of the overall 5-year mortality rate of the treatment and control patients was added to the regression model.49 Study design features examined included study quality, year of publication, and study size. Regression

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analysis was performed with the proc metareg in STATA software (STATA Corporation, College Station, Tex).50

RESULTS
Characteristics of the RCTs
The main features of the trials included in the meta-analysis are shown in TABLE 1. The 14 RCTs included 6426 patients, 3081 of whom received surgical treatment only. The criteria for inclusion were uniform in all but 1 RCT, which included only patients with locally advanced but otherwise operable tumors.17 All studies but 25,11 were multicenter trials. The sample size of each RCT varied greatly, ranging from 313 to 114718 patients. The percentage of males ranged from 54%11 to 100%.6,9

The proportion of patients who underwent resection classified as curative was similar among the studies (curative defined as agreement between surgeon and histopathologist that margins of the resected tissue were free of tumor). The proportion of patients who underwent an abdominoperineal excision differed greatly among the trials, ranging from 0%14 to 94%. 9 The Dukes stage was assessed in all RCTs at operation.51 Data on the preoperative staging of tumor were lacking in almost all trials. The rate of Dukes C stage in patients treated with surgery alone was comparable in all RCTs, ranging from 31%13 to 47%,11 except in the small study by Kligerman5 and the MRC II17 trial in which only locally advanced rectal cancer was included. The proportion of patients with Dukes C stage tumors treated with radiotherapy ranged from 27%11 to 45%.8

The therapeutic regimens of the RCTs are shown in TABLE 2. A large variability of irradiation schedules between trials was found in the total dose (ranging between 57.8 and 455 Gy); the daily dose (ranging between 1.759,12 and 57.8,13-16,18 Gy); the fractions of dose (ranging between 17,8 and 255 given during 1 and 35 days, respectively); and the irradiated volume.

No adequate blinding was used in 8 trials5,7-9,11,12,14,15 and 9 stud-
ies, did not clearly define criteria for handling withdrawals.

**Overall Mortality**

The effect of adjuvant radiotherapy on total mortality (14 RCTs: 5974 patients, 3331 deaths) is shown in **FIGURE 1**. Although the effect of treatment on total mortality favored radiotherapy in 11 of the 14 trials, a significant difference was observed in only 3, 11, 18. The pooled estimate of the treatment effect was significant (OR, 0.84; 95% CI, 0.72-0.98, \( z = -2.21; P = .03 \)) (NNT = 25). The robust analysis shows that evaluation of the 13 trials remaining after omission of the largest trial18 results in a similar effect size but loss of significance for overall mortality (OR, 0.87; 95% CI, 0.75-1.02, \( z = -1.70; P = .09 \)). Sensitivity analysis excluding the 2 RCTs5,17 with patients with advanced-stage disease also showed a similar effect size but marginal statistical significance (OR, 0.85; 95% CI, 0.72-1.01, \( z = -1.89; P = .06 \)).

We performed subgroup analyses to evaluate whether there was evidence of a different effect of preoperative radiotherapy in predefined subgroups of patients. Among the studies that reported mortality by stage, for overall mortality the pooled OR was significant in patients with Dukes B stage (OR, 0.67, 95% CI, 0.52-0.88, \( z = -2.90; P = .004 \)) and Dukes C stage (OR, 0.76, 95% CI, 0.59-0.97, \( z = -2.18; P = .03 \)) but not in those with Dukes A stage (OR, 0.84, 95% CI, 0.58-1.21, \( z = -0.96; P = .34 \)), without a significant trend (\( x^2 = 0.07, P = .93 \)). Analysis by BED showed that the pooled OR was 0.81 (95% CI, 0.65-1.00, \( z = -1.92; P = .055 \)) in patients who received a BED greater than 30 Gy (30 Gy being the mean dose between highest and lowest) and 0.88 (95% CI, 0.75-1.05, \( z = -1.44; P = .15 \)) in those who received a BED of 30 Gy or less, without a significant interaction (\( x^2 = 0.39, P = .53 \)).
The regression analysis, which simultaneously took into account the effects of BED as well as patient and study characteristics, confirmed that treatment effect was not significantly affected by the various adjustments (Table 3). The model was fit to data from 10 RCTs (n=4442 patients). Four RCTs were not included because of lack of data. All the explanatory variables failed to independently influence the reported treatment effect. Introduction of the average of the overall mortality rates in the treatment and control groups as a potential effect modifier did not change the effect size (P=.28). Similarly, neither patient (the proportions of patients with Dukes C stage in surgery alone group and the proportions of male patients) nor study characteristics (study publication year and study size) had an independent effect on the response to treatment. Finally, study quality assessed as allocation concealment and handling of withdrawals failed to independently influence the reported OR of overall mortality.

