Systematic review and meta-analysis of outcomes following pathological complete response to neoadjuvant chemoradiotherapy for rectal cancer

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CRD summary
This review concluded that a pathologic complete response following neoadjuvant chemoradiotherapy and interval proctectomy, in patients with rectal cancer, was associated with excellent long-term survival and low rates of local recurrence and distant disease. These conclusions reflect the data presented, but should be interpreted cautiously due to the possibility of missing studies and limited reporting of the review methods.

Authors' objectives
To evaluate long-term oncological outcomes for patients with rectal cancer, with a pathologic complete response after neoadjuvant chemoradiotherapy followed by interval proctectomy.

Searching
PubMed and The Cochrane Library were searched for studies published in English between 1950 and March 2011; search terms were reported.

Study selection
Studies of at least 40 patients with pathologically verified rectal cancer, who underwent neoadjuvant chemoradiotherapy and radical rectal resection, were eligible for inclusion. Studies were required to report the oncological and survival outcomes, at a mean or median follow-up of at least 40 months. Studies of patients with recurrent lesions, or lesions that had already been treated surgically were excluded.

The mean age of study participants was 60 years and 65% were men. All participants had biopsy-proven rectal adenocarcinoma prior to treatment. About one third of participants had pathologic complete response and the remainder had incomplete or no response. Where reported, about one third of participants had tumour node metastasis stage II disease and the other two thirds had stage III disease. The neoadjuvant chemoradiotherapy consisted of a long course of radiotherapy (45 gray, Gy, in seven studies and 50 to 50.4 Gy in nine studies), with various chemotherapy regimens; almost all included 5-fluorouracil.

The authors did not state how many reviewers assessed studies for inclusion.

Assessment of study quality
The methodological quality of included studies was independently assessed by two reviewers, using the Newcastle-Ottawa Quality Assessment Scale for non-randomised cohort studies. This assessed patient selection, comparability of cohorts and outcome assessment, with a maximum score of nine.

Data extraction
The rates of local recurrence, distant disease recurrence, five-year overall survival and five-year disease-free survival were extracted. These data were used to estimate odds ratios, with 95% confidence intervals, for each outcome, for patients with pathologic complete response, compared with those without. The authors did not report how many reviewers extracted the data.

Methods of synthesis
Pooled odds ratios, with 95% confidence intervals, were calculated using a DerSimonian and Laird random-effects model. Between-study heterogeneity was assessed using the Cochran Q and $I^2$.

Results of the review
Sixteen studies were included in the review, with a total of 3,363 participants; two were prospective cohorts and 14 were retrospective. The mean length of follow-up was 55.5 months (range 40 to 72). The quality scores ranged from six to nine; 12 studies scored eight or nine. Ten studies did not report adequate details of outcome assessment.
Patients with a pathologic complete response were about four times less likely to develop local recurrence (OR 0.25, 95% CI 0.10 to 0.59; nine studies), or distant recurrence or metastases (OR 0.23, 0.11 to 0.47; nine studies) than those with incomplete response. Pathologic complete response had higher five-year overall survival (OR 3.28, 95% CI 1.66 to 6.51; 12 studies) and five-year disease-free survival (OR 4.33, 95% CI 2.31 to 8.09; 12 studies). Heterogeneity was low ($I^2=0$) or moderate ($I^2=45\%$ to 60%) in all analyses.

**Authors’ conclusions**

A pathologic complete response following neoadjuvant chemoradiotherapy was associated with excellent long-term survival, with low rates of local recurrence and distant disease.

**CRD commentary**

This review reported a clear objective and the inclusion criteria were clearly defined, but the searches were limited to two sources and English-language studies, raising the possibility that relevant studies might have been omitted. The methodological quality of the included studies was assessed, using an appropriate tool, and the scores were generally high. The process of quality assessment included measures to minimise error and bias, but it was unclear whether similar measures were included in the other review processes, and whether this could have affected the results. The meta-analytic methods used seem to have been appropriate.

The authors’ conclusions reflect the data presented, but should be interpreted cautiously due to the possibility of missing studies and limited reporting of the review methods.

**Implications of the review for practice and research**

**Practice:** The authors did not specify any recommendations for clinical practice.

**Research:** The authors stated that further research was needed to identify those patients with clinical and pathologic complete responses who did not need radical surgery, and those with a pathologic complete response who would benefit from chemotherapy to minimise the risk of local or distant failure.

**Funding**

Not stated.

**Bibliographic details**


**PubMedID**

22362002

**DOI**

10.1002/bjs.8702

**Original Paper URL**


**Indexing Status**

Subject indexing assigned by NLM

**MeSH**

Adenocarcinoma /therapy; Antimetabolites, Antineoplastic /therapeutic use; Chemoradiotherapy /methods; Disease-Free Survival; Female; Fluorouracil /therapeutic use; Humans; Male; Middle Aged; Neoadjuvant Therapy; Rectal Neoplasms /therapy; Treatment Outcome

**AccessionNumber**

12012037230
Record Status
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.