Preoperative radiotherapy for resectable rectal cancer: a meta-analysis

Camma C, Giunta M, Fiorica F, Pagliaro L, Craxi A, Cottone M

Authors' objectives
To assess the effectiveness of preoperative radiotherapy followed by surgery in the reduction of overall and cancer-related mortality and the prevention of local recurrences and distant metastases in patients with resectable rectal cancer.

Searching
Peer-reviewed reports were sought in MEDLINE and Cancerlit (from inception through December 1999) using the following medical subject headings: 'rectal cancer'; 'radiotherapy'; 'surgery'; 'RCT'; 'randomized'; and 'clinical trial'. Handsearches were conducted of reference lists for all available review articles, primary studies, abstracts from meetings, and bibliographies of books. Non-English publications were eligible.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) that compared preoperative radiotherapy with surgery alone were included if mortality was assessed as an outcome measure of treatment. Studies were excluded if they did not include a surgery alone group, if they were nonrandomised, if they enrolled randomised and nonrandomised patients, if they stopped after accruing only a few patients, and if published as a preliminary report, a final article was subsequently published.

Specific interventions included in the review
Preoperative radiotherapy plus surgery was compared to surgery alone. Irradiation schedules varied with total dose ranging between 5 and 45 Gy, daily dose ranging between 1.75 and 5 Gy, and fractions of dose ranging between 1 and 25 given during 1 and 35 days respectively. Interval between the end of irradiation and surgery ranged between immediately and 45 days. Surgery (when reported) included abdominoperineal resection (proportion undergoing this ranged from 0% to 94%), anterior restorative resection and unspecified other. Combinations of preoperative and postoperative radiotherapy were excluded.

Participants included in the review
Patients with resectable histologically proven rectal adenocarcinoma and without metastatic disease were included. Percentage of males ranged from 54% to 100% among trials. Dukes stage at operation (when stated) included A, B and C.

Outcomes assessed in the review
The primary outcome was mortality including 5-year overall mortality and cancer related mortality. Other outcomes included: 5-year rates of local and distant recurrences; the number of patients who discontinued their original irradiation regime; and postoperative complications.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The two domains of blinding and handling of withdrawals as defined by Nicolucci were used to assess validity (see Other Publications of Related Interest no.1).

Studies were classified as high or low quality for each of these domains. Three independent investigators evaluated and classified each study with discrepancies solved by discussion.

Data extraction
The following data appear to have been extracted: author and date of publication; sample size by treatment arm; %
male; mean age; resected %; curative resection %; type of surgery; Dukes stage at operation; and details of therapeutic regime. Data were extracted where available or calculated on an intention-to-treat basis and odds ratios estimated for each trial. The biological equivalent dose (BED) of the various radiation schedules was estimated. The authors do not state how data were extracted for the review, or how many of the reviewers performed the data extraction.

Methods of synthesis
How were the studies combined?
The overall odds ratio (OR) and 95% CI were calculated according to the DerSimonian and Laird random-effects model. The number-needed-to-treat was calculated (NNT).

How were differences between studies investigated?
Robust analyses were computed by repeating the analyses after excluding each study in turn. The relationship between radiotherapy dose (BED) and survival benefit was evaluated. A chi-squared test for interaction or trend was used to examine the effect of treatment between the subgroups. Meta regression was used to examine the influence of the following factors on the results: differences in therapeutic regime; patient characteristics (proportion of patients with Dukes stage C, and proportion of male patients); and study design features (study quality, study size and year of publication).

Results of the review
Fourteen RCTs were included (6426 patients, 3331 deaths).

5-year overall mortality: preoperative radiotherapy significantly decreased mortality. OR = 0.84 (95% CI: 0.72, 0.98; P = 0.03). NNT = 25. After omission of the largest trial: similar but non significant decrease in mortality with OR = 0.87 (95% CI: 0.75, 1.02; P = 0.09). After excluding two RCTs with advanced-stage disease: similar decrease with marginal significance with OR = 0.85 (95% CI: 0.72, 1.01; P = 0.06).

Mortality by Dukes stage: significant decrease in Dukes stage B with OR = 0.67 (95% CI: 0.52, 0.88; P = 0.004) and Dukes C with OR = 0.76 (95% CI: 0.59, 0.97; P = 0.03) but not Dukes A where OR = 0.84 (95% CI: 0.58, 1.21; P = 0.34). Mortality by BED: non significant decrease in those receiving BED > 30 Gy and those receiving < 30 Gy (results given).

Influence of other factors in meta regression (BED, patient and study characteristics): no factor had an independent effect on effect size.

Mortality by study quality: no independent influence on overall mortality.

5-year cancer related mortality (11 RCTs): preoperative radiotherapy significantly decreased cancer related mortality. OR = 0.71 (95% CI: 0.61, 0.82; P < 0.001). NNT = 13.

5-year rates of local recurrences (11 RCTs): preoperative radiotherapy significantly decreased local recurrences. OR = 0.49 (95% CI: 0.38, 0.62; P < 0.001). NNT = 10.

5-year rates of distant recurrences (9 RCTs): no significant effect on distant metastases. OR = 0.93 (95% CI: 0.73, 1.18; P = 0.54).

Proportion of patients who discontinued their original irradiation regime: 8.1% did not complete planned protocol. 1.3% required a reduction in irradiation dose.

Postoperative complications: the three most frequent complications were sepsis (18.3%), anastomotic leak (5.2%), and intestinal obstruction (5.2%).

Radiotherapy was associated with significantly greater sepsis (21% vs 15.2%; P < 0.001), and other complications (21% vs 17.8%; P = 0.03), and overall rates of postoperative adverse events (57.4% vs 42.3%; P < 0.001).
Postoperative (within 30 days) mortality (10 RCTs): no significant effect of radiotherapy. OR = 1.38 (95% CI: 0.86, 2.32; P = 0.22).

**Authors’ conclusions**
In patients with resectable rectal cancer, preoperative radiotherapy significantly improved overall and cancer-specific survival compared with surgery alone. The magnitude of the benefit is relatively small and criteria are needed to identify patients most likely to benefit from adjuvant radiotherapy.

**CRD commentary**
The aims and inclusion criteria were clearly stated. Relevant details of the primary studies were presented. Validity was assessed and the influence of study validity on results explored. Methods used to assess validity were described and data extracted on an intention-to-treat basis. Examination was conducted of the influence of various factors on the results. The discussion includes consideration of the following limitations of the review: differences in baseline severity of illness, in irradiation techniques and in radiotherapy regimes; lack of data on other confounders; variability between various current surgical procedures and between different surgeons and hospitals in outcomes achieved; and the likelihood of publication bias.

Limiting the primary studies to published studies may have led to publication bias. Methods used to select studies were not described. The inclusion of an evaluation of patient’s quality of life would aid decision making.

The evidence supported the authors’ conclusions.

**Implications of the review for practice and research**
Practice: The authors do not report any clinical implications of the review.

Research: The authors state that further large scale, multicentre RCTs may prove useful to substantiate the benefit on overall survival, and that trials are required in which patients are stratified by Dukes stage by preoperative endorectal ultrasonography and computed tomographic scanning. They also consider that data on the efficacy of different irradiation techniques and on safety are required.

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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.