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

Authors' objectives
To assess the effects of adjuvant radiotherapy for rectal cancer on survival and recurrence.

Searching
The authors stated that the trials were identified through procedures described by the Early Breast Cancer Trialists Collaborative Group, whose methods included the scrutiny of review articles, cancer trials registers and proceedings, a computer-aided literature search and contact with trial investigators.

A secretariat and collaborative group of trial investigators (Colorectal Cancer Collaborative Group) was established to identify trials and undertake the meta-analysis.

Study selection
Study designs of evaluations included in the review
The review included individual patient data (IPD) from randomised controlled trials (RCTs) begun before 1987.

Specific interventions included in the review
Studies of adjuvant pre- or post-operative radiotherapy compared with surgery without radiotherapy were eligible for inclusion. In the included trials, the total radiotherapy dose and the number of fractions varied. The biologically effective dose (BED) of irradiation varied between 7.5 and 37.5 grays (Gy) in the pre-operative trials and between 35.4 and 43.8 Gy in the post-operative trials. Few of the included studies used chemotherapy (no further details were given).

Participants included in the review
Studies in patients with rectal cancer were eligible for inclusion, whereas studies in patients with colon cancer were not. The review included men and women aged from under 55 to over 75 years. Patients with Duke's stage A, B and C rectal cancer were included.

Outcomes assessed in the review
The main outcomes of interest were mortality and local recurrence. The outcomes reported were all-cause, rectal cancer and non-rectal cancer mortality, and any isolated local first recurrence.

How were decisions on the relevance of primary studies made?
The relevance of primary studies appears to have been established through communication with trial investigators.

Assessment of study quality
The authors stated that the data were checked for completeness and internal consistency, and that amendments were made through contact with the investigators. The authors did not state explicitly how judgements of validity were made, in terms of who made the decisions or the criteria used.

Data extraction
The trial investigators were asked to provide IPD for their trial, including first recurrence and the cause of death in patients who died without recorded recurrence.

Methods of synthesis
How were the studies combined?
The studies were combined using a meta-analysis of IPD to determine the absolute reduction in the yearly rate of mortality and recurrence; survival curves were used to determine the absolute difference in survival, and the risk of recurrence at 5 or 10 years. In the meta-analyses, intention-to-treat log rank analysis was used to calculate the log rank statistic and its variance for each individual trial; these were then pooled to obtain a weighted average and standard error (SE). Patients who received radiotherapy in one trial were split between two dose subgroups in such a way that the control group was counted twice in the overall pooling. Non-rectal cancer mortality was estimated from deaths before recurrence, while log rank subtraction from all-cause mortality was used to estimate rectal cancer mortality. Deaths from unknown causes were included with non-rectal cancer deaths in the analyses of cause-specific mortality.

How were differences between studies investigated?
The trials were subgrouped in the meta-analyses by pre- and post-operative radiotherapy, and pre-operative trials were stratified arbitrarily by BED (less than 20, 20 to 29.9, and 30 or more Gy). A chi-squared test of statistical heterogeneity was applied in the meta-analyses.

Results of the review
IPD from 14 RCTs (n=6,350) of pre-operative radiotherapy and 8 RCTs (n=2,157) of post-operative radiotherapy were included. Five other pre-operative trials (n=605) and one post-operative trial (n=17) were identified, but were not included in the review because the data could not be obtained.

Overall survival.
The meta-analysis of all available data (14 pre-operative and 8 post-operative trials) showed a 5.4% (SE=2.9) reduction in the yearly death rate among patients who had radiotherapy compared with those who did not have radiotherapy, but the difference was not statistically significant ($2P=0.06$). The difference in effect between the pre-operative (5.6%) and post-operative (4.6%) radiotherapy subgroups was not statistically significant ($2P=0.09$). There was no statistically significant heterogeneity between the trials. There was no trend between BED and treatment effect.

Recurrence.
The meta-analysis of all available data (11 pre-operative and 7 post-operative trials) showed the yearly rate of isolated local recurrence among patients who had radiotherapy to be 43.4% (SE=5.1) lower than in those who did not have radiotherapy; the difference was statistically significant ($2P<0.00001$). The difference in effect between the pre-operative (46.0%) and post-operative (36.9%) radiotherapy subgroups was not statistically significant. There was statistically significant heterogeneity between the pre-operative trials, among which there was a significant trend towards greater treatment effect with higher BED.

Following apparently curative surgery, pre-operative radiotherapy significantly reduced the absolute risk of any recurrence by 6.9% (SE=1.6) at 5 years and by 5.6% (SE=1.9) at 10 years ($2P<0.00001$). The absolute risk of isolated local recurrence was also significantly reduced, by 12.5% (SE=1.3) at 5 years and 9.2% (SE=1.9) at 10 years ($2P<0.00001$). Post-operative radiotherapy showed a reduction in isolated local recurrence at 5 years but not in the analysis of any recurrence; there were few recurrences after 5 years.

Cause-specific mortality.
The meta-analysis of all available data (13 pre-operative and 8 post-operative trials) showed a significant reduction of 11.8% (SE=3.2) in deaths from rectal cancer with radiotherapy ($2P=0.0003$). However, the overall effect was largely due to the pre-operative trials of 30 Gy or more; in those 6 trials there was a 21.6% (SE=5.1) reduction in deaths from rectal cancer, but also a significant ($P<0.0001$) increase in early deaths from other causes (8% in the radiotherapy group versus 4% in the control group).

The report contained further analyses according to curative resection, radiotherapy dose, age and stage.

Authors' conclusions
Local recurrence and the risk of death from rectal cancer are reduced by pre-operative radiotherapy at a BED of 30 Gy.
or more. In addition, overall survival could be improved if safety can be improved. The authors also concluded that local recurrence is reduced by post-operative radiotherapy, but shorter pre-operative schedules may be as effective as longer schedules that are usually used for post-operative radiotherapy.

CRD commentary
This was a thorough analysis conducted by an international collaborative group who estimated that they had included over 90% of data from all known trials. Procedures for the collection and analysis of IPD appear to have been followed rigorously and the results were presented clearly. The authors’ conclusions and the implications drawn from them are likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that pre-operative radiotherapy at adequate doses appeared to be more beneficial than post-operative radiotherapy; although pre-operative schedules are shorter the potential for greater toxic effects would need to be assessed by longer follow-up. The authors indicated ongoing trials of pathology-guided treatment of rectal cancer, and systemic chemotherapy with radiotherapy.

Research: The authors stated that large-scale participation in well-designed RCTs is needed to confirm or refute whether any further improvements in survival are achievable.

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