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Laparoscopic versus open distal pancreatectomy for pancreatic cancer (Review)

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[Intervention Review]

Laparoscopic versus open distal pancreatectomy for pancreatic cancer

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ABSTRACT

Background

Surgical resection is currently the only treatment with the potential for long-term survival and cure of pancreatic cancer. Surgical resection is provided as distal pancreatectomy for cancers of the body and tail of the pancreas. It can be performed by laparoscopic or open surgery. In operations on other organs, laparoscopic surgery has been shown to reduce complications and length of hospital stay as compared with open surgery. However, concerns remain about the safety of laparoscopic distal pancreatectomy compared with open distal pancreatectomy in terms of postoperative complications and oncological clearance.

Objectives

To assess the benefits and harms of laparoscopic distal pancreatectomy versus open distal pancreatectomy for people undergoing distal pancreatectomy for pancreatic ductal adenocarcinoma of the body or tail of the pancreas, or both.

Search methods

We used search strategies to search the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Science Citation Index Expanded and trials registers until June 2015 to identify randomised controlled trials (RCTs) and non-randomised studies. We also searched the reference lists of included trials to identify additional studies.

Selection criteria

We considered for inclusion in the review RCTs and non-randomised studies comparing laparoscopic versus open distal pancreatectomy in patients with resectable pancreatic cancer, irrespective of language, blinding or publication status..

Data collection and analysis

Two review authors independently identified trials and independently extracted data. We calculated odds ratios (ORs), mean differences (MDs) or hazard ratios (HRs) along with 95% confidence intervals (CIs) using both fixed-effect and random-effects models with RevMan 5 on the basis of intention-to-treat analysis when possible.

Main results

We found no RCTs on this topic. We included in this review 12 non-randomised studies that compared laparoscopic versus open distal pancreatectomy (1576 participants: 394 underwent laparoscopic distal pancreatectomy and 1182 underwent open distal pancreatectomy); 11 studies (1506 participants: 353 undergoing laparoscopic distal pancreatectomy and 1153 undergoing open distal pancreatectomy) provided information for one or more outcomes. All of these studies were retrospective cohort-like studies or case-control studies. Most were at unclear or high risk of bias, and the overall quality of evidence was very low for all reported outcomes.

Differences in short-term mortality (laparoscopic group: 1/329 (adjusted proportion based on meta-analysis estimate: 0.5%) vs open group: 11/1122 (1%); OR 0.48, 95% CI 0.11 to 2.17; 1451 participants; nine studies; I^2 = 0%), long-term mortality (HR 0.96, 95% CI 0.82 to 1.12; 277 participants; three studies; I^2 = 0%), proportion of people with serious adverse events (laparoscopic group: 7/89 (adjusted proportion: 8.8%) vs open group: 6/117 (5.1%); OR 1.79, 95% CI 0.53 to 6.06; 206 participants; three studies; I^2 = 0%), proportion of people with a clinically significant pancreatic fistula (laparoscopic group: 9/109 (adjusted proportion: 7.7%) vs open group: 9/137 (6.6%); OR 1.19, 95% CI 0.47 to 3.02; 246 participants; four studies; I^2 = 61%) were imprecise. Differences in recurrence at maximal follow-up (laparoscopic group: 37/81 (adjusted proportion based on meta-analysis estimate: 36.3%) vs open group: 59/103 (49.5%); OR 0.58, 95% CI 0.32 to 1.05; 184 participants; two studies; I^2 = 13%), adverse events of any severity (laparoscopic group: 33/109 (adjusted proportion: 31.7%) vs open group: 45/137 (32.8%); OR 0.95, 95% CI 0.54 to 1.66; 246 participants; four studies; I^2 = 18%) and proportion of participants with positive resection margins (laparoscopic group: 49/333 (adjusted proportion based on meta-analysis estimate: 14.3%) vs open group: 208/1133 (18.4%); OR 0.74, 95% CI 0.49 to 1.10; 1466 participants; 10 studies; I^2 = 6%) were also imprecise. Mean length of hospital stay was shorter by 2.43 days in the laparoscopic group than in the open group (MD -2.43 days, 95% CI -3.13 to -1.73; 1068 participants; five studies; I^2 = 0%). None of the included studies reported quality of life at any point in time, recurrence within six months, time to return to normal activity and time to return to work or blood transfusion requirements.

Authors' conclusions

Currently, no randomised controlled trials have compared laparoscopic distal pancreatectomy versus open distal pancreatectomy for patients with pancreatic cancers. In observational studies, laparoscopic distal pancreatectomy has been associated with shorter hospital stay as compared with open distal pancreatectomy. Currently, no information is available to determine a causal association in the differences between laparoscopic versus open distal pancreatectomy. Observed differences may be a result of confounding due to laparoscopic operation on less extensive cancer and open surgery on more extensive cancer. In addition, differences in length of hospital stay are relevant only if laparoscopic and open surgery procedures are equivalent oncologically. This information is not available currently. Thus, randomised controlled trials are needed to compare laparoscopic distal pancreatectomy versus open distal pancreatectomy with at least two to three years of follow-up. Such studies should include patient-oriented outcomes such as short-term mortality and long-term mortality (at least two to three years); health-related quality of life; complications and the sequelae of complications; resection margins; measures of earlier postoperative recovery such as length of hospital stay, time to return to normal activity and time to return to work (in those who are employed); and recurrence of cancer.

PLAIN LANGUAGE SUMMARY

Key-hole (laparoscopic) versus standard access (open) abdominal operation for people with pancreatic cancer

Review question

How does key-hole (laparoscopic) abdominal surgery compare with standard access (open) abdominal operation for people with pancreatic cancer?

Background

The pancreas is an organ in the abdomen that secretes pancreatic juice that aids digestion and contains cells that produce important hormones such as insulin. The pancreas can be divided into the head of the pancreas (right part of the pancreas) and the body and tail of the pancreas (left part or distal part of the pancreas). Distal pancreatic cancer is cancer of the body and/or tail of the pancreas. Removal of distal pancreatic cancer by surgery (distal pancreatectomy) is the preferred treatment for people with distal pancreatic cancers limited to the pancreas who are likely to withstand major surgery, because no other treatments have the potential to cure pancreatic cancer. Cancer can be removed through an abdominal operation, either laparoscopic distal pancreatectomy or open distal pancreatectomy. Laparoscopic distal pancreatectomy is a relatively new procedure as compared with the well-established open distal

pancreatectomy. In operations on other parts of the body, laparoscopic surgery has been shown to reduce complications and length of hospital stay as compared with open surgery. However, concerns remain about the safety of laparoscopic distal pancreatectomy in terms of complications after operation (postoperative complications). In addition, it is not clear whether laparoscopic distal pancreatectomy achieves the same amount of cancer clearance as is attained by open distal pancreatectomy. It also is not clear whether laparoscopic distal pancreatectomy is better than open distal pancreatectomy in terms of earlier recovery after operation. We sought to resolve this issue by searching the medical literature for studies on this topic until June 2015.

Study characteristics

No randomised controlled trials have examined this topic. Randomised controlled trials are the best studies for finding out whether one treatment is better or worse than another because they ensure that similar types of people are receiving the treatments being assessed. In the absence of randomised controlled trials, we sought information from non-randomised studies. We identified 12 non-randomised studies that compared laparoscopic versus open distal pancreatectomy in a total of 1576 patients. One of these studies did not provide results in a useable way. Thus, we included 11 studies in which a total of 1506 patients underwent distal pancreatectomy. Some 353 patients underwent laparoscopic distal pancreatectomy, and 1153 patients underwent open distal pancreatectomy. In all studies, historical information was collected from hospital records (retrospective studies). In general, historical information is less reliable than newly collected (prospective) information and findings of randomised controlled trials.

Key results

Differences in short-term deaths, long-term deaths, percentage of people with major complications, percentage of people with a pancreatic fistula (abnormal communication between the pancreas and other organs or the skin), recurrence of cancer at final time of follow-up of participants, percentage of people with any complications and percentage of patients in whom cancer was not completely removed were imprecise. Average length of hospital stay was shorter in the laparoscopic group than in the open group by about two days. However, this is not relevant until we can be sure that cancer cures are similar between laparoscopic surgery and open surgery. No studies have reported quality of life at any point in time, short-term recurrence of cancer, time to return to normal activity, time to return to work or blood transfusion requirements.

Quality of the evidence

The quality of the evidence was very low, mainly because it was not clear whether similar types of participants received laparoscopic and open distal pancreatectomy. In many studies, people with less extensive cancer received laparoscopic surgery, and those with more extensive cancer received open surgery. This makes study findings unreliable. Well-designed randomised controlled trials are necessary if we are to obtain good quality evidence on this topic.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Laparoscopic distal pancreatectomy compared with open distal pancreatectomy for pancreatic cancer

Patient or population: patients with pancreatic cancer
Settings: secondary or tertiary care centre
Intervention: laparoscopic distal pancreatectomy
Comparison: open distal pancreatectomy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Open distal pancreatectomy	Laparoscopic distal pancreatectomy			
Short-term mortality	**10 per 1000**	**5 per 1000** (1 to 22)	**OR 0.48** (0.11 to 2.17)	1451 (9 studies)	⊕◯◯◯ **Very low**[a,b]
Long-term mortality Follow-up: 2 to 3 years	**549 per 1000**	**535 per 1000** (480 to 590)	**HR 0.96** (0.82 to 1.12)	277 (3 studies)	⊕◯◯◯ **Very low**[a,c]
Serious adverse events (proportion)	**51 per 1000**	**88 per 1000** (28 to 247)	**OR 1.79** (0.53 to 6.06)	206 (3 studies)	⊕◯◯◯ **Very low**[a,b,c]
Pancreatic fistula (grade B or C)	**66 per 1000**	**77 per 1000** (32 to 175)	**OR 1.19** (0.47 to 3.02)	246 (4 studies)	⊕◯◯◯ **Very low**[a,b,c,d]

None of the studies reported quality of life at any time point

*The basis for the **assumed risk** is the mean control group proportion. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)
CI: confidence interval; **HR:** hazard ratio; **OR:** odds ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: We are very uncertain about the estimate

[a] We found no randomised controlled trials. The non-randomised studies included in this review were at unclear or high risk of bias for most domains

[b] Confidence intervals were wide

[c] Sample size was small

[d] I^2 was high and little overlap of confidence intervals was evident.

BACKGROUND

Description of the condition

Adenocarcinoma of the pancreas is the most common malignancy of the exocrine pancreas. It is the tenth most common cancer in the United States, the fifth most common cause of cancer-related mortality in the East and the fourth most common cause of cancer-related mortality in the West (Parkin 2001; Parkin 2005; Yamamoto 1998). In 2012, 338,000 people were newly diagnosed with pancreatic cancer, and 330,000 deaths were the result of pancreatic cancer globally (IARC 2014). Global variation has been noted in the incidence of pancreatic cancer, with an age-standardised annual incidence rate of 7.2 per 100,000 in more developed regions and an age-standardised annual incidence rate of 2.8 per 100,000 in less developed regions (IARC 2014). A similar trend has been noted in an age-standardised annual mortality rate of 6.8 per 100,000 population in more developed regions and 2.7 per 100,000 population in less developed regions due to pancreatic cancer (IARC 2014). Mortality rates due to pancreatic cancer are increasing in the United States (Ma 2013). Pancreatic adenocarcinoma has a poor prognosis for many reasons. It is a biologically aggressive cancer that is relatively resistant to chemotherapy and radiotherapy and has a high rate of local and systemic recurrence (Abrams 2009; Ghaneh 2007; Orr 2010). Surgical resection remains the only treatment with the potential for long-term survival and cure. However, about half the people have metastatic disease at presentation, and one-third have locally advanced unresectable disease, leaving only about 10% to 20% of people suitable for resection (Tucker 2008). Overall five-year survival after radical resection ranges from 7% to 25% (Cameron 1993; Livingston 1991; Niederhuber 1995; Nitecki 1995; Orr 2010; Trede 1990), with median survival of 11 to 15 months (British Society of Gastroenterology 2005). With adjuvant chemotherapy, median survival after radical resection ranges between 14 and 24 months (Liao 2013).

