Time to locoregional recurrence after curative resection of rectal carcinoma is prolonged after neoadjuvant treatment: a systematic review and meta-analysis

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CRD summary
The review concluded that longer follow-up was needed to determine the therapeutic impact of neoadjuvant treatments in patients with rectal carcinoma. It was not possible to make a clear statement regarding primary surgery with adjuvant treatment. The authors' conclusions were suitably cautious, but methodological concerns in the review process made the reliability of these conclusions uncertain.

Authors' objectives
To assess the time to locoregional recurrence between different treatment strategies in patients following curative resection of rectal carcinoma.

Searching
PubMed was searched from January to February 2009 for articles published English and German between 1980 and 2007. Search terms were reported. Relevant literature was handsearched. Unpublished data were sought from Erlangen Registry of Colorectal Carcinoma.

Study selection
Studies of local resection of rectal carcinoma (including rectosigmoid) resected by radical surgery that reported mean or median time to locoregional recurrence and/or percentages of local recurrences after two, three and/or five years were eligible for inclusion. Studies were excluded if at least one of these criteria was present: maximum follow-up ≤60 months or not stated; median or mean follow-up ≤36 months or not stated; no separate data for patients treated with surgery alone versus those receiving multimodal therapy; no separate data for rectal/rectosigmoid and colon carcinoma; no separate data for locoregional and systemic recurrences; data only for isolated local recurrences; no separate data for neoadjuvant treatments; studies with neoadjuvant hyperthermia; and studies with radiotherapy with a total dose ≤20Gy.
Definitions were provided in the review.

Most of the included studies considered primary surgery alone, neoadjuvant long-course radiotherapy, neoadjuvant long-course radiochemotherapy and neoadjuvant short-course radiotherapy. Patient characteristics were not reported. The type of study was predominantly cohort design. RCTs were included.

The authors did not state how many reviewers performed the study selection.

Assessment of study quality
Study quality was assessed using the Jadad scale for RCTs to appraise randomisation, blinding, allocation concealment and withdrawals and drop-outs to give a maximum score out of five. Cohort studies were assessed on the basis of patient selection and follow-up time.

The authors did not state how many reviewers performed the validity assessment.

Data extraction
Data were extracted on median time to locoregional recurrence and diagnosis of locoregional recurrence after two, three and five years. Data were used to calculate odds ratios (ORs) and inverse relative risks (iRRs), together with 95% confidence intervals (CIs) or 95% credible intervals (CIs).

The authors did not state how many reviewers performed data extraction.
Methods of synthesis
A random-effects meta-analysis was used to calculate pooled odds ratios and inverse relative risks, together with 95% CIs. Exponential failure models were used for median time calculations. Binomial models were used to calculate event-free rates. Statistical heterogeneity was assessed using the $X^2$ statistic. Sensitivity analysis was conducted for type of surgery.

Results of the review
Twenty-five studies (1,221 participants) were included in the review: four RCTs and 21 observational studies. Trial quality was generally low to moderate: two trials scored 2 and two trials scored 3 out of 5 on the Jadad scale. The quality of the included cohort studies was reported as high.

Compared with neoadjuvant short-course radiotherapy, neoadjuvant long-course radiochemotherapy/radiotherapy had a statistically significantly higher percentage diagnosed with locoregional recurrence after five years (4% versus 24%, OR 0.13, 95% CI 0.01 to 0.76; six studies). This effect was not seen at three years.

Primary surgery alone compared with neoadjuvant long-course chemoradiotherapy/radiotherapy revealed no statistically significant difference in time to local recurrence. There was a statistically significant difference in percentage diagnosed with locoregional recurrence two years (30% versus 72%, OR 6.46, 95% CI 2.83 to 16.24; 11 studies), three years (12% versus 44%, OR 5.88, 95% CI 1.54 to 21.67; five studies) and five years (7% versus 24%, OR 4.61, 95% CI 1.66 to 14.95; 10 studies).

Few data were available to compare primary surgery with neoadjuvant short-course radiotherapy. Results showed that short-course radiotherapy might prolong the time to locoregional recurrence only for a short period.

Where statistical analysis was possible, there were no significant influences of adjuvant therapy on time to locoregional recurrence and percentage diagnosed with locoregional recurrence after two years. The type of surgery did not significantly affect the results.

Authors’ conclusions
The authors appear to state that longer follow-up was needed to determine the therapeutic impact of neoadjuvant treatments or surgery alone in patients with rectal carcinoma. It was not possible to make a clear statement of time to local recurrence for patients with primary surgery followed by adjuvant therapy in these patients.

CRD commentary
Inclusion criteria for the review were broadly defined and the range of data sources was limited. There was the potential for language bias, as only articles in English and German were included. Publication bias was not assessed and could not be ruled out. The authors did not state how many reviewers conducted study selection, quality assessment and data extraction, which risked errors and bias in the review process. Quality assessment was undertaken for the RCTs using a standard checklist. The quality assessment of cohort studies was less rigorous and claims to high quality may have been over-estimated given the studies’ retrospective design.

Participant characteristics from the individual studies were not displayed, which made it difficult to determine the comparability and generalisability of studies. The authors acknowledged considerable differences in the definitions of local recurrences across the studies. It appeared that the chosen method of synthesis was appropriate given the authors’ statement regarding clinical heterogeneity. Statistical heterogeneity was not reported.

The authors’ conclusions were suitably cautious, but methodological concerns in the review process made the reliability of the findings uncertain.

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

Research: The authors stated that for a definite assessment of the therapeutic effects of local control, minimum follow-up of seven to eight years after adjuvant long-course chemoradiotherapy/radiotherapy and five years after surgery alone...
was necessary.

**Funding**
Not stated.

**Bibliographic details**

**PubMedID**
19895596

**DOI**
10.1111/j.1463-1318.2009.02110.x

**Original Paper URL**

**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Humans; Neoadjuvant Therapy; Neoplasm Recurrence, Local; Rectal Neoplasms /surgery /therapy; Time Factors

**AccessionNumber**
12011001364

**Date bibliographic record published**
06/07/2011

**Date abstract record published**
14/12/2011

**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.