Postoperative adjuvant radiotherapy and/or chemotherapy for resected stage II or III rectal cancer


CRD summary
This review examined the role of post-operative adjuvant radiotherapy and/or chemotherapy for patients with resected stage II or III rectal cancer. The authors concluded that radiotherapy alone does not improve survival, whereas either chemotherapy alone or combined chemotherapy and radiotherapy improve survival compared with observation. The authors' conclusions appear to follow from the results presented.

Authors' objectives
To examine the role of post-operative adjuvant radiotherapy and/or chemotherapy for patients with resected stage II or III rectal cancer, in terms of improving survival and delaying local recurrence.

Searching
The systematic review was initially completed in 1998 with the data being reviewed periodically; the most recent update was December 2001. For the initial review, MEDLINE, Cancerlit and the Cochrane Library (Issue 4, 1997) were searched from 1966 to April 1997 (the search terms were provided). The MEDLINE searches were limited to RCTs or practice guidelines. In addition, personal reprint files were searched, the reference lists of retrieved articles were checked, and PDQ was searched for relevant ongoing trials. This search has been updated using MEDLINE (to December 2001), Cancerlit (to November 2001), the Cochrane Library (Issue 2, 2001) and the proceeding of the annual meetings of the American Society of Clinical Oncology (1999, 2000, 2001). PDQ was also searched for relevant ongoing trials.

Study selection
Study designs of evaluations included in the review
Any synthesis of evidence in the form of evidence-based practice guidelines, or systematic reviews and randomised controlled trials (RCTs) with appropriate comparison groups, were eligible for inclusion. Where reported, the median follow-up (for RCTs) ranged from 38 to 108 months.

Specific interventions included in the review
Studies examining radiotherapy, chemotherapy, or combined modality versus each other or observation were eligible for inclusion. Studies comparing different chemotherapy schedules were excluded. The interventions examined by the included studies were radiotherapy, systemic chemotherapy, combined treatment radiotherapy and chemotherapy, and portal vein infusion chemotherapy. The chemotherapy used was 5-fluorouracil (FU)-based; details of the specific chemotherapy and radiotherapy regimes used were provided in summary tables.

Participants included in the review
Studies that enrolled patients with stage II or III rectal cancer who had undergone rectal resection with curative intent were eligible for inclusion. Studies that included patients with colorectal cancer were only eligible if they presented the data for patients with rectal cancer separately from those for patients with colon cancer.

Outcomes assessed in the review
The primary outcomes in the review were survival and local control; the secondary outcome was disease-free survival.

How were decisions on the relevance of primary studies made?
The evidence was selected by four members of the Cancer Care Ontario Practice Guidelines Initiative's (CCOPGI's) Gastrointestinal Cancer Disease Site Group (DSG) and methodologists.
Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

When survival and disease-free survival were not reported, they were estimated from published graphs. When the actual numbers of deaths or disease recurrences were reported, these data were extracted and used in the pooled analysis.

Methods of synthesis
How were the studies combined?
During the initial review in 1997, the authors pooled the data using a random-effects model (the actual method used was not reported). The pooled results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs).

Data on local recurrence at the time of follow-up in each study were pooled, even though the follow-up times were different across the studies.

How were differences between studies investigated?
Statistical heterogeneity was investigated using the z-test. Summary effect estimates of individual studies were also presented graphically in forest plots.

Results of the review
Twenty-five RCTs (including one Japanese RCT that examined a chemotherapy preparation which is not currently available in Northern America), 5 meta-analyses and 2 evidence-based consensus statements were included. The review also included data from 2 reports of additional analyses of adverse effects and a review of the morbidities of adjuvant radiotherapy and chemotherapy.

Radiotherapy versus observation (7 RCTs, 1,849 patients with rectal cancer).

There was a benefit in terms of local control for radiotherapy (OR 0.73 for local recurrence, 95% CI: 0.55, 0.96, P=0.022, z=-2.29), but not survival (OR 0.92 for death, 95% CI: 0.77, 1.11, P=0.40, z=-0.84).

One further RCT (497 patients with rectal cancer), for which only preliminary results were available (presented as an abstract only), showed no significant difference in survival between the groups.

Chemotherapy versus observation (5 RCTs and 2 meta-analyses).

A pooled analysis of 3 RCTs (1,086 patients with rectal cancer) showed a survival benefit for chemotherapy (OR 0.65 for death, 95% CI: 0.51, 0.83, P=0.0006, z=-3.43), but no benefit in terms of local control (OR 0.71 for local recurrence, 95% CI: 0.44, 1.16, P=0.17, z=-1.37). Two additional Japanese RCTs (77 and 834 patients with rectal cancer), which were not included in the meta-analysis found no difference in survival between oral (with or without intravenous) 5-FU and observation. A meta-analysis of individual patient data (3 RCTs, 2,310 patients with rectal cancer) reported a mortality risk ratio (0.875, 95% CI: 0.734, 0.999, P=0.049) and a disease-free survival ratio (0.767, 95% CI: 0.656, 0.882, P=0.0003) that favoured adjuvant chemotherapy (with oral fluoropyridimides) to surgery alone. A published meta-analysis found a significant survival benefit favouring adjuvant chemotherapy (OR 0.64, 95% CI: 0.48, 0.85), but one of the 3 RCTs in this meta-analysis compared chemotherapy plus radiotherapy to radiotherapy.

One further RCT (299 patients with rectal cancer), for which only preliminary results were available (presented as an abstract only), showed no significant difference in survival between the groups.