Pancreatic cancer can occur in the head of the pancreas or in the body and tail of the pancreas. In early pancreatic cancer (with no invasion of adjacent structures such as the superior mesenteric vein, portal vein or superior mesenteric artery), surgical resection remains the primary treatment of choice for people likely to withstand major surgery.

Description of the intervention

Surgical resection is provided as pancreaticoduodenectomy for cancers of the head of the pancreas and as distal pancreatectomy for cancers of the body and tail of the pancreas (Park 2013). In open distal pancreatectomy, surgical access to the abdominal cavity (and hence the pancreas) is attained by upper midline incision, bilateral subcostal incision (roof-top or Chevron incision) or transverse abdominal incision (Fernandez-Cruz 2006). In laparoscopic distal pancreatectomy, surgical access to the abdominal cavity (and hence the pancreas) is typically attained by four small ports (holes) of about 1 cm each through which laparoscopic instruments can be inserted after the abdomen is distended using carbon dioxide pneumoperitoneum. For people with pancreatic cancer, the pancreas and the spleen are removed together (en bloc) after isolation and mobilisation of the distal pancreas, spleen and surrounding lymph nodes from surrounding structures such as the stomach, colon, diaphragm and kidneys by dividing attachments and blood vessels (Fernandez-Cruz 2006). Although splenic preservation is possible in open or laparoscopic distal pancreatectomy (Fernandez-Cruz 2006), the spleen is usually removed during distal pancreatectomy for cancers because of concern about cancer clearance in spleen preservation surgeries (Fernandez-Cruz 2005). However, no evidence suggests that splenectomy improves cancer clearance.

After resection of the body and tail of the pancreas, the cut surface of the pancreatic remnant (pancreatic stump) is usually closed with staples or sutures (Diener 2011). Despite this, a high incidence of clinically significant pancreatic fistula (11%) has been reported (Diener 2011; Montorsi 2012), and various interventions including somatostatin analogues may be used to decrease pancreatic fluid secretion (Gurusamy 2013), and fibrin sealants (in the form of glue (Suzuki 1995) or patches (Montorsi 2012)) to seal the pancreatic stump.

Distal pancreatectomy can also be performed with the assistance of a robot (robot-assisted distal pancreatectomy). In robot-assisted distal pancreatectomy, laparoscopic instruments are controlled by a robot. This is generally considered distinct from laparoscopic distal pancreatectomy (Daouadi 2013). The term 'minimally invasive distal pancreatectomy' is usually used to describe both laparoscopic distal pancreatectomy and robot-assisted distal pancreatectomy.

How the intervention might work

For many surgical procedures, laparoscopic surgery is currently preferred over open surgery. Laparoscopic surgery includes surgical procedures such as cholecystectomy (removal of gallbladder), colon cancer treatment and hysterectomy (Bijen 2009; Keus 2006; Reza 2006; Talseth 2014; Walsh 2009). Laparoscopic surgery is preferred over open surgery because it is associated with decreased pain, decreased blood loss, shorter hospital stay, earlier postoperative recovery, better cosmesis (physical appearance) and decreased costs (Bijen 2009; Keus 2006; Kooby 2008; Reza 2006; Rutz 2014; Talseth 2014; Walsh 2009).

Why it is important to do this review

A smaller incision and earlier postoperative recovery appear to be potential advantages of laparoscopic distal pancreatectomy; however, the safety of this approach for a procedure that has a high complication rate and cancer clearance after laparoscopic distal pancreatectomy must be ensured before the method can be widely recommended. Healthcare providers have expressed concerns about cancer clearance because port-site metastases (recurrence of cancer at the laparoscopic port site) have been reported after laparoscopic surgery for many different cancers (Kais 2014; Palomba 2014; Song 2014). Animal research has shown that increased intra-abdominal pressure during laparoscopy (pneumoperitoneum) may drive malignant cells into ports, resulting in seeding of the port site and port-site metastases (Hopkins 1999). Also, malignant cells may be adherent to laparoscopic instruments that are introduced and removed through the ports, resulting in seeding of the port site and port-site metastases (Hopkins 1999). Other issues include the adequacy of cancer clearance in terms of resection margins and the extent of lymph nodes removed through laparoscopy. Therefore, oncological efficacy (cancer clearance) is an important issue with laparoscopic distal pancreatectomy. No Cochrane review has examined this topic.

OBJECTIVES

To assess the benefits and harms of laparoscopic distal pancreatectomy versus open distal pancreatectomy for people undergoing distal pancreatectomy for pancreatic ductal adenocarcinoma of the body or tail of the pancreas, or both.

METHODS

Criteria for considering studies for this review

Types of studies

We planned to include only randomised controlled trials (RCTs) in this review. However, we found no RCTs on the topic, so we performed a meta-analysis of observational studies clearly highlighting the bias involved in interpretation of results. We included studies reported as full text, studies published as abstract only and unpublished data.

Types of participants

We included adults undergoing distal pancreatectomy for pancreatic ductal adenocarcinoma. Although we excluded people undergoing distal pancreatectomy for neuroendocrine cancers (cancers that arise from neural and endocrine cells; Rindi 2011), when possible we included trials in which no separate outcome data were available for people undergoing distal pancreatectomy for pancreatic adenocarcinoma, provided that distal pancreatectomy for other causes including neuroendocrine cancer was performed in less than 10% of participants included in the trial.

Types of interventions

We included trials comparing laparoscopic distal pancreatectomy versus open distal pancreatectomy provided that the only difference between groups was the use of the laparoscopic or open method of access to the pancreas. We excluded studies that compared different methods of laparoscopic distal pancreatectomy, robotic distal pancreatectomy or open distal pancreatectomy.

Types of outcome measures

Primary outcomes

1. Mortality.
   i) Short-term mortality (in-hospital mortality or mortality within three months).
   ii) Long-term mortality.
2. Serious adverse events (within three months). We will accept the following definitions of serious adverse events.
   i) Clavien-Dindo classification (Clavien 2009; Dindo 2004): grade III or greater.
   ii) International Conference on Harmonisation - Good Clinical Practice (ICH-GCP) guideline (ICH-GCP 1996): serious adverse events defined as any untoward medical occurrences that result in death, are life-threatening, require hospitalisation or prolongation of existing hospitalisation or result in persistent or significant disability/incapacity.
   iii) Individual complications that can clearly be classified as grade III or greater with the Clavien-Dindo classification (Clavien 2009; Dindo 2004), or as a serious adverse event with the ICH-GCP classification.
   iv) Clinically significant pancreatic fistulas (type B or type C International Study Group on Pancreatic Fistula (ISGPF) definition) (Bassi 2005).
3. Health-related quality of life (using any validated scale).
   i) Short-term (four weeks to three months).
   ii) Medium-term (longer than three months to one year).

Secondary outcomes

1. Recurrence (local recurrence, surgical wound recurrence (also called port-site metastasis in the laparoscopic group) or distal metastasis).
   i) Short-term recurrence (within six months).
   ii) Long-term recurrence (recurrence at maximal follow-up).

2. Adverse events (within three months). We will accept all adverse events reported by the study author irrespective of their severity.

3. Perioperative blood transfusion requirements (during surgery or within one week after surgery) (whole blood or red cell transfusion).

i) Proportion of people requiring blood transfusion.

ii) Quantity of blood transfusion.

4. Measures of earlier postoperative recovery.

i) Length of hospital stay (including the index admission for distal pancreatectomy and any surgical complication-related re-admissions).

ii) Time to return to normal activity (return to preoperative mobility with no additional carer support).

iii) Time to return to work (for people who were employed previously).

5. Positive resection margins (presence of macroscopic or microscopic cancer tissue at the plane of resection) at histopathological examination after surgery.

We based our choice of clinical outcomes (above) on the necessity to assess whether laparoscopic surgery results in adequate cancer clearance, is safe and is beneficial in terms of decreased blood transfusion requirements; earlier postoperative recovery, allowing earlier discharge from hospital, return to normal activity and return to work; and improvement in health-related quality of life. We highlighted that positive resection margins at histopathological examination after surgery represent a surrogate outcome, and we have included this to explore whether positive resection margins after surgery are responsible for any differences in survival or mortality.

We included studies that met the inclusion criteria irrespective of whether they reported our secondary outcomes.

Search methods for identification of studies

Electronic searches

We conducted a literature search to identify all published and unpublished RCTs and non-randomised studies and to identify potential studies in all languages. We translated non-English language papers and assessed them for potential inclusion in the review as necessary.

We searched the following electronic databases to identify potential studies.

1. The Cochrane Central Register of Controlled Trials (CENTRAL) (2015, Issue 6) (Appendix 1).

2. MEDLINE (1966 to June 2015) (Appendix 2).

3. EMBASE (1988 to June 2015) (Appendix 3).

4. Science Citation Index (1982 to June 2015) (Appendix 4).

We also conducted a search of ClinicalTrials.gov (ClinicalTrials.gov; Appendix 5) and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP; www.who.int/ictrp/en/; Appendix 6) on 20 June 2015.

Searching other resources

We checked the reference lists of all primary studies and review articles for additional references. We contacted authors of identified trials and asked them to identify other published and unpublished studies.

We searched PubMed for errata or retractions from eligible trials (www.ncbi.nlm.nih.gov/pubmed) on 14 December 2015.

Data collection and analysis

Selection of studies

Two review authors (D Riviere and K Gurusamy) independently screened titles and abstracts for inclusion of all potential studies identified as a result of the search and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We retrieved full-text study reports, and two review authors (D Riviere and K Gurusamy) independently screened these reports, identified studies for inclusion and identified and recorded reasons for exclusion of ineligible studies. We resolved disagreements through discussion and identified and excluded duplicates and collated multiple reports of the same study, so that each study, rather than each report, was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram and Characteristics of excluded studies table.

Data extraction and management

We used a standard data collection form that had been piloted on at least one study in the review to record study characteristics and outcome data. Two review authors (D Riviere and K Gurusamy) extracted study characteristics from included studies and detailed them in a Characteristics of included studies table. We extracted the following study characteristics.

1. Methods: study design, total study duration and run-in, number of study centres and locations, study settings, withdrawals, date of study.

2. Participants: number, mean age, age range, gender, American Society of Anesthesiologists (ASA) status (ASA 2014), inclusion criteria, exclusion criteria.

3. Interventions: intervention, comparison, concomitant interventions.

4. Outcomes: primary and secondary outcomes specified and collected, time points reported.

5. Notes: funding for trial, notable conflicts of interest of trial authors.

Two review authors (D Riviere and K Gurusamy) independently extracted outcome data from included studies. If outcomes were reported multiple times for the same time frame, for example, if short-term health-related quality of life was reported at six weeks and at three months, we chose the later time point (i.e. three months) for data extraction. For time-to-event outcomes for which data were censored, we extracted data to calculate the natural logarithm of the hazard ratio (HR) and its standard error using the methods suggested by Parmar et al. (Parmar 1998).

We included all randomised participants for medium-term and long-term outcomes (e.g. mortality, quality of life), and this will not be conditional upon short-term outcomes (e.g. being alive at three months, having a low or high quality-of-life index at three months).

We noted in the Characteristics of included studies table whether outcome data ware reported in an unuseable way. We resolved disagreements by consensus. One review author (D Riviere) copied data from the data collection form into Review Manager 5 (RevMan 2014). We double-checked that the data were entered correctly by comparing study reports versus how the data were presented in the systematic review.

Assessment of risk of bias in included studies

Two review authors (D Riviere and K Gurusamy) independently assessed risk of bias for each study. We planned to use the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). However, because randomised controlled trials on the topic were insufficient, we used relevant risk of bias domains from 'A Cochrane Risk Of Bias Assessment Tool: for Non-Randomized Studies of Interventions' (ACROBAT-NRSI) (Sterne 2014).

We assessed risk of bias according to the following domains.

1. Bias due to confounding.
2. Bias due to selection of participants.
3. Bias due to departure from intended intervention.
4. Bias in measurement of outcomes.
5. Bias due to missing data.
6. Bias in selection of reported findings.

We resolved disagreements by discussion.

