The impact of radiotherapy on survival in resectable gastric carcinoma: a meta-analysis of literature data


CRD summary
This review concluded that adjuvant radiotherapy offered a small benefit over surgery alone in three- and five-year survival rates for patients with resectable gastric carcinoma, although there was not enough evidence to determine whether postoperative chemoradiotherapy or preoperative radiotherapy offered more benefit. The review contains some methodological flaws which mean the findings should be treated with caution.

Authors' objectives
To determine whether surgery combined with preoperative radiotherapy or postoperative chemoradiotherapy was more beneficial than surgery alone in reducing all-cause mortality in patients with resectable gastric carcinoma.

Searching
The Cochrane Library, MEDLINE, EMBASE and CANCERLIT were searched from inception to December 2006. Key search terms were listed. Reference lists of review articles, primary studies, books and meeting abstracts were scanned.

Study selection
Randomised controlled trials (RCTs) that compared preoperative radiotherapy plus surgery or chemoradiotherapy following surgery to surgery alone for patients with resectable or resected histologically proven gastric carcinoma without metastatic disease were eligible for inclusion in the review if the outcome of all-cause mortality was reported. Quasi-randomised trials, non-randomised trials and observational studies were excluded, as were studies that did not use surgery alone as a control group or used only intraoperative radiotherapy.

Two reviewers selected studies for inclusion in the review. Disagreements were resolved by discussion. Preliminary reports subsequently published as final papers were not included in the review. Where more than one publication of a study was found, only the most recent and complete data were included in the review.

The mean age of participants ranged from 54 to 60 years. The percentage of males ranged from 55% to 90%. The sample size of included studies ranged from 23 to 281 participants. In most included studies most patients were staged as having positive nodes (N+) and the type of surgery was radical. Irradiation schedules varied between included studies: total dose ranged from 20Gy to 45Gy; daily dose ranging between 1.56Gy and 4Gy; and fraction of dose between 5 and 30. All but one trial delivered radiation with anterior-posterior fields and all but three used radiation from a Co60 source.

Assessment of study quality
Validity of included studies was assessed according to adequacy of allocation concealment and handling of withdrawals and dropouts. Validity was assessed independently by three reviewers. Disagreements were resolved by discussion.

Data extraction
Data were extracted on three-year and five-year all-cause mortality rates. Where these data were not available, the Kaplan-Meier estimates of three-year and five-year mortality in each group as reported in the text were used. Therapeutic effectiveness was evaluated using the intention to treat method. Odds ratios were calculated for each study.

Data were also extracted on the numbers of dropouts due to side effects, and on the scales, grades and sites of acute toxicity (grouped as haematological or gastrointestinal).

The authors stated neither how the data were extracted for the review nor how many reviewers performed the data extraction.
Methods of synthesis
Pooled odds ratios with 95% confidence intervals (CIs) were calculated using random- and fixed-effect models. The number needed to treat (NNT) and the number needed to harm (NNH) were calculated.

Sensitivity analysis was performed excluding each study in turn and excluding two studies that used surgery plus postoperative chemotherapy as a control group.

The biologically effective dose (BED) and the linear quadratic equivalent dose (LQED) of the various radiation schedules were estimated.

Statistical heterogeneity was assessed using the $\chi^2$ test. Subgroup analyses and meta-regression were used to explore any heterogeneity. Variables included in the meta-regression model were: mean age; proportion with positive nodes in the surgery alone group; proportion of male patients; methodological quality; study size; and publication year.

Publication bias was assessed using the Begg and Egger tests.

Results of the review
Nine RCTs (n=1,701) were included in the review.

Validity assessment: Two studies did not use adequate allocation concealment and two studies did not have clear criteria for handling withdrawals.

