The use of preoperative radiotherapy in the management of patients with clinically resectable rectal cancer

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CRD summary
The main part of this reasonably well-conducted review compared radiotherapy followed by surgery with surgery alone for the treatment of patients with rectal cancer. The authors concluded that adding radiotherapy reduces the risk of local recurrence of cancer and may improve overall survival. The conclusions are likely to be reliable.

Authors' objectives
To determine the role of pre-operative radiotherapy (RT) in the management of patients with resectable rectal cancer, and to compare pre-operative RT with post-operative combined RT and chemotherapy.

Searching
MEDLINE (1966 to December 2001), Cancerlit (1983 to October 2001) and the Cochrane Library (Issue 4, 2001) were searched without language restrictions; the search terms were reported. The PDQ clinical trials database and the proceedings of meetings of the American Society of Clinical Oncology (1998 to 2001) and the American Society for Therapeutic Radiology and Oncology (1999 to 2001) were searched for new and ongoing trials. The reference lists of items retrieved as full papers were also checked. Update searches for all sources, except Cancerlit, were performed in January 2004. EMBASE (1980 to week 3, 2004) was also searched.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials (RCTs) were included in the review.

Specific interventions included in the review
Studies comparing pre-operative RT and surgery with surgery alone, or another alternative treatment, were eligible for inclusion.

Participants included in the review
Eligible studies were required to have a well-defined population that preferably included only patients with rectal carcinoma (defined by tumours located within 15 cm of the pectinate line or anal verge on sigmoidoscopy) or rectosigmoid tumours assessed as surgically resectable for cure. The patients were required to have been screened by clinical and imaging procedures for metastases and co-morbidity. Some included studies excluded patients with small tumours, or were limited to those with locally advanced tumours or those requiring abdomino-perineal resection.

Outcomes assessed in the review
The outcomes specified in the inclusion criteria were overall survival and/or local failure rate (proportion of patients unable to have tumour removal and those with recurrent disease after resection). Other outcomes assessed included adverse effects (morbidity and mortality), downstaging (decrease in the proportion of patients with stage III disease) and resectability (total and curative).

How were decisions on the relevance of primary studies made?
The authors stated that evidence was selected by four members of the Gastrointestinal Cancer Disease Site Group. They did not state whether the selection process was independent or how any disagreements were resolved.

Assessment of study quality
Validity was assessed for studies of pre-operative RT versus surgery alone using the method described by Detsky et al.
(reference provided), which assesses randomisation, outcomes, patient eligibility, treatment description and statistical procedures. Each study was assigned a quality score of between 0 and 1; studies with a score of greater than 0.5 were considered to be of high quality. Five reviewers independently assessed each study. The final quality score was an average of the scores assigned by the different reviewers.

**Data extraction**
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. For overall mortality, local failure, tumour resectability, tumour downstaging and adverse events, data on the numbers of events in each group were extracted and used to calculate the risk ratio (RR) and its 95% confidence interval (95% CI). Odds ratios and absolute risk differences were also calculated.

**Methods of synthesis**

*How were the studies combined?*
Studies of pre-operative RT versus surgery alone were combined in a meta-analysis using a random-effects model. Studies comparing pre-operative RT with other alternative treatments were classified by the type of comparison (pre-operative RT versus post-operative adjuvant RT in high-risk cases, pre-operative RT alone versus pre-operative RT plus chemotherapy, and pre-operative RT with surgery at different intervals) and combined in a narrative.

*How were differences between studies investigated?*
In the meta-analysis, statistical heterogeneity was assessed using a chi-squared test and the I-squared statistic. Heterogeneity was also investigated using pre-specified sensitivity analyses to examine the effects of biologically effective RT dose, RT fraction size, contemporary RT prescription, delay of surgery after completion of RT and composition of the study population. A sensitivity analysis, which excluded studies with a quality score of less than 0.5, was also performed.

**Results of the review**
Fifteen RCTs with 7,985 randomised participants were included in the comparison of pre-operative RT versus surgery alone. Five RCTs with 1,366 participants compared pre-operative RT with other alternative treatments.

**Pre-operative RT versus surgery alone.**
Overall mortality was lower in the treatment group (pre-operative RT) compared with the control groups (14 studies; RR 0.94, 95% CI: 0.89, 0.99, P=0.021). The median follow-up was 5 years or more in most studies.

The pooled results for local failure rate (13 studies; RR 0.71, 95% CI: 0.57, 0.89, P=0.0025) and incidence of stage III tumours (15 studies; RR 0.84, 95% CI: 0.74, 0.95, P=0.006) significantly favoured the treatment group. For local failure rate, there was no significant treatment effect in trials using a biologically effective dose (BED) of 7.5 to 26.8 (3 studies; RR 0.95, 95% CI: 0.79, 1.11, P=0.58), while trials using doses of 30 BED or more showed significantly reduced local failures (10 studies; RR 0.63, 95% CI: 0.48, 0.83, P=0.0011).

Total tumour resectability (12 studies; RR 1.00, 95% CI: 0.99, 1.00, P=0.36) and curative resectability (14 studies; RR 0.99, 95% CI: 0.98, 1.01, P=0.36) did not differ significantly between groups.

Pre-operative RT did not significantly increase 30-day post-operative mortality (13 studies; RR 1.33, 95% CI: 0.87, 2.05, P=0.19) or post-operative morbidity (11 studies; RR 1.11, 95% CI: 0.85, 1.30, P=0.18).

Significant heterogeneity was present for all outcomes except those related to resectability. The results were not significantly affected by factors considered in the sensitivity analyses.

**Pre-operative RT versus alternative treatments.**
Most comparisons between groups showed no significant differences. In one study, local failure rate was significantly lower in patients randomised to pre-operative RT than in those receiving selective post-operative RT.
Authors' conclusions
Pre-operative RT followed by surgery was significantly more effective than surgery alone for preventing local recurrence of rectal cancer, and may also improve survival.

CRD commentary
The research question was clearly stated and the inclusion criteria were clear. The alternative treatments (other than surgery alone) to which post-operative RT was being compared were not clearly defined, and this could have affected the selection of studies for inclusion. The authors searched a range of sources without restriction by language, thus minimising the risk of language bias. Publication bias was not investigated. The methods used to select the studies and extract the data were not reported in detail, so it was difficult to assess the risk of bias and errors being introduced during the review process. The authors used a recognised method to assess the quality of the included studies and used the results in a sensitivity analysis.

Relevant details of the included studies were presented in the text and tables. The results of studies comparing pre-operative RT with surgery alone were pooled, and various sources of heterogeneity were explored in pre-specified analyses. The authors' conclusions from the meta-analysis were in line with the evidence presented and are likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that, because RT was mainly of benefit to patients at high risk of recurrence, if pre-operative RT is added to surgery many patients who will not benefit will be exposed to the risk of radiation-induced morbidity and mortality.

Research: The authors stated that RCTs are required to compare pre-operative RT with post-operative RT and chemotherapy combined, and to compare optimal surgery (including total mesorectal excision) with adjuvant RT.

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