Systematic review and meta-analysis of standard and extended lymphadenectomy in pancreaticoduodenectomy for pancreatic cancer

CRD summary
This review assessed the impact of extended lymphadenectomy (ELA) compared with standard lymphadenectomy on survival rates in patients with pancreatic cancer. The authors concluded that ELA is not associated with improved survival and there may be a trend to increased morbidity. This was a generally well-conducted review; however, insufficient information on study quality and the review process makes it difficult to assess the reliability of these conclusions.

Authors' objectives
To compare survival rates following pancreaticoduodenectomy with or without extended lymphadenectomy (ELA).

Searching
MEDLINE (January 1966 to February 2006) and the Cochrane CENTRAL Register (February 2006) were searched without language restrictions. The references of available reviews and selected articles were checked, and experts in the field were contacted for further data. The authors searched the Internet and personal libraries for further published or unpublished studies.

Study selection
Study designs of evaluations included in the review
Prospective non-randomised and randomised studies were included. Case reports, studies without control groups and retrospective studies were excluded.

Specific interventions included in the review
Studies of ELA compared with standard lymphadenectomy (SLA) were eligible for inclusion. In one study a subgroup received adjuvant chemoradiation in addition to ELA. Details were not provided on the use of adjuvant therapy in other studies.

Participants included in the review
Studies of patients with pancreatic adenocarcinoma were eligible for inclusion. Studies of patients with distal bile duct, ampullary or duodenal carcinoma were excluded. Some studies included a third arm of patients with node-negative or node-positive cancer. One study was of periampullary tumours, of which only 57% were pancreatic in origin.

Outcomes assessed in the review
Studies of survival rate were eligible for inclusion. The secondary outcomes were number of resected lymph nodes, mortality and morbidity. Morbidity was calculated separately for delayed gastric emptying, pancreatic fistula, pancreatitis, bile leak, ulcer, small bowel obstruction, abscess, percutaneous drain, wound infection, cholangitis and pneumonia.

How were decisions on the relevance of primary studies made?
Three authors independently carried out a literature search. It was unclear whether study selection was also done independently by multiple authors.

Assessment of study quality
The authors did not state how the validity assessment was performed. However, they reported that validity was assessed following recently published protocols (see Other Publications of Related Interest) and initial methodological quality was assessed using the levels of evidence for studies on therapies of the Health Service Research and Development Centre for Evidence-Based Medicine. Randomised controlled trials (RCTs) were assessed according to description of randomisation process and
allocation concealment, definition of outcome parameters and complications, completeness of follow-up and statistical analysis.

**Data extraction**
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. The data extracted were details of operative technique, mean number and standard deviation of resected lymph nodes, percentage survival at 1, 3 and 5 years, number and percentage mortality and morbidity.

**Methods of synthesis**

How were the studies combined?
The results of the studies were tabulated and discussed in the text. The weighted mean difference (WMD) of the extent of lymphadenectomy was calculated using a random-effects model. Hazard ratios (HRs) for overall survival were pooled for 3 studies using the inverse variance method. Morbidity and mortality were calculated using a pooled odds ratio with 95% confidence intervals (CIs) using the random-effects model of DerSimonian and Laird. Studies were weighted by the sample size and quality of allocation concealment.

How were differences between studies investigated?
Clinical heterogeneity was assessed by comparing studies on the following parameters: number of participants, grade or stage of disease, number of resected lymph nodes, operative procedure, and neoadjuvant or adjuvant treatment. Statistical heterogeneity was calculated by inspecting the forest plot and using the I-squared statistic. Non-randomised studies and randomised studies were analysed and discussed separately.

**Results of the review**

Nine studies (n=969) were included: 5 prospective non-randomised studies (n=545) and 4 prospective randomised studies (n=424).

Survival.

Three randomised trials were combined in the meta-analysis of survival. No significant difference was found in the survival rate for ELA compared with SLA (weighted mean log HR 0.93, 95% CI: 0.77, 1.13, p=0.48). No statistical heterogeneity was detected (I-squared 59.3%; p=0.09). The results of the non-randomised studies were difficult to interpret as potential differences between the groups affected the reliability and validity of the findings. No differences in survival rates were observed between ELA and SLA groups. However, one study found increased survival rates 5 years postsurgery for patients with node-negative cancer undergoing ELA (48% versus 22%, p<0.01).

Number of resected lymph nodes.

A meta-analysis was conducted of 5 non-randomised studies and 3 RCTs. Participants receiving ELA had a significantly higher number of resected lymph nodes (WMD 15.08, 95% CI: 10.38, 19.77, p<0.001). However, there was evidence of significant statistical heterogeneity (I-squared 89.6%; p<0.001).

The meta-analysis showed no significant differences in morbidity and mortality between ELA and SLA groups. However, the narrative synthesis of individual study results revealed that 2 non-randomised studies and 2 RCTs found higher incidence of diarrhoea in patients undergoing ELA (no p-values reported).

**Authors' conclusions**

ELA is not associated with improved survival rates and there may be a trend towards increased morbidity.

**CRD commentary**

Inclusion criteria for the intervention, participants and outcomes were clearly stated. Several relevant sources were searched without language restrictions for both published and unpublished data, thereby minimising the risk that important data were missed. The methods used for the study selection, data
extraction and quality assessment processes were not presented in sufficient detail to rule out the possibility of error and bias. A quality assessment was performed; however, there was insufficient information on its findings to determine the quality of the included studies and the potential impact upon the findings of the review. The decision to combine only RCTs in the meta-analysis for survival, morbidity and mortality was appropriate. However, the outcome 'extent of lymphadenectomy' would have best been discussed in a narrative given the differences in study designs and the presence of significant statistical heterogeneity.

Limited reporting of the review process and the characteristics and quality of the included studies makes it difficult to assess the reliability of the authors' conclusions on survival rates. The authors' conclusion, that a trend towards increased morbidity with ELA may exist, is not supported by the findings of the review.

Implications of the review for practice and research
Practice: SLA is the optimal procedure for pancreaticoduodenectomy in patients with pancreatic cancer. ELA should only be carried out in RCTs, if at all.

Research: The authors did not state any implications for further research.

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Other publications of related interest

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MeSH
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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.