Three-year mortality: The pooled odds ratio showed a statistically significant benefit of adjuvant radiotherapy compared to surgery alone (odds ratio 0.67, 95% CI 0.55 to 0.82, $p=0.0001$, number needed to treat was 14, no significant heterogeneity; nine RCTs). Sensitivity analyses did not change the result.

Five-year mortality: The pooled odds ratio again showed a statistically significant benefit of adjuvant radiotherapy over surgery alone (odds ratio 0.54, 95% CI 0.43 to 0.68, $p<0.00001$, number needed to treat was eight, no significant heterogeneity; seven RCTs). Sensitivity analyses did not change the result.

Subgroup analyses: Subgroup analyses revealed that preoperative radiotherapy was beneficial for both three-year mortality (odds ratio 0.57, 95% CI 0.43 to 0.76, $p=0.0001$; four RCTs) and five-year mortality (odds ratio 0.62, 95% CI: 0.46 to 0.84, $p=0.002$, number needed to treat was 10; four RCTs). Post-operative chemoradiotherapy showed a benefit in five-year mortality (odds ratio 0.45, 95% CI: 0.32 to 0.64, $p<0.00001$, number needed to treat was six; three RCTs).

Subgroup analyses also indicated that the pooled odds ratio for three-year mortality was significant in RCTs given a dose equivalent of 40Gy or greater, but not in those given a dose equivalent of less than 40Gy. Subgroup analyses by radiation machine all indicated statistically significant benefit.

The meta-regression for three-year mortality showed that the result was affected only by study sample size.

Adverse effects: The authors stated that compliance with preoperative radiotherapy was generally satisfactory, but that compliance with postoperative chemoradiotherapy was not. Analysis indicated no increased risk of postoperative mortality or anastomotic leakage with preoperative radiotherapy. Postoperative chemoradiotherapy, however, was associated with greatly increased risks of toxic effects (odds ratio 4.61, 95% CI: 2.89 to 7.36, $p<0.00001$; five RCTs).

Publication bias: Both tests for publication bias found no statistical evidence of bias, although the authors stated that the risk was substantial.

Authors' conclusions
The authors concluded that adjuvant radiotherapy significantly reduced three-year and five-year mortality in patients with resectable gastric carcinoma, but the size of the benefit was relatively small. There was insufficient evidence available to determine whether postoperative chemoradiotherapy was superior to preoperative radiotherapy.
This review addressed a clear research question with explicit inclusion criteria. The search strategy was comprehensive, although no specific attempts were made to locate unpublished studies. Steps were taken to reduce bias and error in the selection of studies and validity assessment; it was unclear whether these same steps were taken in data extraction. Details of data extraction, conversion and analysis were provided. The methods used for pooling studies and investigating heterogeneity and publication bias seemed robust and exhaustive, although statistical tests for publication bias may be unreliable with a small number of studies and hazard ratios rather than odds ratios are the preferred method for summarising time to event data. The mortality findings may need to be treated with some caution because of this, although no heterogeneity was seen in the results. There was no evidence of publication bias in statistical tests, although the review authors still felt that the risk was substantial, so it was possible that some studies may have been missed. The authors stated that information on adverse events provided in the included studies was variable, so the pooled results for toxicity may also need to be treated with some caution. Overall, the authors’ conclusions seem to be supported by the data presented, but caution is advised due to potential flaws in that data.

Implications of the review for practice and research

Practice: The authors stated that the benefits of postoperative chemoradiotherapy may outweigh the risks for patients at high local and distant recurrence rates and the risks outweigh the benefits for patients with low probability of local and distant failure.

Research: The authors stated that large RCTs that stratified patients by pre-treatment staging according to endoscopic ultrasonography and CT scan were needed. Studies should be conducted with broadly accepted and standardised radiation techniques to obtain comparable data on the efficacy and safety profiles, particularly regarding total and daily dose of radiation and type and dose of drug. Data were also needed on type and quality of current surgical procedures, particularly regarding the type of resection, extension of lymph node surgical dissection and N-ratio.

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