We graded each potential source of bias as critical, serious, moderate, low or no information and provided a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We summarised risk of bias judgements across different studies for each of the domains listed. We considered blinding separately for different key outcomes when necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different from a participant-reported pain scale). When information on risk of bias relates to unpublished data or correspondence with a trialist, we noted this in the 'Risk of bias' table.

When considering treatment effects, we took into account the risk of bias for studies that contributed to each outcome.

Assessment of bias in conducting the systematic review

We conducted the review according to the published protocol and reported deviations from it in the Differences between protocol and review section of the systematic review.

Measures of treatment effect

We analysed dichotomous data as odds ratio (OR) and continuous data as mean difference (MD) when the outcome was reported or was converted to the same units in all trials (e.g. hospital stay). We planned to calculate standardised mean difference (SMD) when different scales were used for measuring the outcome (e.g. quality of life) and planned to ensure that higher scores for continuous outcomes have the same meaning for the particular outcome, explain the direction to the reader and report when the directions were reversed, if this was necessary. We planned to calculate the rate ratio (RaR) for outcomes such as adverse events and serious adverse events, when it was possible for the same person to develop more than one adverse event (or serious adverse event). If study authors had calculated the RaR of adverse events (or serious adverse events) in the intervention versus control based on Poisson regression, we planned to obtain the RaR by the Poisson regression method in preference to RaR calculated on the basis of the number of adverse events (or serious adverse events) that occurred during a certain period. We calculated the HR for time-to-event outcomes such as long-term mortality.

We undertook meta-analyses only when this was meaningful (i.e. when treatments, participants and the underlying clinical question were similar enough for pooling to make sense).

Trialists commonly indicate when they have skewed data by reporting medians and interquartile ranges. When we encountered this, we planned to note that the data were skewed by following the rough guide for identifying skewed distribution available in the *Cochrane Handbook for Systematic Reviews of Interventions* and considered the implication of this.

When multiple trial arms were reported in a single trial, we included only the relevant arms. If two comparisons (e.g. laparoscopic distal pancreatectomy method 1 vs open pancreatectomy, laparoscopic distal pancreatectomy method 2 vs open pancreatectomy) must be entered into the same meta-analysis, we planned to half the control group to avoid double-counting. The alternative way of including such trials with multiple arms is to pool the results of laparoscopic distal pancreatectomy method 1 and laparoscopic distal pancreatectomy method 2 and compare these with open pancreatectomy. We planned to perform a sensitivity analysis to determine whether results of the two methods of dealing with multi-arm trials led to different conclusions. However, we found no study with more than two arms that could be included in this review.

Unit of analysis issues

The unit of analysis was the individual participant undergoing distal pancreatectomy. As expected, we found no cluster-randomised trials for this comparison.

Dealing with missing data

We contacted investigators or study sponsors to verify key study characteristics and to obtain missing numerical outcome data when possible (e.g. when a study was identified as abstract only). If we were not able to obtain the information from investigators or study sponsors, we imputed mean from median (i.e. considered median as the mean) and calculated standard deviation from standard error, interquartile range or P value according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), but we assessed the impact of including such studies as indicated in a sensitivity analysis. Standard deviation could be calculated from P values; therefore, we did not impute standard deviation as the highest standard deviation in remaining trials included in the outcome.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identified substantial heterogeneity as per the *Cochrane Handbook for Systematic Reviews of Interventions* (> 50% to 60%; Higgins 2011), we planned to explore this through prespecified subgroup analysis).

Assessment of reporting biases

We attempted to contact study authors to ask them to provide missing outcome data. When this was not possible, and when missing data were thought to introduce serious bias, we planned to explore the impact of including such studies in the overall assessment of results by using a sensitivity analysis**.**

If we were able to pool more than 10 trials, we created and examined a funnel plot to explore possible publication biases. We used Egger's test to determine the statistical significance of the reporting bias (Egger 1997). We considered a P value less than 0.05 as statistically significant reporting bias.

Data synthesis

We performed analyses using Review Manager 5 (RevMan 2014). We calculated 95% confidence intervals for the treatment effect and used the Mantel-Haenszel method for dichotomous data, the inverse variance method for continuous data and generic inverse variance for time-to-event data. We planned to use the inverse variance method for count data. We used both fixed-effect (Demets 1987) and random-effects models (DerSimonian 1986) for the analysis. In case of discrepancy between the two models, we reported both results; otherwise, we reported only results from the fixed-effect model.

'Summary of findings' table

We created a 'Summary of findings' table by using all selected outcomes. We used the five GRADE (Grades of Recommendation, Assessment, Development and Evaluation Working Group) considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to studies that contributed data to the meta-analyses for prespecified outcomes. We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and GRADEpro software. We justified all decisions to downgrade or upgrade the quality of studies by using footnotes, and we made comments to aid the reader's understanding of the review when necessary. We considered whether any additional outcome information was provided that we were unable to incorporate into meta-analyses, and we planned to note this in the comments and state whether it supports or contradicts information derived from the meta-analyses.

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses.

1. People with different anaesthetic risk (ASA I (a healthy person) or II (a person with mild systemic disease) vs ASA III or greater (a person with severe systemic disease or worse)).
2. Different body mass index (BMI) (healthy weight (BMI 18.5 to 25) vs overweight or obese (BMI $\geq$ 25)).
3. Use of fibrin sealants versus no use of fibrin sealants.
4. Stapler closure versus suture closure of pancreatic stump.

We used all primary outcomes in the subgroup analyses.

We planned to use the formal Chi^2 test for subgroup differences to test for subgroup interactions.

Sensitivity analysis

We planned to perform sensitivity analysis defined a priori to assess the robustness of our conclusions by:

1. excluding trials at unclear or high risk of bias ($\geq$ 1 risk of bias domain (other than blinding of surgeon) classified as unclear or high);
2. excluding trials in which either mean or standard deviation or both are imputed;
3. excluding cluster RCTs in which adjusted effect estimates are not reported; and
4. using different methods of dealing with multi-arm trials (see Measures of treatment effect).

Reaching conclusions

We based our conclusions only on findings from the quantitative or narrative synthesis of studies included in this review. We avoided making recommendations for practice and believe that our implications for research will give the reader a clear sense of

where the focus of any future research in the area should be and will reveal remaining uncertainties.

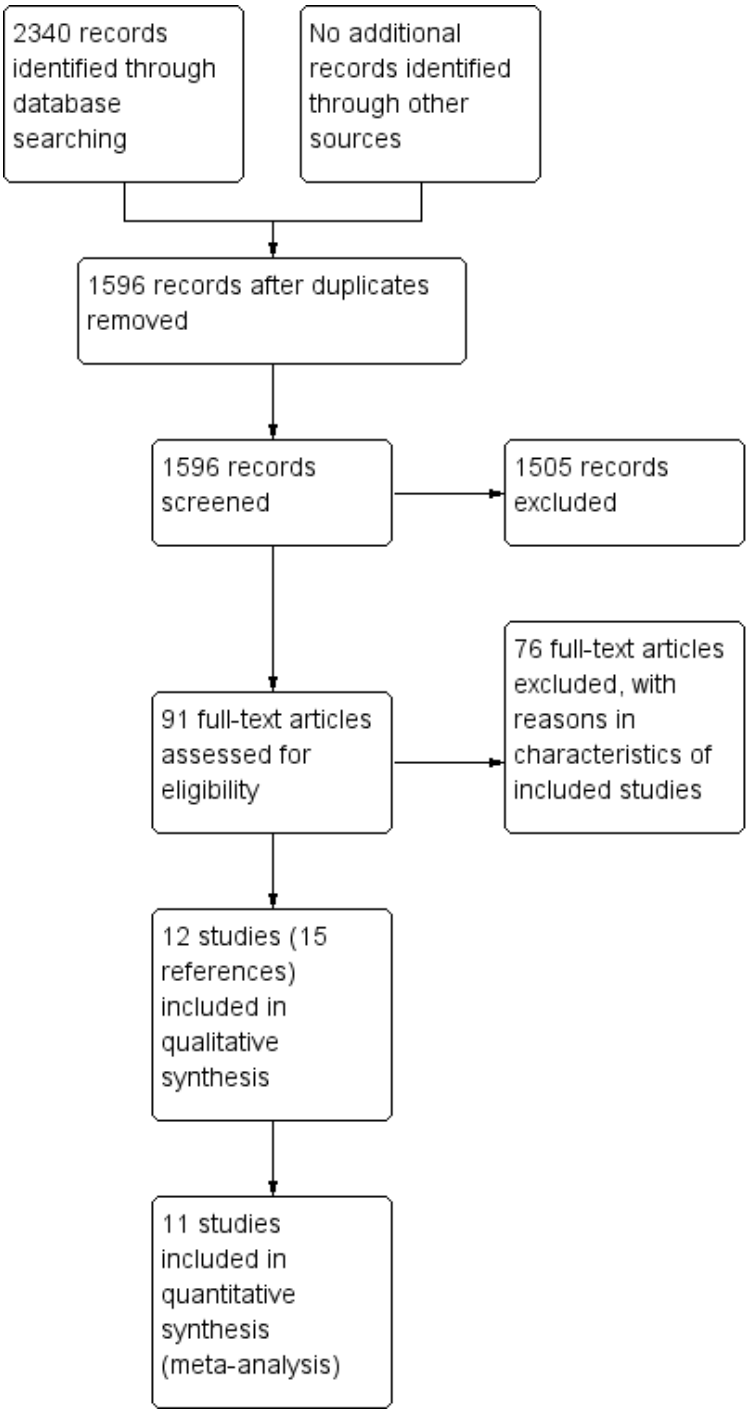
RESULTS

Description of studies

Results of the search

We identified 2340 references through electronic searches of *The Cochrane Library* (Wiley) (n = 1), MEDLINE (OvidSP) (n = 650), EMBASE (OvidSP) (n = 1382), Science Citation Index Expanded (n = 488), ClinicalTrials.gov (n = 2) and the World Health Organization (WHO) Trials Register (n = 7). After duplicate references were removed, 1596 references remained. We excluded 1505 clearly irrelevant references by reading the abstracts. We retrieved from the full publication a total of 91 references for further detailed assessment. We excluded 76 references (62 studies) for the reasons listed in the Characteristics of excluded studies table. Fifteen references reporting 12 non-randomised studies fulfilled the inclusion criteria (Characteristics of included studies). The reference flow is shown in Figure 1.

Figure 1. Study flow diagram.



Included studies

We included a total of 12 non-randomised studies (Braga 2015; Ceppa 2013; Dancea 2012; Hu 2014; Kooby 2010; Lee 2015; Rehman 2014; Sharpe 2015; Shin 2015; Stauffer 2015; Vijan 2010; Zhang 2014). All 12 were retrospective studies (Braga 2015; Ceppa 2013; Dancea 2012; Hu 2014; Kooby 2010; Lee 2015; Rehman 2014; Sharpe 2015; Shin 2015; Stauffer 2015; Vijan 2010; Zhang 2014). Nine studies were single institutional studies (Ceppa 2013; Dancea 2012; Hu 2014; Lee 2015; Rehman 2014; Shin 2015; Stauffer 2015; Vijan 2010; Zhang 2014). Two were multi-centre studies (Kooby 2010; Sharpe 2015). It was not clear whether one study was a single-centre or a multi-centre study (Braga 2015). Nine were cohort studies (Ceppa 2013; Dancea 2012; Hu 2014; Lee 2015; Rehman 2014; Sharpe 2015; Shin 2015; Stauffer 2015; Zhang 2014), and the remaining three were case-control studies (Braga 2015; Kooby 2010; Vijan 2010).

Only one study reported ASA status (Shin 2015). Most participants in this study belonged to ASA I and II. Only one participant with ASA IV was included in this study (Shin 2015). This study did not report outcome data separately by ASA status. None of the studies reported individuals with healthy weight versus overweight or obese participants. Fibrin sealant was not used routinely, or its use was not reported in any of the studies. Two studies routinely used stapler closure (Shin 2015; Zhang 2014). Information on stapler use was not available for the remaining studies.

