Preoperative chemoradiation vs radiation alone for stage II and III resectable rectal cancer: a meta-analysis

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CRD summary
This review found that preoperative chemoradiotherapy was associated with higher rates of complete response, but also higher rates of toxicity, compared with preoperative radiotherapy alone in patients with stage II/III rectal cancer. Limitations of the review process and reporting mean that the results (particularly for the short-course radiotherapy analyses) should be interpreted with caution.

Authors' objectives
To compare the safety and efficacy of preoperative radiotherapy with preoperative chemoradiotherapy in patients with stage II/III resectable rectal cancer.

Searching
The authors stated that they conducted a search of PubMed, Cochrane and Ovid from 1950 to 2007, but it was not clear exactly which databases were searched. Broad MeSH terms were used in the search.

Study selection
Randomised controlled trials (RCTs) of patients with stage II/III resectable rectal cancer, who were randomised to receive either preoperative chemoradiotherapy or long-course/short-course preoperative radiotherapy followed by surgery, were eligible for inclusion.

The outcomes of interest were: survival, recurrence, postoperative morbidity and mortality, resectability, resection leaving no residual tumour (R0), sphincter preservation, and pathologic complete response.

In the included trials, patients had rectal cancer of stage T2 to T4. The radiotherapy dose given ranged from 34.5 to 50 Grays. Chemotherapy consisted of 5-fluorouracil in most trials; in one trial, capecitabine plus oxaliplatin was given. The interval from preoperative treatment to surgery ranged from 10 days to 10 weeks.

The authors did not state further details of how the papers were selected for the review.

Assessment of study quality
Trial quality was assessed using the (5-point) Jadad scale.

The authors did not state how the validity assessment was performed.

Data extraction
Odds ratios (OR) with 95% confidence intervals (CI) were calculated for dichotomous outcomes.

For the comparison of short-course radiotherapy with chemoradiotherapy, the authors appeared to derive a mathematical model to compare the effect of chemoradiotherapy from the five trials in the review with the effect of short-course radiotherapy from one of these five trials, plus four additional trials.

Methods of synthesis
Meta-analysis was used to combine the trial results. For the comparison of any radiotherapy versus chemoradiotherapy, it was not clear in the methods whether random-effects or fixed-effect meta-analysis was used. In the modelling of short-course radiotherapy versus chemoradiotherapy, random-effects meta-analysis was used.

Heterogeneity between trials was assessed using the Cochrane Q statistic.
Publication bias was assessed using Egger's and Begg's tests.

Results of the review
Five RCTs, with 2,519 patients, were included in the review. One trial was scored with 1 point on the Jadad scale; the remaining four trials scored 2 points. There was no evidence of publication bias.

The meta-analysis showed no statistically significant differences between the radiotherapy and chemoradiotherapy groups for survival, cancer-related survival, local recurrence, resectability, curative resectability, sphincter preservation, postoperative mortality or postoperative morbidity.

Chemoradiotherapy was associated with a higher complete response rate (OR 3.0296, 95%CI 1.9449 to 4.7192; five RCTs), but higher rates of toxicity (OR 3.9939, 95%CI 1.7364 to 9.1867; three RCTs). For the toxicity result, the authors stated that there was significant heterogeneity, but no further investigation of this was reported.

The meta-analysis of preoperative short-course radiotherapy versus preoperative chemoradiotherapy showed no difference between the two groups for survival, local recurrence, mortality, resectability or sphincter preservation. Morbidity was lower following chemoradiotherapy (OR 0.3219, 95%CI 0.1854 to 0.559; five RCTs) and the rate of resection leaving no residual tumour was higher following chemoradiotherapy (OR 2.7253, 95%CI 1.7089 to 4.3463; five RCTs) compared with short-course radiotherapy.

Authors' conclusions
Preoperative chemoradiotherapy in patients with stage II/III resectable rectal cancer gave better complete response rates that radiotherapy alone, but was associated with higher toxicity.

CRD commentary
The research question was clearly stated. The description of the search conducted was not sufficiently clear to replicate; it was not clear which databases were searched and the search terms appeared to be very broad. No details were given of any language restrictions, so it was not clear whether the results could have been affected by language bias. The authors did not appear to have made attempts to locate unpublished data; they stated that there was no evidence of publication bias, but this assessment would not be very accurate when based on a low number of trials. The authors did not state how the study selection, data extraction or validity assessment were conducted, so it was unclear whether steps were taken to minimise errors during the review process.

The validity assessment did not consider pertinent criteria of the quality of RCTs (such as allocation concealment). The quality of the included trials was not taken into account in the data synthesis, and the overall quality of the included studies appeared to be low. Meta-analysis was appropriately used for one of the research questions, although no investigation of reasons for heterogeneity between trials was presented. The authors acknowledged that it was inappropriate to compare trial results from different trials in the two arms, as was done in the analysis of short-course radiotherapy versus chemoradiotherapy.

Given the lack of clarity on the reporting of the review process, the possibility of language and publication bias, and the overall low quality of the included trials, the results should be interpreted with caution.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further trials of short-course radiotherapy versus chemoradiotherapy and studies assessing the selection of patients for observation after successful chemoradiotherapy are required.

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