Cancer-Related Mortality
Mortality due to rectal cancer was reported in 11 studies (n=5021 patients and 2091 deaths). The benefit of radiotherapy on cancer-related mortality is shown in Figure 2. Radiotherapy decreased mortality in all but 1 RCT, and a significant difference was observed in 5 studies. The highest therapeutic benefit of radiotherapy was observed in the outlier RCT of Reis Neto et al, which is a small single-center trial. The OR of each trial ranged from 0.18 to 1.01. The pooled estimate of the treatment effect was significant (OR, 0.71; 95% CI, 0.61-0.82, z=-4.62; P<.001) (NNT=13). In all the robust analyses the pooled estimate of the treatment effect was significant.

Local Recurrence and Distant Metastases
A total of 11 RCTs (n=4494 patients) were available for evaluating the 5-year rate of local recurrence (Figure 3). Preoperative radiotherapy was superior to surgery alone in all but 1st study, reaching statistical significance in 6 RCTs. The pooled OR was 0.49 (95% CI, 0.38-0.62, z=-5.71; P<.001) (NNT=10).

The combination of data from 9 RCTs (n=3722 patients) failed to show a statistically significant effect of radiotherapy on distant metastases (OR, 0.93; 95% CI, 0.73-1.18, z=-0.62; P=.54) (data not shown).

Compliance, Postoperative Complications, and Mortality
Compliance was satisfactory. Only 179 (8.1%) of 2204 irradiated patients did not complete the planned protocol and only 28 (1.3%) required a reduction in irradiation dose.

The 3 most frequent complications were sepsis (18.3%), anastomotic leak (5.2%), and intestinal obstruction (5.2%). In the radiotherapy groups there was a significantly greater amount of sepsis (21% vs 15.2%, P<.001) and other complications (21% vs 17.8%, 15.2%).
P = .03) than in the groups treated with surgery alone. The overall rate of postoperative adverse events was 57.4% (1291/2246) in the radiotherapy groups and 42.3% (958/2264) in the surgery alone groups (P < .001).

The risk for postoperative mortality (within 30 days) was higher in the radiotherapy group in 5 trials and reached statistical significance in only 2, in which a high-dose per fraction radiation (5 Gy) was given with anterior-posterior portals. The combination of data from 10 RCTs (n = 5112 patients) failed to show a significant effect of radiotherapy on postoperative mortality (OR, 1.38; 95% CI, 0.86-2.32; z = 1.24; P = .22). There was evidence that the effect of preoperative radiotherapy was more detrimental in patients who received a BED higher than 30 Gy (P for trend = .002).

**COMMENT**

This meta-analysis of data from 14 RCTs shows that in resectable rectal cancer, preoperative radiotherapy significantly improves overall and cancer-specific 5-year survival vs surgery alone. An impressive reduction in the rate of local recurrence was observed in almost all trials, whereas no significant reduction of the risk of metastatic recurrence was found. Overall complications in the immediate postoperative period were significantly increased by radiotherapy, probably due to more cases of sepsis. However, there was no evidence that radiotherapy significantly increases postoperative mortality.