Investigators in four studies used four ports to perform laparoscopic distal pancreatectomy (Hu 2014; Rehman 2014; Vijan 2010; Zhang 2014). Information on the number of ports was not available for the remaining studies. Four studies included participants who underwent distal pancreatectomy with or without splenectomy (Braga 2015; Hu 2014; Vijan 2010; Zhang 2014). The remaining studies did not state whether they included participants who underwent distal pancreatectomy with splenectomy. Two studies routinely placed one or more drains (Braga 2015; Hu 2014). One study reported selective drain use (Vijan 2010). Information on drain use was not available for the remaining studies.

The 12 studies included a total of 1593 participants. One study excluded 17 patients (metastatic disease (n = 12) and conversion to open procedure (n = 5)) (Shin 2015). After these 17 patients were excluded, a total of 1576 participants underwent laparoscopic distal pancreatectomy (n = 394) or open distal pancreatectomy (n = 1182). One study did not report any outcomes of interest for this review (Stauffer 2015). Upon exclusion of this study, a total of 1506 participants undergoing laparoscopic distal pancreatectomy (353 participants) or open distal pancreatectomy (1153 participants) contributed to one or more outcomes in this review. Mean or median age ranged from 50 years to 66 years in the five studies that reported this information (Hu 2014; Kooby 2010; Rehman 2014; Sharpe 2015; Shin 2015). The average proportion of females ranged from 36.7% to 72.7% in the four studies that reported this outcome (Hu 2014; Kooby 2010; Rehman 2014; Shin 2015).

The average follow-up period was one month in one study (Braga 2015). In another study, the follow-up period was 12 to 72 months (range) (Hu 2014). Information on the follow-up period was not available for the remaining studies.

Outcomes reported in these studies are summarised in Characteristics of included studies.

Data were available for the entire cohort of participants who underwent laparoscopic and open distal pancreatectomy and for those who underwent laparoscopic distal pancreatectomy versus matched controls of open distal pancreatectomy in one study (Kooby 2010). We used data from the matched control analysis because long-term mortality was available for this analysis only.

Excluded studies

We excluded 38 studies because separate data on patients with pancreatic cancer were not provided Abu Hilal 2012; Baker 2011; Baker 2013; Barrie 2014; Belli 2012; Cao 2014; Cheek 2014; Cho 2011; de Rooij 2015; DiNorcia 2010; Duran 2014; Durlik 2013; Ejaz 2014; Eom 2008; Ferrara 2014; Finan 2009; Fox 2012; Jayaraman 2010; Jeon 2014; Kang 2010; Kooby 2008; Lee 2014; Limongelli 2012; Magge 2013; Malde 2012; Matejak-Gorska 2013; Mehta 2012; Nakamura 2009; Pieretti-Vanmarcke 2014; Rooij 2014; Rosales-Velderrain 2012; Sherwinter 2012; Soh 2012; Stauffer 2013; Tseng 2011; Velanovich 2006; Zhao 2010; Zibari 2014). We excluded nine studies because they excluded patients with benign or premalignant disease (Butturini 2011; Casadei 2010; Chen 2012; Chung 2014; Gumbs 2008; Matsumoto 2008; Morikawa 2012; Sahay 2011; Slepavicius 2014). We excluded seven studies because the indication for surgery was not stated (Kausar 2010; Liao 2014; Newman 2010; Parikh 2015; Stauffer 2012; Vicente 2013; Yoon 2012). Two studies did not include open distal pancreatectomy as control (Daouadi 2011; Tang 2007). One study did not include distal pancreatectomy (Langan 2014). We excluded five studies because they were reviews or provided comments (Ahmed 2015; Limongelli 2014; Mehrabi 2015; Nigri 2011; Ricci 2015).

Risk of bias in included studies

Bias due to confounding

Risk of bias due to confounding was critical in five studies (Ceppa 2013; Lee 2015; Rehman 2014; Sharpe 2015; Shin 2015) because the open distal pancreatectomy group had more extensive cancer.

Risk of bias due to confounding was 'no information' for the seven remaining studies (Braga 2015; Dancea 2012; Hu 2014; Kooby 2010; Stauffer 2015; Vijan 2010; Zhang 2014). Although some studies reported no baseline differences between groups, these studies were not powered to measure baseline differences.

Bias due to selection of participants

In three studies, the decision to perform laparoscopic distal pancreatectomy or open distal pancreatectomy was based on surgeon preference (Ceppa 2013; Lee 2015; Rehman 2014). In two studies, the decision to perform laparoscopic distal pancreatectomy or open distal pancreatectomy was based on participant preference (Hu 2014; Shin 2015). One study excluded patients who underwent conversion to open surgery despite meeting inclusion criteria (Shin 2015). This study was considered to be at critical risk of bias related to selection of participants. Risk of bias was 'no information' for the remaining four of the five studies for which decisions to perform laparoscopic distal pancreatectomy or open distal pancreatectomy were based on surgeon or participant preference (Ceppa 2013; Hu 2014; Lee 2015; Rehman 2014). The criteria used to perform laparoscopic or open distal pancreatectomy were not stated in the remaining studies (Braga 2015; Dancea 2012; Kooby 2010; Sharpe 2015; Stauffer 2015; Vijan 2010; Zhang 2014), so risk of bias remains 'no information' in these studies.

Bias due to departures from intended intervention

Three studies were at moderate risk of bias; study authors replied that no differences were noted in postoperative management of participants (Ceppa 2013; Kooby 2010; Lee 2015). None of the remaining studies reported whether participant care other than laparoscopic or open procedure was identical in the two groups. These studies were classified as 'no information'.

Bias in measurement of outcomes

Three study authors replied that outcome assessors were not blinded (Ceppa 2013; Kooby 2010; Lee 2015). This might have introduced bias in measurement of outcomes other than mortality. So we classified these studies as 'no information'. Risk of bias was classified as 'no information' for the remaining studies because information on outcome assessor blinding was not reported.

Bias due to missing data

Two studies were at low risk of bias; all eligible participants were included in the study (Ceppa 2013), and a clear participant flow indicated that all participants who underwent laparoscopic or open distal pancreatectomy were included (Hu 2014). Two studies were at critical risk of bias because participants who underwent conversion to open surgery were excluded despite meeting inclusion criteria (Shin 2015), or because some participants in the open group were not matched for the laparoscopic group (Kooby 2010). It was not clear whether any participants were excluded from analysis in the remaining studies. Therefore, we classified these studies as 'no information'.

Bias in selection of reported findings

Four studies reported mortality and morbidity adequately and can be considered at low risk of bias for selective outcome reporting (Ceppa 2013; Hu 2014; Rehman 2014; Shin 2015). The remaining studies were considered to be at serious or critical risk of bias depending upon whether they did not report morbidity alone, or whether they did not report both mortality and morbidity, because one would expect that studies comparing laparoscopic distal pancreatectomy versus open distal pancreatectomy would report data on mortality and morbidity in a detailed manner.

Effects of interventions

See: **Summary of findings for the main comparison** Laparoscopic distal pancreatectomy compared with open distal pancreatectomy for pancreatic cancer; **Summary of findings 2** Laparoscopic distal pancreatectomy compared with open distal pancreatectomy for pancreatic cancer

The effect of intervention is summarised in Summary of findings for the main comparison and Summary of findings 2.

Mortality

Nine studies reported short-term mortality (perioperative mortality) (Braga 2015; Ceppa 2013; Hu 2014; Kooby 2010; Lee 2015; Rehman 2014; Sharpe 2015; Shin 2015; Zhang 2014). Investigators reported no statistically significant differences in short-term mortality between the two groups (laparoscopic group: 1/329 (adjusted proportion based on meta-analysis estimate: 0.5%) vs open group: 11/1122 (1%); OR 0.48, 95% CI 0.11 to 2.17; 1451 participants; nine studies; I^2 = 0%) (Analysis 1.1). A random-effects meta-analysis revealed no change in results.

Three studies reported long-term mortality (Hu 2014; Kooby 2010; Shin 2015). Three-year mortality was between 44% and 75% in these studies (Hu 2014; Kooby 2010; Shin 2015). Researchers noted no statistically significant differences in long-term mortality between the two groups (HR 0.96, 95% CI 0.82 to 1.12; 277 participants; three studies; I^2 = 0%) (Analysis 1.2). A random-effects meta-analysis revealed no change in results.

Serious adverse events

Three studies reported the proportions of participants with serious adverse events (Hu 2014; Rehman 2014; Shin 2015). One

study reported no serious adverse events (Hu 2014). Serious adverse events in the other studies included complications that required radiological or surgical re-intervention and grade III pancreatic fistula (Rehman 2014; Shin 2015). Investigators reported no statistically significant differences in the proportions of people with serious adverse events between the laparoscopic group (7/89: adjusted proportion: 8.8%) and the open group (6/117: 5.1%) (OR 1.79, 95% CI 0.53 to 6.06; 206 participants; three studies; I^2 = 0%) (Analysis 1.3). A random-effects meta-analysis revealed no change in results.

Pancreatic fistula

Four studies reported the proportions of participants with clinically significant pancreatic fistula (grade B or C) (Ceppa 2013; Hu 2014; Rehman 2014; Shin 2015). Researchers noted no statistically significant differences in the proportions of people with pancreatic fistula between the laparoscopic group (9/109: adjusted proportion: 7.7%) and the open group (9/137: 6.6%) (OR 1.19, 95% CI 0.47 to 3.02; 246 participants; four studies; I^2 = 61%) (Analysis 1.4). The I^2 statistic and visual inspection of forest plots provided evidence of heterogeneity, i.e. lack of overlap of confidence intervals. However, the Chi^2 test for heterogeneity was not statistically significant (P value = 0.08). A random-effects meta-analysis revealed no change in results.

Quality of life

None of the studies reported quality of life at any point in time.

Recurrence

None of the studies reported recurrence within six months. Two studies reported recurrence at maximal follow-up (Hu 2014; Shin 2015). In one study, two participants (18%) in the laparoscopic group versus 11 participants (48%) in the open group had recurrence at maximal follow-up of 12 to 72 months (Hu 2014). In another study, 35 participants (49%) in the laparoscopic group versus 48 participants (60%) in the open group had recurrence at maximal follow-up (follow-up period not stated) (Shin 2015). Details were insufficient to permit calculation of the hazard ratio for recurrence. So we calculated the odds ratio of recurrence at maximal follow-up. Results showed no statistically significant differences between groups (laparoscopic group: 37/81 (adjusted proportion based on meta-analysis estimate: 36.3%) vs open group: 59/103 (49.5%); OR 0.58, 95% CI 0.32 to 1.05; 184 participants; two studies; I^2 = 13%) (Analysis 1.5). A random-effects meta-analysis revealed no change in results.

Adverse events

Four studies reported the proportions of participants with adverse events of any severity (Ceppa 2013; Hu 2014; Rehman 2014; Shin 2015). Researchers reported no statistically significant differences in the proportions of people with adverse events between the laparoscopic group (33/109: adjusted proportion: 31.7%) and the open group (45/137: 32.8%) (OR 0.95, 95% CI 0.54 to 1.66; 246 participants; four studies; I^2 = 18%) (Analysis 1.6). A random-effects meta-analysis revealed no change in results.

Measures of earlier postoperative recovery

Five studies reported length of hospital stay (Hu 2014; Kooby 2010; Rehman 2014; Sharpe 2015; Shin 2015). The median of mean lengths of hospital stay in these studies was 9.4 days in the open distal pancreatectomy group. Mean length of hospital stay was statistically significantly shorter in the laparoscopic group than in the open group (MD -2.43 days, 95% CI -3.13 to -1.73; 1068 participants; five studies; I^2 = 0%) (Analysis 1.7). We imputed mean and SD from median and P value for length of hospital stay for two studies (Rehman 2014; Shin 2015). No change in results occurred when we excluded these two studies (MD -2.25 days, 95% CI -3.03 to -1.47; 896 participants; three studies; I^2 = 0%) (Analysis 3.1). A random-effects meta-analysis revealed no change in results.

No studies reported any of the other measures of earlier postoperative recovery such as return to normal activity and return to work.

Blood transfusion requirements

None of the studies reported blood transfusion requirements.

