Systematic review of D2 lymphadenectomy versus D2 with para-aortic nodal dissection for advanced gastric cancer

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CRD summary
This review found that D2 lymphadenectomy (lymph node removal) plus para-aortic lymph node dissection could be performed as safely as standard D2 lymphadenectomy alone without increasing postoperative mortality, but it did not improve overall survival in patients with advanced gastric cancer. This was generally a well-conducted review and these conclusions are likely to be reliable.

Authors' objectives
To evaluate the feasibility and therapeutic effects of para-aortic nodal dissection (lymph nodes) for advanced gastric cancer.

Searching
PubMed, EMBASE, China Biological Medicine Database, CNKI and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from 1980 to February 2009 with no language restriction. Search terms were reported. Reference lists were scanned. Experts in the field of gastroenterology were contacted to identify unpublished data.

Study selection
Studies that compared D2 lymphadenectomy versus D2 lymphadenectomy plus para-aortic nodal dissection for the surgical treatment of gastric adenocarcinoma were eligible for inclusion. Eligible studies had to report five-year overall survival, postoperative morbidity and mortality, and/or wound degree of surgery. Trials in which patients had distant metastasis, gastric stump cancer, disseminated cancer cells, synchronous malignancy in other organs, serious cardiovascular or respiratory disorders, or hepatic or renal failure were excluded. Trials were also excluded if patients received preoperative or postoperative chemotherapy in addition to surgery. Although not specified as an inclusion criteria, two studies in which almost 50% of participants were lost to follow-up were reported to have been excluded.

Included patients all had histologically proven gastric cancer. In some studies this was reported to be curable or advanced. Mean/median age of included patients ranged from 54 to 65 years; two studies were restricted to patients aged less than 75 years. In some studies only surgeons experienced in the surgical techniques participated in the studies.

Two reviewers independently assessed studies for inclusion. Disagreements were resolved through consensus.

Assessment of study quality
Study quality was assessed using the Cochrane Risk of Bias Tool which assessed sequence generation, allocation concealment, blinding, incomplete outcome assessment, selective reporting, and other bias. Studies were rated as yes (low risk of bias) or no (high risk of bias) for each item.

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

Data extraction
Two reviewers independently extracted data to calculate relative risks (RR) for dichotomous data or mean differences (MD) for continuous data together with 95% confidence intervals (CIs). Where necessary, study authors were contacted for additional information. Disagreements were resolved through discussion.

Methods of synthesis
Summary relative risks and weighted mean differences (WMDs) were estimated using fixed-effect models in the absence of heterogeneity; otherwise random-effects models were used. Heterogeneity was assessed using the $X^2$ statistic. Data from randomised controlled trials (RCTs) and non-randomised studies were pooled separately. Studies
that reported continuous data as medians and ranges rather than means and confidence intervals were excluded from the meta-analyses. The authors planned to use funnel plots to assess publication bias.

Results of the review
Four RCTs (n=1,120 patients) and four non-randomised studies (n=901 patients; two prospective, two retrospective) were included in the review. The studies were all of good quality. All RCTs fulfilled or probably fulfilled criteria for sequence generation and allocation concealment. All included studies fulfilled or probably fulfilled criteria for blinding, incomplete outcome data addressed, free of selective reporting, and free of other bias.

Based on the RCTs, there was no significant difference in five-year overall survival (two RCTs) or post-operative mortality (four RCTs) between patients treated with D2 lymphadenectomy plus para-aortic nodal dissection and those who received D2 lymphadenectomy alone. Operation time in the D2 lymphadenectomy plus para-aortic nodal dissection was significantly longer than in the D2 lymphadenectomy group (WMD 195.3 minutes, 95% CI 114.6 to 276.1; two RCTs). There was no evidence of statistical heterogeneity for any of these analyses (p>0.20).

One RCT reported significantly greater blood loss in the D2 lymphadenectomy plus para-aortic nodal dissection group (WMD 301mL, 95% CI 151.6 to 450.5). Data on post-operative morbidity were too different to allow combination in meta-analysis as studies reported different measures and conflicting results.

Results from non-randomised studies were similar to those of the RCTs.

There were too few studies to permit assessment of publication bias.

Authors’ conclusions
D2 lymphadenectomy plus para-aortic nodal dissection could be performed as safely as standard D2 lymphadenectomy (resection) without increasing postoperative mortality, but failed to benefit overall survival in patients with advanced gastric cancer.

CRD commentary
The review addressed a clear question supported by defined inclusion criteria. However, two studies were excluded because a large proportion of patients were lost to follow-up; this was not specified as an exclusion criterion. A relevant range of databases were used to identify published studies, authors were contacted to locate unpublished data, and no language restrictions were applied. The authors did plan to assess publication bias in their review but there were too few studies. Appropriate steps were taken to minimise reviewer bias and error when selecting studies and extracting data, but it was unclear whether such steps were also taken for the quality assessment.

Study quality was assessed using appropriate criteria; the results of the assessment were clearly presented. Methods used to pool data were appropriate and included stratification based on study design.

The authors’ conclusions are supported by the data and are likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that D2 plus para-aortic nodal dissection can be performed as safely as standard D2 resection, but operation time and blood loss is greater, so D2 plus para-aortic nodal dissection should be performed prudently.

Research: The authors stated that research on the relationship between prognosis of gastric cancer patients and combined organ resection and potential survival benefit of D2 plus para-aortic nodal dissection for some specific stages of advanced gastric cancer are urgently needed.

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