Laparoscopy-assisted versus open distal gastrectomy for early gastric cancer: evidence from randomized and nonrandomized clinical trials

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CRD summary
The authors concluded that laparoscopic-assisted distal gastrectomy, with less than D2 or D2 lymphadenectomy, was a feasible alternative to open distal gastrectomy, for patients with early gastric cancer, when it was performed in experienced surgical centres. Limitations in the evidence mean that the reliability of the results is not clear, and the authors' recommendation for research seems reasonable.

Authors' objectives
To determine the efficacy and safety of laparoscopy-assisted distal gastrectomy, compared with open distal gastrectomy, for patients with early gastric cancer.

Searching
EMBASE, PubMed, The Cochrane Library and CNKI were searched for published articles, in English or Chinese, from January 1994 to the end of December 2010. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) or non-randomised controlled trials, of patients with early gastric cancer, were eligible for inclusion if they compared laparoscopy-assisted distal gastrectomy with open distal gastrectomy and reported at least one critical clinical outcome. The critical clinical outcomes included: the number of retrieved lymph nodes, operation time, duration of postoperative hospital stay, intra-operative blood loss, postoperative analgesic consumption, time to first flatus, overall postoperative complications, postoperative cancer recurrence rate, and long-term survival rate. Studies of hand-assisted laparoscopic surgery, gasless laparoscopic surgery, robotic surgery, and pylorus-preserving gastrectomy were excluded. Studies that included malignant stromal tumour, benign disease, emergency operation, or high-ratio advanced cases were excluded. Studies in which the baseline cases were not comparable or from which data could not be extracted were excluded.

In the included studies, reconstruction included Billroth (I and II), oesophagus jejunum anastomosis, and Roux-en-Y. Lymph node classification and resection were defined according to the Japanese Gastric Cancer Association. The level of lymphadenectomy included: D1 resection, D1 plus alpha resection, D1 plus beta resection, and D2 resection. The study intervals ranged from one to 10 years. All included studies were conducted in East Asia.

The authors did not state how many reviewers selected studies for inclusion in the review.

Assessment of study quality
The methodological quality of included RCTs was assessed using the Jadad scale. Non-randomised trials were assessed using the Methodological Index for Non-Randomized Studies (MINORS). The authors did not state how many reviewers assessed study quality.

Data extraction
Means and standard deviations were extracted for the calculation of continuous outcomes, and the number of events and total number of participants were extracted for the calculation of binary outcomes. The authors did not state how many reviewers extracted the data.

Methods of synthesis
Pooled estimates and their associated 95% confidence intervals were calculated in a meta-analysis. A fixed-effect model was used unless significant heterogeneity was found, in which case a random-effects model was used. Heterogeneity was investigated using $X^2$ (a $p<0.01$ was considered significant) and $I^2$. Mean differences or standardised mean differences were pooled using the inverse-variance model. The Mantel-Haenszel model was used for pooling the relative risks and risk differences.
Subgroup analyses were carried out for study design and levels of lymphadenectomy (less than D2 resection, D2 resection, and mixed cases undergoing less than D2 resection or D2 resection). Funnel plots were visually inspected to detect publication bias; asymmetry of the funnel plot was assessed using the Egger test.

**Results of the review**

Twenty-two studies, with 3,411 participants (1,596 for laparoscopic surgery and 1,815 for open surgery), were included in the meta-analyses. Five studies were RCTs and seventeen were non-RCTs. Jadad scores ranged from two to three (out of a possible five), and MINORS scores ranged from 10 to 17 (out of a possible 24).

No significant between-group difference was found for the number of retrieved lymph nodes across all levels of lymphadenectomy. Evidence of significant heterogeneity was found for less than D2 resection ($I^2=98\%$) and mixed cases ($I^2=81\%$). When study design was considered, a significant difference in the mixed cases subgroup in favour of open distal gastrectomy was found in RCTs (MD -6.10, 95% CI -10.04 to -2.16; one RCT), and a significant difference was found in favour of laparoscopic-assisted distal gastrectomy in non-RCTs (MD 2.40, 95% CI 0.73 to 4.07, $I^2=0$; three studies).

A significant reduction in duration of postoperative hospital stay was found in favour of laparoscopic-assisted distal gastrectomy for less than D2 resection (MD -4.70, 95% CI -7.72 to -1.69; $I^2=98\%$), D2 resection (MD -7.27, 95% CI -11.44 to -3.11; $I^2=78\%$), and mixed cases (MD -1.76, 95% CI -2.11 to -1.42; $I^2=68.5\%$). When study design was considered, no significant between-group difference was found for RCTs in the less than D2 resection and D2 resection subgroups.

A significant reduction in overall postoperative complications was found in favour of laparoscopic-assisted distal gastrectomy (RR 0.58, 95% CI 0.46 to 0.74, $I^2=0$; two RCTs and four non-RCTs). A similar result was found across all levels of lymphadenectomy. Visual inspection of the funnel plot indicated asymmetry, but Egger's test was not significant ($p=0.109$).

No significant between-group difference was found for postoperative cancer recurrence across all lymphadenectomy subgroups. Three non-RCTs reported long-term survival rates; estimates were not pooled and no significant between-group differences were found.

There were significant differences favouring laparoscopic-assisted distal gastrectomy for operation time, for D2 resection and for less than D2 resection; for intra-operative blood loss, across all subgroups; for postoperative analgesic consumption, across all subgroups; and for time to first flatus, for D2 resection and less than D2 resection. Substantial heterogeneity was reported for most of these results.

The results for the learning curve (learning cases varied from 20 to 300 cases) and conversion rates (varied from zero to 2.94%; five RCTs and eight non-RCTs) were presented.

**Cost information**

Two studies from Japan found no significant between-group differences for operation theatre costs or total hospital costs. One study from China found a significant difference in favour of open distal gastrectomy for operation theatre costs, but no significant between-group difference in total hospitalisation costs.

**Authors' conclusions**

The review suggested that laparoscopic-assisted distal gastrectomy, with less than D2 or D2 lymphadenectomy, was a feasible alternative to open distal gastrectomy, for patients with early gastric cancer, when it was performed in experienced surgical centres.

**CRD commentary**

The review question was supported by clear inclusion and exclusion criteria. Several relevant databases were searched, but only published articles, in English or Chinese, were eligible and the possibility of language and publication bias cannot be ruled out. The authors did not state whether appropriate procedures were taken to minimise bias and error in the selection of studies, extraction of data, and assessment of study quality. Methodological quality was assessed using standardised tools and the overall quality of the included studies was considered to be low.
Few patient and study characteristics were reported. There was evidence of substantial heterogeneity and this might indicate that pooling was not appropriate for all analyses. The authors did not pre-specify the primary and secondary outcomes and the results were reported as primary or secondary, without justifying this selection. They acknowledged a number of limitations, including enrolment across wide study intervals, the difficulty of generalising to a Western population, and insufficient sample sizes to distinguish differences for some analyses (postoperative recurrence and total hospitalisation costs).

Given the limitations of the evidence, the reliability of the results is uncertain, and the authors’ conclusion that further research was necessary seems reasonable.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that high-quality comparative trials were needed.

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