Positive resection margins

Ten studies reported the proportions of participants with positive resection margins (Braga 2015; Dancea 2012; Hu 2014; Kooby 2010; Lee 2015; Rehman 2014; Sharpe 2015; Shin 2015; Vijan 2010; Zhang 2014). The fixed-effect model revealed a statistically significantly lower proportion of people with positive resection margins between the two groups (laparoscopic group: 49/333 (adjusted proportion: 14.3%) vs open group: 208/1133 (18.4%); OR 0.69, 95% CI 0.48 to 1.00; 1466 participants; 10 studies; I^2 = 6%) (Analysis 1.8). The random-effects model revealed no statistically significant differences between groups in the proportions of people with positive resection margins (OR 0.74, 95% CI 0.49 to 1.10).

Assessment of reporting biases

We assessed reporting bias only for the positive resections margin because this was the only outcome included in 10 trials. We found no evidence of reporting bias upon visualisation of the funnel plot and completion of Egger's test (P value = 0.9798).

Subgroup analysis

Stapler closure

Stapler closure was standard procedure in two studies (Shin 2015; Zhang 2014). The remaining studies did not report whether stapler closure was performed or did not report outcome data separately for stapler closure. We found no change in the results of short-term mortality, long-term mortality, proportions of people with serious adverse events or clinically significant pancreatic fistula in this subgroup as compared with the main analysis (Analysis 2.1; Analysis 2.2; Analysis 2.3; Analysis 2.4).

We examined no other subgroups. So we were not able to use the formal Chi^2 test for differences in subgroup interactions.

Other subgroup analyses

We were not able to perform subgroup analyses of different anaesthetic risks or weights or fibrin sealants because the studies did not report this information or did not report outcome data separately for different categories.

Sensitivity analysis

We performed no other planned sensitivity analysis other than exclusion of studies in which standard deviation was calculated from the P value because no studies were at low risk of bias and we identified no cluster RCTs.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Laparoscopic distal pancreatectomy compared with open distal pancreatectomy for pancreatic cancer

Patient or population: patients with pancreatic cancer
Settings: secondary or tertiary care centre
Intervention: laparoscopic distal pancreatectomy
Comparison: open distal pancreatectomy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Open distal pancreatectomy	Laparoscopic distal pancreatectomy			
Recurrence at maximal follow-up	**495 per 1000**	**363 per 1000** (239 to 507)	**OR 0.58** (0.32 to 1.05)	184 (2 studies)	⊕◯◯◯ **Very low**[a,b,c]
Adverse events (proportion)	**328 per 1000**	**317 per 1000** (209 to 448)	**OR 0.95** (0.54 to 1.66)	246 (4 studies)	⊕◯◯◯ **Very low**[a,b,c]
Length of hospital stay	Mean length of hospital stay in the control groups was **9.4 days**	Mean length of hospital stay in the intervention groups was **2.43 lower** (3.13 to 1.73 lower)		1068 (5 studies)	⊕◯◯◯ **Very low**[a]
Positive resection margins	**184 per 1000**	**143 per 1000** (99 to 198)	**OR 0.74** (0.49 to 1.10)	1466 (10 studies)	⊕◯◯◯ **Very low**[a,b]

None of the studies reported perioperative transfusion requirements, time to return to normal activity or time to return to work

*The basis for the **assumed risk** is the mean control group proportion. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)
CI: confidence interval; **OR:** odds ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: We are very uncertain about the estimate

[a] We found no randomised controlled trials. The non-randomised studies included in this review were at unclear or high risk of bias for most domains
[b] Confidence intervals were wide
[c] Sample size was small

DISCUSSION

Summary of main results

In this systematic review, we compared the benefits and harms of laparoscopic versus open distal pancreatectomy. We found no randomised controlled trials (RCTs) on this topic. We included in this review 12 observational studies that compared laparoscopic versus open distal pancreatectomy; 11 studies (1506 participants: 394 underwent laparoscopic distal pancreatectomy and 1182 open distal pancreatectomy) provided information for one or more outcomes. People with less extensive cancer underwent laparoscopic distal pancreatectomy, and those with more extensive cancer underwent open distal pancreatectomy in some studies (Ceppa 2013; Rehman 2014; Sharpe 2015). We found no statistically significant differences between laparoscopic and open distal pancreatectomy in terms of short-term mortality, long-term mortality, proportions of participants with serious adverse events, pancreatic fistula (grade B or C), recurrence at maximal follow-up, proportions of participants with any adverse events and proportions of people with positive resection margins. None of the studies reported quality of life, short-term recurrence, proportions of participants requiring blood transfusion, time to return to normal activity (return to preoperative mobility with no additional carer support) or time to return to work. Mean length of hospital stay was 2.4 days shorter in the laparoscopic distal pancreatectomy group than in the open distal pancreatectomy group. For other surgeries, laparoscopic procedures have been shown to be advantageous over open procedures in terms of fewer complications, shorter hospital stay or both (Bijen 2009; Keus 2006; Reza 2006; Walsh 2009). So the reduction in hospital stay may be due to quicker postoperative recovery resulting from the minimally invasive nature of laparoscopic surgery. It may also be due to bias to confounding, as people with less extensive cancer received laparoscopic distal pancreatectomy and those with more extensive cancer underwent open distal pancreatectomy. Differences in length of hospital stay are important only if laparoscopic distal pancreatectomy provides equivalent cancer clearance as open distal pancreatectomy. Although the confidence intervals were relatively narrow for long-term mortality, it is not possible to conclude that laparoscopic distal pancreatectomy provides cancer clearance equivalent to that of open distal pancreatectomy because of bias due to confounding, as discussed in the Quality of the evidence section. In addition to bias, the relatively small sample size for most outcomes makes study findings unreliable on the basis of random error.

Overall completeness and applicability of evidence

The studies included in this review examined ductal adenocarcinoma of the distal pancreas and different stages (I to III) of pancreatic cancer. Hence, the findings of this review are applicable only to distal pancreatic ductal adenocarcinomas that are amenable to potentially curative surgery. One study clearly mentioned that investigators included participants classified as American Society of Anesthesiologists (ASA) stage I to IV (Shin 2015). Remaining studies did not state the ASA status of participants. In any case, all included studies examined only participants who could withstand major surgery. Hence, the findings of this review are applicable only to patients who can withstand major surgery.

Quality of the evidence

The overall quality of evidence was very low. Major reasons for this were that the studies were observational; consequently, the risk of confounding bias was unclear or high. Studies did not report baseline differences for all confounding factors, and the sample size was not sufficient to reveal differences in confounding factors. Even if the sample size was large and all confounding factors were reported, one cannot rule out the problem of residual confounding. It is not clear whether this would have introduced bias into the results.

In three studies, the decision to perform laparoscopic distal pancreatectomy or open distal pancreatectomy was based on surgeon preference (Ceppa 2013; Lee 2015; Rehman 2014). In two studies, the decision to perform laparoscopic distal pancreatectomy or open distal pancreatectomy was based on participant preference (Hu 2014; Shin 2015). Surgeon preference could be the result of the surgeon's experience with either technique, which one study author reported in the reply (Lee 2015). Also, it is quite possible that participants with less extensive cancer were operated laparoscopically or were given the choice between laparoscopic and open distal pancreatectomy, and those with more extensive cancer were operated by open surgery. Open distal pancreatectomy was associated with greater tumour size, lymph node sampling and the presence of lymph node metastasis in one study (Ceppa 2013). In another study, participants with large tumours (> 10 cm) considered difficult to mobilise laparoscopically were reserved for open resections (Rehman 2014). In a third study, more participants in the open group received neoadjuvant chemotherapy or radiation and had larger tumours (Sharpe 2015). All of these factors are associated with more advanced disease. This suggests that participants with more advanced disease had open distal pancreatectomy and those with less advanced disease underwent laparoscopic distal pancreatectomy.

Unless RCTs ensure that the same types of participants receive laparoscopic and open distal pancreatectomy, one cannot present reliable conclusions on the safety and effectiveness of laparoscopic versus open distal pancreatectomy because of residual confounding. In terms of other types of bias, many outcomes were subjective, and the retrospective nature of most of the studies means that blinding of outcome assessors is extremely unlikely, even though we have classified this risk as unclear because such information was not provided in the study reports. This may also introduce

bias. Complications were not reported adequately in most studies, leading to selective outcome reporting bias.
Another factor that decreased the quality of evidence was the small sample size resulting in wide confidence intervals for many outcomes. Future studies should be adequately powered to measure differences in clinically important outcomes. Heterogeneity was not significant in the effect estimates for most outcomes despite differences in study design.

Potential biases in the review process

We planned to include only RCTs in this review. However, in the absence of any RCTs, we have reported the best available evidence on this topic. We removed the RCT filter to ensure that observational studies were not removed by electronic filters. Two review authors independently selected studies with no language restrictions and extracted data, decreasing potential errors in study selection and data extraction. However, this is a systematic review of non-randomised studies. Mandatory registration was not required; therefore, studies showing that laparoscopic distal pancreatectomy had poorer results than open distal pancreatectomy may not have been submitted to the journals by study authors because laparoscopic distal pancreatectomy is a new procedure compared with the established treatment of open distal pancreatectomy. So we cannot rule out publication bias.
We imputed mean and calculated standard deviation from median and P values for length of hospital stay in two studies (Rehman 2014; Shin 2015). Exclusion of these two studies did not alter effect estimates for length of hospital stay, suggesting that this imputation of mean and calculation of standard deviation are unlikely to result in bias. We calculated the hazard ratio for long-term mortality using methods suggested by Parmar et al (Parmar 1998), which assume constant proportional hazards. Kaplan-Meier curves in these studies indicated that proportional hazards appeared constant.

Agreements and disagreements with other studies or reviews

This is the first systematic review on laparoscopic distal pancreatectomy versus open distal pancreatectomy with specific reference to pancreatic cancer. Seven study authors concluded that laparoscopic distal pancreatectomy is a safe and feasible surgical modality (Ceppa 2013; Hu 2014; Lee 2015; Rehman 2014; Sharpe 2015; Shin 2015; Zhang 2014). Four study authors suggested that laparoscopic distal pancreatectomy offers equivalent oncological outcomes (Hu 2014; Lee 2015; Rehman 2014; Sharpe 2015). Despite the statement made by one of the study authors that a randomised controlled trial comparing cancer outcomes for laparoscopic and open distal pancreatectomy for pancreatic ductal adenocarcinoma is likely to fail because of the small target patient population that would satisfy the criteria for enrolment (Kooby 2010), we agree with three study authors that a randomised controlled trial is necessary to assess the role of laparoscopic surgery in the treatment of people undergoing distal pancreatectomy (Ceppa 2013; Hu 2014; Rehman 2014).

AUTHORS' CONCLUSIONS

Implications for practice

Currently, no randomised controlled trials have compared laparoscopic distal pancreatectomy versus open distal pancreatectomy for patients with pancreatic cancer. In observational studies, laparoscopic distal pancreatectomy is associated with shorter hospital stay as compared with open distal pancreatectomy. However, this association is unlikely to be causal. Currently no available information has revealed a causal association in the differences between laparoscopic versus open distal pancreatectomy.

Implications for research

Future studies should try to address as many issues mentioned below as possible. The rationale for the study design is mentioned alongside.

Study design: randomised controlled trial (only a randomised controlled trial can establish a causal association in this situation).

Participants: people with potentially resectable distal pancreatic cancer (stages I and II adenocarcinoma of the pancreas) fit to undergo major surgery. Alternatively, people undergoing distal pancreatectomy for benign or malignant pancreatic disease but stratified according to benign or malignant pancreatic lesions.

Intervention: laparoscopic distal pancreatectomy.

Control: open distal pancreatectomy.

Outcomes: important patient-oriented measures such as short-term mortality and long-term mortality (at least two to three years), health-related quality of life, complications and the sequelae of complications, resection margins, measures of earlier postoperative recovery such as length of hospital stay, time to return to normal activity and time to return to work (for those who are employed) and recurrence of cancer. In addition, information on resource use can be collected if the purpose was cost-effectiveness in addition to effectiveness.

Two to three years of follow-up has been suggested because three-year mortality was between 44% and 75% in these studies (Hu 2014; Kooby 2010; Shin 2015) .