The key clinical question is whether all patients with resectable rectal cancer should receive preoperative radiotherapy or whether adjuvant radiotherapy should be administered only to a subgroup of patients who clearly stand to benefit. It has been suggested that the benefit of preoperative radiotherapy is higher in the advanced stages of a tumor (ie, Dukes B and C) than in the early stage (Dukes A). We failed to demonstrate a significant improvement of overall survival in the subgroup of patients with Dukes stage A. The effect of radiotherapy on overall survival is much more pronounced and statistically significant in patients with Dukes B and C stage tumors. Data on mortality according to Dukes stages are missing in several trials and caution must be exercised when interpreting results from exploratory analyses. Moreover, Dukes stage in patients who underwent preoperative irradiation is not an accurate and reliable measure of pretreatment staging because of the downstaging effect of radiotherapy, and therefore not directly comparable with the Dukes stage of patients who did not receive radiotherapy. Further large RCTs stratifying patients according to Dukes stage by preoperative endorectal ultrasonography and computed tomographic scanning are needed to avoid overtreatment of patients with a Dukes stage A lesion and to confirm the benefit from radiotherapy in patients with Dukes B or C rectal cancer.

Many RCTs have been conducted to identify the optimal radiotherapy regimen that would increase the cost-effectiveness of treatment. Glimelius et al reported a clear dose-response relationship between radiation dose and decrease in local recurrence rates. There was considerable variation in the irradiation procedures among the studies we evaluated, suggesting that global standardized radiation techniques are needed to obtain comparable data on efficacy and safety, particularly regarding the extension of the irradiated field. We believe the available information is inadequate to determine whether a short course of high-dose radiation (25 Gy over 5-7 days) is better than a conventional long-course regimen (2 Gy over 14-28 days). Similar to results of Glimelius et al, we found that higher postoperative mortality was observed in only 2 RCTs in which a high-dose per fraction radiation (5 Gy) was given with anterior-posterior portals. Exploratory analysis by irradiation dose suggested postoperative mortality was higher for patients who received a BED higher than 30 Gy. However, firm conclusions on the results of direct comparisons between high and low irradiation dose are hampered by the fact that in many trials postoperative mortality...
and early and late adverse effects are not formally reported. Therefore, data on efficiency of different irradiation techniques and on safety are needed.

The results of this retrospective analysis are subject to several limitations. Differences in the baseline severity of illness in the population of the studies, in the irradiation techniques, and in the radiotherapy regimens may limit the accuracy of this meta-analysis. We attempted to control for these differences by including covariates that described the patients studied and the study design features. These summary results describe only between-study, not between-patient, variation because they reflect group averages rather than individual data. Lack of data on other potential confounders, like fixity and height of the tumor, also could affect the accuracy of the results. Moreover, the available data indicate a substantial variability between various current surgical procedures, particularly total mesorectal excision, and between various surgeons and hospitals in the outcomes they achieve. The meta-analysis was performed using summary data and more detailed treatment comparisons could be achieved with a meta-analysis of individual patient data. The screening of the non-English literature and the extensive manual and computer search for studies make us confident that no important published trials were overlooked.

Publication bias was probably not substantial and considered unlikely to change the direction of our pooled estimate of treatment effect. Although the issues of quality assessment may be important in this review, the quality of individual trials seems not to bias the results of our meta-analysis. The available evidence is sufficient to conclude the following: (1) preoperative radiotherapy as a single adjuvant reduces overall and cancer-related mortality; (2) the risk of local recurrence is definitely reduced by irradiation; (3) the rate of distant metastases is probably not influenced by preoperative radiotherapy as a single adjuvant; and (4) postoperative mortality is not significantly increased by irradiation despite the higher rate of adverse effects. The magnitude of the overall effect is small but clinically relevant. Further large-scale, multicenter RCTs may prove useful to substantiate the benefit on overall survival.

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**REFERENCES**


Research has been called good business, a necessity, a gamble, a game. It is none of these—it’s a state of mind.
—Martin H. Fischer (1879-1962)