Chemotherapy versus radiotherapy alone (3 RCTs, 717 patients with rectal cancer).
There was no difference in terms of survival or local control for either intervention (OR 0.80 for death (favouring chemotherapy), 95% CI: 0.58, 1.10, P=0.17, z=-1.37).

Chemotherapy by portal vein infusion versus observation (3 RCTs, 717 patients with rectal cancer; one meta-analysis of individual patient data, 673 patients with rectal cancer in 10 trials).

One RCT found 5-FU portal vein infusion to be associated with a survival benefit in patients with Dukes C rectal cancer (P=0.006) in a subgroup analysis. The remaining 2 RCTs did not find any statistically-significant benefit associated with 5-FU portal vein infusion in rectal cancer. The meta-analysis found a statistically non-significant 4% reduction in the annual odds of death at 5 years associated with portal vein infusion (P-value not reported).

Chemotherapy plus radiotherapy versus observation (2 RCTs).

One trial (n=104) showed improved survival associated with chemotherapy plus radiotherapy (52% versus 28%, P=0.01). A second RCT (n=144) reported a significant decrease in local recurrence (12% versus 30%, P=0.01), and improvements in 5-year overall survival (64% versus 50%, P=0.05) and 5-year recurrence-free survival (64% versus 46%, P=0.01), which favoured chemotherapy plus radiotherapy.

Three further RCTs (220, 177 and 206 patients with rectal cancer), for which only preliminary results were available, showed no significant difference in survival between the groups in terms of disease-free survival or survival.

Chemotherapy plus radiotherapy versus radiotherapy alone (3 RCTs, 548 patients with rectal cancer).

There was a benefit in terms of survival and local control associated with chemotherapy plus radiotherapy (OR 0.58 for death, 95% CI: 0.37, 0.92, P=0.019, z=2.34; OR 0.50 for local recurrence, 95% CI: 0.27, 0.92, P=0.025, z=2.24).

Chemotherapy plus radiotherapy versus chemotherapy alone (3 RCTs).

A pooled analysis of 2 RCTs (342 patients with rectal cancer) showed that there was no apparent benefit associated with chemotherapy plus radiotherapy in terms of either survival or local control (OR 0.80 for death, 95% CI: 0.48, 1.32, P=0.37). In the third trial, the addition of radiotherapy to chemotherapy did not significantly improve disease-free survival (hazard ratio, HR=0.99, 95% CI: 0.80, 1.22, P=0.90) or overall survival (HR 0.98, 95% CI: 0.78, 1.24, P=0.89).

Comparison of chemotherapy plus radiotherapy regimens (6 RCTs, 3,220 patients).

One study found that when chemotherapy with 5-FU was given concurrently with radiotherapy, continuous intravenous infusion of 5-FU was more effective than administration by bolus injection. One study found that the addition of semustine to 5-FU was ineffective. The remaining 4 studies reported non-significant findings for the following: 5-FU and radiotherapy, 5-FU plus leucovorin and radiotherapy, 5-FU plus levamisole and radiotherapy, 5-FU plus leucovorin, levamisole and radiotherapy; post-operative radiotherapy and concomitant bolus 5-FU, with or without chemotherapy with 5-FU and high-dose leucovorin; adjuvant 5-FU plus leucovorin and radiotherapy, with or without interferon alpha-2b; post-operative radiotherapy plus 6 or 12 months of 5-FU plus medium-dose folinic acid.

Adverse effects.

Enteritis, diarrhoea, bowel obstruction or perforation, fibrosis within the pelvis, nausea, skin reactions, radiation cystitis and fatigue were associated with radiotherapy. A greater number of haematological and non-haematological reactions were associated with combined modality than other treatments, but a single quality-of-life study using Q-TWIST showed, retrospectively, no persistent impairment on treated patients.

Authors' conclusions

The data suggested that adjuvant therapy with radiotherapy alone does not improve survival for patients with resected stage II and stage III rectal cancer, whereas either chemotherapy alone or combined chemotherapy and radiotherapy improve survival in comparison with observation. Chemotherapy plus radiation has become widely used, yet it has not
been shown to be superior to chemotherapy alone. The study results showed a trend in favour of this combination, but the trials testing it had small numbers of patients.

**CRD commentary**
This review addressed an appropriate question and had broad inclusion criteria. The literature search was comprehensive and included an attempt to identify unpublished data, but the possibility of publication bias was not investigated. Information about the review process was rather limited and the validity of the included studies was not assessed. The authors reported that the evidence was selected and reviewed by four members of the CCOPGI's Gastrointestinal Cancer DSG and methodologists. However, it was not stated whether more than one reviewer was involved in making decisions about the relevance of the individual studies or in extracting the data. It was also not stated how any discrepancies were resolved. Relevant data for the included studies were presented in tabular format. The authors investigated statistical heterogeneity and the data were pooled appropriately. The results of individual studies were presented in forest plots. The authors’ conclusions appear to follow from the results presented.

**Implications of the review for practice and research**
Practice: The authors stated that patients with resected stage II or III rectal cancer should be offered adjuvant therapy with the combination of radiotherapy and chemotherapy. If the goal of adjuvant therapy is to improve survival, no evidence exists to support the use of radiotherapy alone. Evidence that chemotherapy should include 5-FU, but not semustine, does exist. During the concurrent component of combination therapy, interactive infusion with 5-FU is more effective than bolus injection.

Research: The authors stated that the different methods of administrating 5-FU based chemotherapy need to be further tested against one another.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.