Other aspects of study design:

- observer-blinded randomised controlled trial: to control for selection bias and detection bias;
- identical care apart from laparoscopic versus open distal pancreatectomy: to control for performance bias; and
- inclusion of all participants in the analysis and performance of an intention-to-treat analysis: to control for attrition bias.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Braga 2015

Methods	Study design: case-control study with propensity score matching
Participants	Country: Italy Number eligible: 64 Number excluded: not stated Number analysed: 64 Average age: not stated Females: not stated ASA I or II: not stated ASA III or IV: not stated Stapler closure: not stated Fibrin sealant: not stated Mean BMI: not stated Study setting: not clear Period of recruitment: 2010 to 2013 Follow-up in months: 1 **Inclusion criteria** Patients with pancreatic cancer (adenocarcinoma) undergoing distal pancreatectomy Note: The study included patients without pancreatic adenocarcinoma who were excluded from the analysis **Exclusion criteria** 1. Borderline resectable cancer 2. Cardiovascular dysfunction 3. Respiratory dysfunction 4. BMI > 35 5. Refusal to consent to laparoscopy
Interventions	Group 1: laparoscopic distal pancreatectomy (n = 30) Further details: number of ports: not stated; with or without splenectomy; 1 drain placed routinely Group 2: open distal pancreatectomy (n = 34) Further details: not stated
Outcomes	Outcomes reported were mortality and resection margins
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Bias due to confounding	Unclear risk	**No information** Comment: Study authors used propensity score matching for matching laparoscopic

Braga 2015 (*Continued*)

		and open groups. Although the presence of malignancy was considered a factor in the matching, the size of the tumour and involvement of adjacent structures were not considered in the matching
Bias due to selection of participants to intervention and control	Unclear risk	**No information** Comment: It was not clear whether eligible patients were excluded from the report
Bias due to differences in co-interventions which were different between the groups	Unclear risk	**No information** Comment: This information was not available
Bias in the measurement of outcomes	Unclear risk	**No information** Comment: This information was not available
Bias due to missing data	Unclear risk	**No information** Comment: This information was not available
Bias in selection of the reported findings	High risk	**Serious risk of bias** Comment: Complications were not reported in participants with pancreatic cancer

Ceppa 2013

Methods	Study design: retrospective cohort study
Participants	Country: USA Number eligible: 40 Number excluded: not stated Number analysed: 40 Average age: not stated Females: not stated ASA I or II: not stated ASA III or IV: not stated Stapler closure: not stated Fibrin sealant: not stated Mean BMI: not stated Study setting: single centre; Indiana University School of Medicine, Indianapolis, USA Period of recruitment: 2005 to 2012 Follow-up in months: not stated **Inclusion criteria** Patients with pancreatic adenocarcinoma undergoing distal pancreatectomy

Ceppa 2013 (*Continued*)

Interventions	Group 1: laparoscopic distal pancreatectomy (n = 20) Further details: not stated Group 2: open distal pancreatectomy (n = 20) Further details: not stated The choice of laparoscopic vs open method was based on surgeon preference	
Outcomes	Outcomes reported were short-term mortality and complications	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Bias due to confounding	High risk	**Critical risk of bias** Quote: "Open DP was associated with greater tumor size (4.3 +/- 0.4 cm vs. 2.9 +/- 0.3 cm), lymph node sampling (18 +/- 2 vs. 13 +/- 2) and presence of lymph node metastasis (80% vs. 25%)" Comment: Participants undergoing open distal pancreatectomy had more extensive cancer
Bias due to selection of participants to intervention and control	Low risk	**Moderate risk of bias** Comment: All eligible participants were included
Bias due to differences in co-interventions which were different between the groups	Low risk	**Moderate risk of bias** Quote: "The postoperative care for these patients was and is identical. So no differences in how the patients are managed postoperatively (author replies)"
Bias in the measurement of outcomes	High risk	**Critical risk of bias** Quote: "the assessors were not blinded (author replies)"
Bias due to missing data	Low risk	**Low risk of bias** Comment: Participants with pancreatic cancer who underwent distal pancreatectomy were not excluded from the analysis (author replies)
Bias in selection of the reported findings	Low risk	**Low risk of bias** Comment: Mortality and complications were reported

Dancea 2012

Methods	Study design: retrospective cohort study
Participants	Country: USA Number eligible: 14 Number excluded: not stated Number analysed: 14 Average age: not stated Females: not stated ASA I or II: not stated ASA III or IV: not stated Stapler closure: not stated Fibrin sealant: not stated Mean BMI: not stated Study setting: single centre; Geisinger Medical Center, Danville, USA Period of recruitment: 1999 to 2011 Follow-up in months: not stated **Inclusion criteria** Patients with pancreatic malignancy undergoing distal pancreatectomy Notes: The study included patients without pancreatic malignancy who were excluded from the analysis
Interventions	Group 1: laparoscopic distal pancreatectomy (n = 4) Further details: not stated Group 2: open distal pancreatectomy (n = 10) Further details: not stated
Outcomes	The outcome reported was resection margins
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Bias due to confounding	Unclear risk	**No information** Comment: This information was not available
Bias due to selection of participants to intervention and control	Unclear risk	**No information** Comment: It was not clear whether eligible participants were excluded from the report
Bias due to differences in co-interventions which were different between the groups	Unclear risk	**No information** Comment: This information was not available
Bias in the measurement of outcomes	Unclear risk	**No information** Comment: This information was not available

Dancea 2012 (*Continued*)

Bias due to missing data	Unclear risk	**No information** Comment: This information was not available
Bias in selection of the reported findings	High risk	**Critical risk of bias** Comment: Mortality and complications were not reported

Hu 2014

Methods	Study design: retrospective cohort study
Participants	Country: China Number eligible: 34 Number excluded: not stated Number analysed: 34 Average age: 50 years Females: 14 (41.2%) ASA I or II: not stated ASA III or IV: not stated Stapler closure: not stated Fibrin sealant: not stated Mean BMI: not stated Study setting: single centre; The General Hospital of Chinese People's Liberation Army, Beijing, China Period of recruitment: 2007 to 2011 Follow-up in months: 12 to 72 (range) **Inclusion criteria** 1. Patients with resectable distal pancreatic cancer undergoing distal pancreatectomy 2. Tumour size < 4 cm **Exclusion criteria** 1. Involvement of the superior mesenteric artery 2. Requirement for an extended resection 3. Previous history of upper abdominal surgery 4. Serious cardiopulmonary or hepatorenal insufficiency
Interventions	Group 1: laparoscopic distal pancreatectomy (n = 11) Further details: 4 ports; with or without splenectomy; 2 drains were placed Group 2: open distal pancreatectomy (n = 23) Further details: not stated The choice of laparoscopic or open method was made at the sole discretion of the participant
Outcomes	Outcomes reported were short-term and long-term mortality, complications, operating time, length of hospital stay, recurrence at maximal follow-up
Notes	Adjuvant treatment: Two-cycle gemcitabine was given 1 month after distal pancreatectomy

Hu 2014 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Bias due to confounding	Unclear risk	**No information** Quote: "The choice of either technique was at the sole discretion of the patient..... The two groups were comparable in terms of age, sex, body mass index, American Society of Anesthesiology classification, Eastern Cooperative Oncology Group grading, tumor size, location and staging, CA 19-9 levels, previous history of abdominal surgery, and concomitant medical/surgical conditions (all P[0.05))" Comment: The sample size was small and was not powered to identify baseline differences between groups
Bias due to selection of participants to intervention and control	Unclear risk	**Moderate risk of bias** Comment: All eligible participants were included
Bias due to differences in co-interventions which were different between the groups	Unclear risk	**No information** Comment: This information was not available
Bias in the measurement of outcomes	Unclear risk	**No information** Comment: This information was not available
Bias due to missing data	Low risk	**Low risk of bias** Comment: A clear participant flow indicated that all participants who underwent laparoscopic or open distal pancreatectomy were included
Bias in selection of the reported findings	Low risk	**Low risk of bias** Comment: Mortality and complications were reported

Kooby 2010

Methods	Study design: retrospective case-control study
Participants	Country: USA Number eligible: 93 Number excluded: not stated

	Number analysed: 93 Average age: 65 years Females: 55 (59.1%) ASA I or II: not stated ASA III or IV: not stated Stapler closure: not stated Fibrin sealant: not stated Mean BMI: 26 (28%) Study setting: multi-centre USA; USA Period of recruitment: 2000 to 2008 Follow-up in months: not stated **Inclusion criteria** Patients undergoing distal pancreatectomy for pancreatic cancer **Exclusion criteria** 1. Adenocarcinoma with a background of intraductal papillary mucinous neoplasm or mucinous cystadenocarcinoma 2. Insufficient demographic, operative and outcomes data available for analysis and reporting
Interventions	Group 1: laparoscopic distal pancreatectomy (n = 23) Further details: not stated Group 2: open distal pancreatectomy (n = 70) Further details: not stated Of 23 participants who underwent laparoscopic distal pancreatectomy, 4 underwent hand access procedures and another 4 procedures had to be converted to open procedures
Outcomes	Outcomes reported were long-term mortality, operating time, length of hospital stay and positive margins
Notes	Adjuvant therapy (use of preoperative or postoperative chemotherapy with or without radiation therapy): laparoscopic distal pancreatectomy (n = 13), open distal pancreatectomy (n = 45)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Bias due to confounding	Unclear risk	**No information** Quote: "Three factors were used to select patients for the matched cohort comparison: age (years), ASA status (1 to 4), and tumor size (cm)". "We excluded patients who needed vascular resection and other organ resections (author replies)" Comment: Tumours were not matched for all known confounding factors, for example, lymph node status, body mass index

Kooby 2010 (*Continued*)

Bias due to selection of participants to intervention and control	Unclear risk	**No information** Comment: We were not able to assess this information because control participants were excluded because they did not match intervention participants
Bias due to differences in co-interventions which were different between the groups	Low risk	**Moderate risk of bias** Quote: "No difference in the care between patients apart from laparoscopic or open approach (author replies)"
Bias in the measurement of outcomes	High risk	**Critical risk of bias** Outcome assessors were not blinded Quote: "..this was a retrospective study (author replies)"
Bias due to missing data	High risk	**Critical risk of bias** Comment: Several participants were excluded because complete data were not available, and because some participants in the open group were not matched for the laparoscopic group
Bias in selection of the reported findings	High risk	**Critical risk of bias** Comment: Short-term mortality and complications were not reported

Lee 2015

Methods	Study design: retrospective cohort study
Participants	Country: USA Number eligible: 268 Number excluded: not stated Number analysed: 268 Average age: not stated Females: not stated ASA I or II: not stated ASA III or IV: not stated Stapler closure: not stated Fibrin sealant: not stated Mean BMI: not stated Study setting: single centre; Memorial Sloan Kettering Cancer Center, New York, USA Period of recruitment: 2000 to 2013 Follow-up in months: not stated **Inclusion criteria** Patients with pancreatic malignancy undergoing distal pancreatectomy

	Notes: The study included patients without pancreatic malignancy who were excluded from the analysis **Exclusion criteria** Patients with additional organ resection
Interventions	Group 1: laparoscopic distal pancreatectomy (n = 19) Further details: not stated Group 2: open distal pancreatectomy (n = 249) Further details: not stated
Outcomes	The outcome reported was resection margins
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Bias due to confounding	High risk	**Critical risk of bias** Quote: "Selection was purely by individual surgeon. Some us do more MIS, some do more open. In the MIS group some of us do robotics and some laparoscopy. The only exclusion criteria is portal vein involvement - none of us will do a case minimally invasive if we think this may be what we find (author replies)" Comment: It appears that the cancer involvement of adjacent tissues was greater in the open group than in the laparoscopic group
Bias due to selection of participants to intervention and control	Unclear risk	**No information** Comment: It was not clear whether eligible participants were excluded from the report
Bias due to differences in co-interventions which were different between the groups	Low risk	**Moderate risk of bias** Quote: "No other difference in the care - they all follow the same general pathways (author replies)"
Bias in the measurement of outcomes	High risk	**Critical risk of bias** Quote: "Complications are filled into our database prospectively, so no one is blinded (author replies)"
Bias due to missing data	Unclear risk	**No information** Comment: This information was not available

Bias in selection of the reported findings	High risk	**Serious risk of bias** Comment: Complications were not reported

