Survival after radiotherapy in gastric cancer: systematic review and meta-analysis

Valentini V, Cellini F, Minsky BD, Mattiucci GC, Balducci M, D'Agostino G, D'Angelo E, Dinapoli N, Nicolotti N, Valentini C, La Torre G

CRD summary
This review assessed the impact of radiotherapy on three-year and five-year survival in patients with resectable gastric cancer. The authors concluded that there was a statistically significant five-year survival benefit with the addition of radiotherapy to surgery. This conclusion should be treated with some caution due to the poor quality of the evidence available.

Authors’ objectives
To assess the impact of radiotherapy on three-year and five-year survival in patients with resectable gastric cancer.

Searching
PubMed, the Cochrane Library, Scopus and EMBASE were searched up to May 2008 for English language journal papers. Search terms were reported. Reference lists of review articles were also searched.

Study selection
Randomised controlled trials (RCTs) that assessed the effect on survival of radiotherapy plus surgery compared with surgery alone, in patients with biopsy-proven adenocarcinoma of the stomach or of the gastro-esophageal junction, were eligible for inclusion. Preoperative, postoperative and/or intraoperative radiotherapy were eligible and studies in which chemotherapy was a treatment component were also included. Patients with metastatic or unresectable disease were excluded.

The majority of participants in the included trials received radical, total or partial gastrectomy, where reported. The proportion of control patients with no regional lymph node metastases ranged from 15 to 66%. The majority of trials used postoperative radiotherapy. One third of trials used chemoradiotherapy; all used fluorouracil in varying doses. The total radiotherapy dose ranged from 20 to 50 Gy; the daily dose, number of days treatment and the biological equivalent and linear quadratic equivalent dose varied between trials.

Titles and abstracts were independently screened by three reviewers. The authors did not state how full papers were screened.

Assessment of study quality
Trial quality was assessed using a method proposed by Chalmers, which was composed of 30 items related to internal validity, external validity, data presentation, organisational aspects, side effects and other items. The maximum possible score was 102. The median quality score was calculated and trials scoring below the median were classified as low quality; those equal to or above the median score were classified as high quality.

The authors did not state how the validity assessment was performed.

Data extraction
The proportion of participants who had survived at three-year and five-year follow-up were extracted on an intention-to-treat (ITT) and per protocol basis, and the relative risk (RR) and 95% confidence intervals (CI) were calculated. No extrapolations were made from Kaplan-Meier curves.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Three-year and five-year survival were pooled in separate meta-analyses using a fixed-effect model, except where there was statistically significant heterogeneity when a random-effects model was used. Separate analyses were undertaken.
based on intention-to-treat and per protocol data. Statistical heterogeneity was assessed using the $X^2$ (statistically significant where p value was 0.05 or less) and $I^2$ statistics.

Sensitivity analyses were undertaken based on: trial quality (high and low); timing of radiotherapy (preoperative, postoperative and intraoperative); quadratic equivalent dose adjusted at 2Gy (LQED$_2$) (under 40 Gy and 40Gy and over); and time of publication (cut-off 1990). The possibility of publication bias was assessed using funnel plots, Begg's test and Egger's test.

Results of the review
Nine RCTs were included in the review (n=2,025 participants). The quality score of the included trials ranged from 10 to 48. Based on the median score of 36, five trials were classified as high quality and four as low quality.

There was statistically significant greater likelihood of survival in the radiotherapy plus surgery group compared with surgery alone group at five-year follow-up (RR 1.26, 95% CI 1.08 to 1.48; seven RCTs), but not three-year follow-up (RR 1.12, 95% CI 0.99, 1.27; 5 RCTs) based on the intention-to-treat data. There was statistical heterogeneity in the analysis of three-year follow-up intention-to-treat data ($I^2$=53%). The findings from the analysis of per protocol data were broadly similar.

Only a very small number of trials reported toxicity data. Haematological toxicity ranged from 1.31 to 77.14% for radiotherapy, and from 5.33 to 56.41 for surgery; gastrointestinal toxicity ranged from 13 to 56.41% in radiotherapy, and 21.33 to 34% in surgery

The authors reported a statistically significant greater likelihood of survival at five-years in the subgroup of lower quality trials, trials with a LQED$_2$ under 40 Gy, trials using preoperative radiotherapy, trials not using intraoperative radiotherapy, and in trials published after 1990 (based on intention-to-treat data), but not in the other subgroups.

There was no evidence of publication bias.

Authors' conclusions
There was a statistically significant five-year survival benefit with the addition of radiotherapy to surgery in patients with resectable gastric cancer.

CRD commentary
The review had clearly stated inclusion criteria and several relevant databases were searched for relevant trials. Despite the finding of no evidence of publication bias, this was based on a small number of trials: relevant trials may have been missed due to the exclusion of unpublished trials, as well as trials in languages other than English. It was unclear whether appropriate methods were used to reduce error and bias in the screening of full papers, quality assessment and data extraction.

The statistical pooling seems appropriate, although the subgroup analyses should be treated with considerable caution: the statistical significance of results within the separate subgroups was assessed rather than the differences between subgroups, which was inappropriate. In addition, although an attempt was made to take into account in the analysis the quality of the included trials; the dichotomy between good and poor quality using the median quality score was a somewhat artificial one (even the best quality trial scored less that half the possible maximum quality score), therefore it was likely that all the trials were low quality.

The overall conclusion is reasonable, but should be treated with some caution due to the poor quality of the available evidence.

Implications of the review for practice and research
Practice: The authors stated that radiotherapy remains a standard component in the treatment of resectable gastric cancer.
Research: The authors stated that RCTs are required to assess the impact of new conformal radiotherapy technologies.

Funding
Not stated.

Bibliographic details

PubMedID
19586672

DOI
10.1016/j.radonc.2009.06.014

Original Paper URL
http://www.thegreenjournal.com/article/S0167-8140(09)00324-7/abstract

Indexing Status
Subject indexing assigned by NLM

MeSH
Humans; Odds Ratio; Randomized Controlled Trials as Topic; Stomach Neoplasms /mortality /radiotherapy

AccessionNumber
12009107822

Date bibliographic record published
16/12/2009

Date abstract record published
29/09/2010

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.