Rehman 2014

Methods	Study design: retrospective cohort study
Participants	Country: UK Number eligible: 22 Number excluded: not stated Number analysed: 22 Average age: 64 years Females: 16 (72.7%) ASA I or II: not stated ASA III or IV: not stated Stapler closure: not stated Fibrin sealant: not stated Mean BMI: not stated Study setting: single centre; Freeman Hospital, Newcastle upon Tyne, UK Period of recruitment: 2008 to 2011 (another report with a larger number of participants was included for resection margins and operating time; the period of recruitment was 2005 to 2012) Follow-up in months: not stated **Inclusion criteria** Patients undergoing distal pancreatectomy for pancreatic adenocarcinoma **Exclusion criteria** Patients with > 10 cm tumour were excluded in laparoscopic group and underwent open distal pancreatectomy
Interventions	Group 1: laparoscopic distal pancreatectomy (n = 8) Further details: 4 ports; splenectomy: not stated; drains: not stated Group 2: open distal pancreatectomy (n = 14) Further details: not stated The choice of laparoscopic versus open method was based on the surgeon who operated on the participant
Outcomes	Outcomes reported were short-term mortality, complications, operating time, positive resection margins and length of hospital stay
Notes	Additionally 5 participants in the laparoscopic distal pancreatectomy group and 8 in the open distal pancreatectomy group received adjuvant chemotherapy Significant overlap of participants was noted between the Rehman 2014 reference and the Rehman 2013 reference. We have obtained information from the Rehman 2014 reference in full text; the Rehman 2013 reference was a conference abstract

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Rehman 2014 (*Continued*)

Bias due to confounding	High risk	**Critical risk of bias** Quote: "In general patients with large tumours (> 10 cm) considered difficult to mobilise laparoscopically were reserved for open resections"
Bias due to selection of participants to intervention and control	Unclear risk	**No information** Comment: It was not clear whether eligible participants were excluded from the report
Bias due to differences in co-interventions which were different between the groups	Unclear risk	**No information** Comment: This information was not available
Bias in the measurement of outcomes	Unclear risk	**No information** Comment: This information was not available
Bias due to missing data	Unclear risk	**No information** Comment: This information was not available
Bias in selection of the reported findings	Low risk	**Low risk of bias** Comment: Mortality and complications were reported

Sharpe 2015

Methods	Study design: retrospective cohort study
Participants	Country: USA Number eligible: 769 Number excluded: not stated Number analysed: 769 Average age: 66 years Females: not stated ASA I or II: not stated ASA III or IV: not stated Stapler closure: not stated Fibrin sealant: not stated Mean BMI: not stated Study setting: National Cancer Data Base (USA) (Joint Project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society; captures information from approximately 1500 Commission on Cancer-accredited hospitals and more than 70% of all newly diagnosed malignancies in the United States) Period of recruitment: 2010 and 2011 Follow-up in months: not stated **Inclusion criteria**

Sharpe 2015 (*Continued*)

	Adults (18 years or older) undergoing distal pancreatectomy for pancreatic adenocarcinoma **Exclusion criteria** Metastatic disease or concomitant cancer diagnosis
Interventions	Group 1: laparoscopic distal pancreatectomy (n = 144) Further details: not stated Group 2: open distal pancreatectomy (n = 625) Further details: not stated
Outcomes	Outcomes reported were short-term mortality, resection margins and length of hospital stay
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Bias due to confounding	High risk	**Critical risk of bias** Quote: "More patients in the open group received neoadjuvant chemotherapy (11% vs 2%, P < .001) or radiation (6% vs 2%, P = .049). Patients in the open group had larger tumours than those in the laparoscopic group (4.2 ± 3.2 vs 3.7 ± 1.9 cm, P = .018)"
Bias due to selection of participants to intervention and control	Unclear risk	**No information** Comment: It was not clear whether eligible participants were excluded from the report
Bias due to differences in co-interventions which were different between the groups	Unclear risk	**No information** Comment: This information was not available
Bias in the measurement of outcomes	Unclear risk	**No information** Comment: This information was not available
Bias due to missing data	Unclear risk	**No information** Comment: This information was not available
Bias in selection of the reported findings	High risk	**Serious risk of bias** Comment: Complications were not reported

Shin 2015

Methods	Study design: retrospective cohort study
Participants	Country: South Korea Number eligible: 167 Number excluded: 17 (10.2%) Number analysed: 150 Average age: 63 years Females: 55 (36.7%) ASA I or II: 133(88.7%) ASA III or IV: 17 (11.3%) Stapler closure: 150 (100%) Fibrin sealant: not stated Mean BMI: not stated Study setting: single centre; Asan Medical Center, Seoul, South Korea Period of recruitment: 2006 to 2013 Follow-up in months: not stated
Interventions	Group 1: laparoscopic distal pancreatectomy (n = 70) Further details: not stated Group 2: open distal pancreatectomy (n = 80) Further details: not stated The choice of laparoscopic or open method was made at the sole discretion of the participant
Outcomes	Outcomes reported were short-term and long-term mortality, recurrence, complications, operating time, resection margins and hospital stay
Notes	Adjuvant chemotherapy: laparoscopic distal pancreatectomy (n = 55) and open distal pancreatectomy (n = 55) Reasons for exclusions: metastatic disease (12) and conversion to open procedure (5)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Bias due to confounding	High risk	**Critical risk of bias** Comment: Tumour size was smaller in laparoscopic group
Bias due to selection of participants to intervention and control	High risk	**Critical risk of bias** Comment: People who met eligibility criteria were excluded because they underwent conversion to open surgery
Bias due to differences in co-interventions which were different between the groups	Unclear risk	**No information** Comment: This information was not available

Shin 2015 (*Continued*)

Bias in the measurement of outcomes	Unclear risk	**No information** Comment: This information was not available
Bias due to missing data	High risk	**Critical risk of bias** Comment: Participants who met eligibility criteria were excluded. This could have affected the outcome
Bias in selection of the reported findings	Low risk	**Low risk of bias** Comment: Mortality and complications were reported

Stauffer 2015

Methods	Study design: retrospective cohort study
Participants	Country: USA Number eligible: 70 Number excluded: not stated Number analysed: 70 Average age: not stated Females: not stated ASA I or II: not stated ASA III or IV: not stated Stapler closure: not stated Fibrin sealant: not stated Mean BMI: not stated Study setting: single centre; Mayo Clinic Florida, Jacksonville, USA Period of recruitment: not stated Follow-up in months: not stated **Inclusion criteria** Patients undergoing distal pancreatectomy for pancreatic adenocarcinoma
Interventions	Group 1: laparoscopic distal pancreatectomy (n = 41) Further details: not stated Group 2: open distal pancreatectomy (n = 29) Further details: not stated
Outcomes	None of the outcomes of interest were reported
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Stauffer 2015 (*Continued*)

Bias due to confounding	Unclear risk	**No information** Comment: This information was not available
Bias due to selection of participants to intervention and control	Unclear risk	**No information** Comment: It was not clear whether eligible participants were excluded from the report
Bias due to differences in co-interventions which were different between the groups	Unclear risk	**No information** Comment: This information was not available
Bias in the measurement of outcomes	Unclear risk	**No information** Comment: This information was not available
Bias due to missing data	Unclear risk	**No information** Comment: This information was not available
Bias in selection of the reported findings	High risk	**Critical risk of bias** Comment: Mortality and complications were not reported

Vijan 2010

Methods	Study design: case-control study
Participants	Country: USA Number eligible: 41 Number excluded: not stated Number analysed: 41 Average age: not stated Females: not stated ASA I or II: not stated ASA III or IV: not stated Stapler closure: not stated Fibrin sealant: not stated Mean BMI: not stated Study setting: single centre; Mayo Clinic, Rochester, USA Period of recruitment: 2004 to 2009 Follow-up in months: not stated **Inclusion criteria** Patients with pancreatic malignancy undergoing distal pancreatectomy Notes: The study included participants without pancreatic malignancy who were excluded from the analysis

Vijan 2010 (*Continued*)

Interventions	Group 1: laparoscopic distal pancreatectomy (n = 20) Further details: 4 ports; with or without splenectomy; selective closed suction drain Group 2: open distal pancreatectomy (n = 21)	
Outcomes	The outcome reported was resection margins	
Notes		

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Bias due to confounding	Unclear risk	**No information** Quote: "Following institutional review board approval, 100 patients undergoing LDP were matched by patient age (± 8 years), pathologic diagnosis (benign vs malignant), and pancreatic specimen length (± 2 cm) to a cohort (n = 100) undergoing ODP" Comment: Matching does not take all confounding factors into account, for example, stage of tumour
Bias due to selection of participants to intervention and control	Unclear risk	**No information** Comment: It was not clear whether eligible participants were excluded from the report
Bias due to differences in co-interventions which were different between the groups	Unclear risk	**No information** Comment: This information was not available
Bias in the measurement of outcomes	Unclear risk	**No information** Comment: This information was not available
Bias due to missing data	Unclear risk	**No information** Comment: This information was not available
Bias in selection of the reported findings	High risk	**Critical risk of bias** Comment: Mortality and complications were not reported

Zhang 2014

Methods	Study design: retrospective cohort study
Participants	Country: China Number eligible: 11 Number excluded: not stated Number analysed: 11 Average age: not stated

	Females: not stated ASA I or II: not stated ASA III or IV: not stated Stapler closure: 11 (100%) Fibrin sealant: not stated Mean BMI: not stated Study setting: single centre; The Third Affiliated Hospital of Soochow University, Changzhou, China Period of recruitment: 2009 to 2013 Follow-up in months: not stated **Inclusion criteria** Patients with pancreatic malignancy undergoing distal pancreatectomy Notes: The study included participants without pancreatic malignancy who were excluded from the analysis
Interventions	Group 1: laparoscopic distal pancreatectomy (n = 4) Further details: 4 ports; with or without splenectomy; drain use not stated Group 2: open distal pancreatectomy (n = 7)
Outcomes	Outcomes reported were short-term mortality and resection margins
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Bias due to confounding	Unclear risk	**No information** Comment: This information was not available
Bias due to selection of participants to intervention and control	Unclear risk	**No information** Comment: It was not clear whether eligible participants were excluded from the report
Bias due to differences in co-interventions which were different between the groups	Unclear risk	**No information** Comment: This information was not available
Bias in the measurement of outcomes	Unclear risk	**No information** Comment: This information was not available
Bias due to missing data	Unclear risk	**No information** Comment: This information was not available
Bias in selection of the reported findings	High risk	**Serious risk of bias** Comment: Complications were not reported

Abbreviations:
ASA: American Society of Anethesiologists
BMI: body mass index

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abu Hilal 2012	No separate data available on people with pancreatic cancer
Ahmed 2015	Review
Baker 2011	No separate data available on people with pancreatic cancer
Baker 2013	No separate data available on people with pancreatic cancer
Barrie 2014	Includes metastatic renal carcinoma
Belli 2012	No separate data available on people with pancreatic cancer
Butturini 2011	Study performed in people with benign or premalignant lesions
Cao 2014	No separate data available on people with pancreatic cancer
Casadei 2010	Study performed in people with benign or premalignant lesions
Cheek 2014	No separate data available on people with pancreatic cancer
Chen 2012	Study performed in people with benign or premalignant lesions
Cho 2011	No separate data available on people with pancreatic cancer
Chung 2014	Study performed in people with benign or premalignant lesions
Dancea 2012a	No separate data available on people with pancreatic cancer
Daouadi 2011	No open distal pancreactectomy as control group
de Rooij 2015	No separate data available on people with pancreatic cancer
DiNorcia 2010	No separate data available on people with pancreatic cancer
Duran 2014	No separate data available on people with pancreatic cancer
Durlik 2013	No separate data available on people with pancreatic cancer

(*Continued*)

Ejaz 2014	No separate data available on people with pancreatic cancer
Eom 2008	No separate data available on people with pancreatic cancer
Ferrara 2014	No separate data available on people with pancreatic cancer
Finan 2009	No separate data available on people with pancreatic cancer
Fox 2012	No separate data available on people with pancreatic cancer
Gumbs 2008	Study performed in people with benign or premalignant lesions
Jayaraman 2010	No separate data available on people with pancreatic cancer
Jeon 2014	No separate data available on people with pancreatic cancer
Kang 2010	No separate data available on people who underwent laparoscopic distal pancreatectomy
Kausar 2010	Indication for surgery not stated
Kooby 2008	No separate data available on people with pancreatic cancer
Langan 2014	Not on distal pancreatectomy
Lee 2014	No separate data available on people who underwent laparoscopic distal pancreatectomy
Liao 2014	Indication for surgery not stated
Limongelli 2012	No separate data available on people with pancreatic cancer
Limongelli 2014	Comment on an excluded study (Cho 2011)
Magge 2013	No separate data available on people who underwent laparoscopic distal pancreatectomy
Malde 2012	No separate data available on people with pancreatic cancer
Matejak-Gorska 2013	No separate data available on people with pancreatic cancer
Matsumoto 2008	Study performed in people with benign or premalignant lesions
Mehrabi 2015	Review
Mehta 2012	No separate data available on people with pancreatic cancer
Morikawa 2012	Study performed in people with benign lesions

(*Continued*)

Nakamura 2009	No separate data available on people with pancreatic cancer
Newman 2010	Indication for surgery not stated
Nigri 2011	Review
Parikh 2015	Indication for surgery not stated
Pieretti-Vanmarcke 2014	No separate data available on people with pancreatic cancer
Ricci 2015	Review
Rooij 2014	No separate data available on people with pancreatic cancer
Rosales-Velderrain 2012	No separate data available on people with pancreatic cancer
Sahay 2011	Study performed in people with non-cancerous lesions
Sherwinter 2012	No separate data available on people with pancreatic cancer
Slepavicius 2014	Study performed in people with benign and borderline lesions
Soh 2012	No separate data available on people with pancreatic cancer
Stauffer 2012	Indication for surgery not stated
Stauffer 2013	No separate data available on people with pancreatic cancer
Tang 2007	No control group of open distal pancreatectomy
Tseng 2011	No separate data available on people with pancreatic cancer
Velanovich 2006	No separate data available on people with pancreatic cancer
Vicente 2013	Indication for surgery not stated
Yoon 2012	Indication for surgery not stated
Zhao 2010	No separate data available on people with pancreatic cancer
Zibari 2014	No separate data available on people who underwent laparoscopic distal pancreatectomy

DATA AND ANALYSES

Comparison 1. Laparoscopic distal pancreatectomy versus open distal pancreatectomy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Short-term mortality	9	1451	Odds Ratio (M-H, Fixed, 95% CI)	0.48 [0.11, 2.17]
2 Long-term mortality	3	277	Hazard Ratio (Fixed, 95% CI)	0.96 [0.82, 1.12]
3 Serious adverse events (proportion)	3	206	Odds Ratio (M-H, Fixed, 95% CI)	1.79 [0.53, 6.06]
4 Pancreatic fistula (grade B or C)	4	246	Odds Ratio (M-H, Fixed, 95% CI)	1.19 [0.47, 3.02]
5 Recurrence at maximal follow-up	2	184	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.32, 1.05]
6 Adverse events (proportion)	4	246	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.54, 1.66]
7 Length of hospital stay	5	1068	Mean Difference (IV, Random, 95% CI)	-2.43 [-3.13, -1.73]
8 Positive resection margins	10	1466	Odds Ratio (M-H, Random, 95% CI)	0.74 [0.49, 1.10]

Comparison 2. Subgroup analysis (stapler only)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Short-term mortality	2	161	Odds Ratio (M-H, Random, 95% CI)	0.38 [0.02, 9.38]
2 Long-term mortality	1		Hazard Ratio (Fixed, 95% CI)	0.88 [0.67, 1.15]
3 Serious adverse events (proportion)	1	150	Odds Ratio (M-H, Fixed, 95% CI)	3.0 [0.56, 15.98]
4 Pancreatic fistula (grade B or C)	1	150	Odds Ratio (M-H, Fixed, 95% CI)	3.31 [0.84, 13.01]

Comparison 3. Sensitivity analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Length of hospital stay	3	896	Mean Difference (IV, Random, 95% CI)	-2.25 [-3.03, -1.47]

Analysis 1.1. Comparison 1 Laparoscopic distal pancreatectomy versus open distal pancreatectomy, Outcome 1 Short-term mortality.

Review: Laparoscopic versus open distal pancreatectomy for pancreatic cancer

Comparison: 1 Laparoscopic distal pancreatectomy versus open distal pancreatectomy

Outcome: 1 Short-term mortality

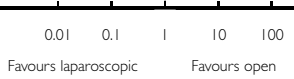
Study or subgroup	Laparoscopic dist pancr n/N	Open dist pancr n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Braga 2015	0/30	0/34			Not estimable
Ceppa 2013	1/20	0/20		8.0 %	3.15 [0.12, 82.16]
Hu 2014	0/11	0/23			Not estimable
Kooby 2010	0/23	0/70			Not estimable
Lee 2015	0/19	0/249			Not estimable
Rehman 2014	0/8	0/14			Not estimable
Sharpe 2015	0/144	10/625		68.0 %	0.20 [0.01, 3.48]
Shin 2015	0/70	1/80		24.0 %	0.38 [0.02, 9.38]
Zhang 2014	0/4	0/7			Not estimable
Total (95% CI)	**329**	**1122**		**100.0 %**	**0.48 [0.11, 2.17]**

Total events: 1 (Laparoscopic dist pancr), 11 (Open dist pancr)

Heterogeneity: $Chi^2 = 1.66$, df = 2 (P = 0.44); $I^2 = 0.0\%$

Test for overall effect: Z = 0.95 (P = 0.34)

Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1 Laparoscopic distal pancreatectomy versus open distal pancreatectomy, Outcome 2 Long-term mortality.

Review: Laparoscopic versus open distal pancreatectomy for pancreatic cancer

Comparison: 1 Laparoscopic distal pancreatectomy versus open distal pancreatectomy

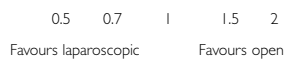
Outcome: 2 Long-term mortality

Study or subgroup	Laparoscopic dist pancr N	Open dist pancr N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
Hu 2014	11	23	-0.11584 (0.136025)		32.5 %	0.89 [0.68, 1.16]
Kooby 2010	23	70	0.10366 (0.129256)		35.9 %	1.11 [0.86, 1.43]
Shin 2015	70	80	-0.13174 (0.137829)		31.6 %	0.88 [0.67, 1.15]
Total (95% CI)	**104**	**173**			**100.0 %**	**0.96 [0.82, 1.12]**

Heterogeneity: Chi^2 = 1.99, df = 2 (P = 0.37); I^2 =0.0%

Test for overall effect: Z = 0.54 (P = 0.59)

Test for subgroup differences: Not applicable

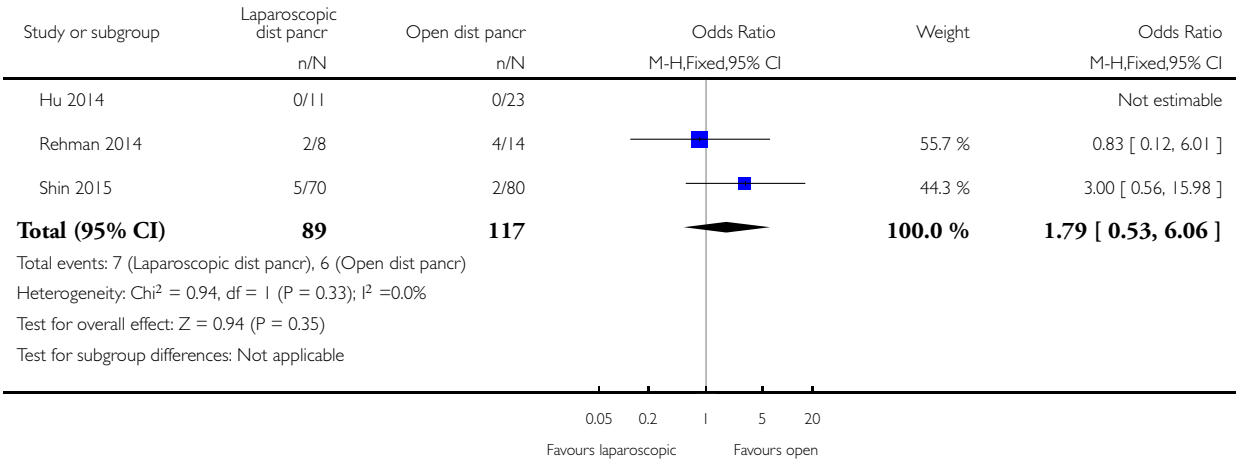


Analysis 1.3. Comparison 1 Laparoscopic distal pancreatectomy versus open distal pancreatectomy, Outcome 3 Serious adverse events (proportion).

Review: Laparoscopic versus open distal pancreatectomy for pancreatic cancer

Comparison: 1 Laparoscopic distal pancreatectomy versus open distal pancreatectomy

Outcome: 3 Serious adverse events (proportion)



Analysis 1.4. Comparison 1 Laparoscopic distal pancreatectomy versus open distal pancreatectomy, Outcome 4 Pancreatic fistula (grade B or C).

Review: Laparoscopic versus open distal pancreatectomy for pancreatic cancer

Comparison: 1 Laparoscopic distal pancreatectomy versus open distal pancreatectomy

Outcome: 4 Pancreatic fistula (grade B or C)

Study or subgroup	Laparoscopic dist pancr n/N	Open dist pancr n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Ceppa 2013	0/20	4/20		53.9 %	0.09 [0.00, 1.78]
Hu 2014	0/11	0/23			Not estimable
Rehman 2014	1/8	2/14		15.6 %	0.86 [0.07, 11.26]
Shin 2015	8/70	3/80		30.4 %	3.31 [0.84, 13.01]
Total (95% CI)	**109**	**137**		**100.0 %**	**1.19 [0.47, 3.02]**

Total events: 9 (Laparoscopic dist pancr), 9 (Open dist pancr)

Heterogeneity: $Chi^2 = 5.08$, df = 2 (P = 0.08); $I^2 = 61\%$

Test for overall effect: Z = 0.37 (P = 0.71)

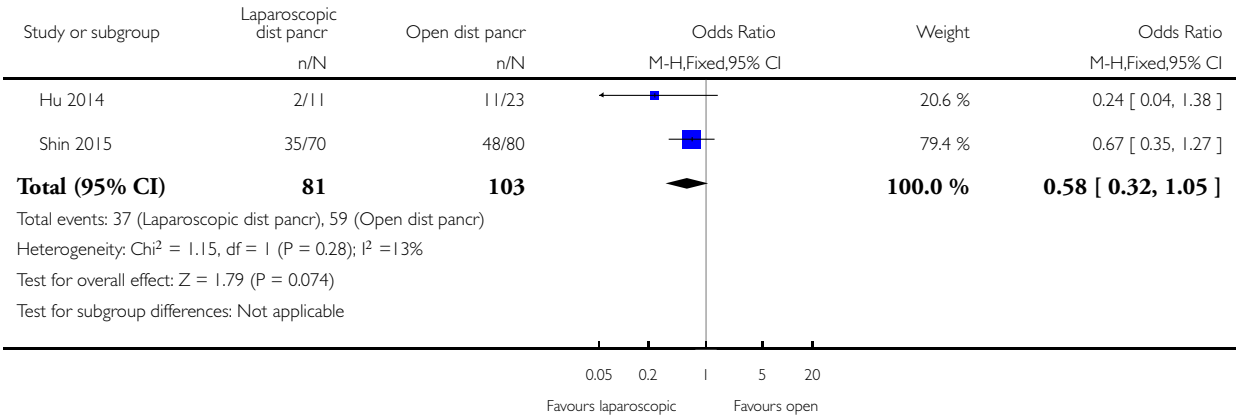
Test for subgroup differences: Not applicable

Analysis 1.5. Comparison 1 Laparoscopic distal pancreatectomy versus open distal pancreatectomy, Outcome 5 Recurrence at maximal follow-up.

Review: Laparoscopic versus open distal pancreatectomy for pancreatic cancer

Comparison: 1 Laparoscopic distal pancreatectomy versus open distal pancreatectomy

Outcome: 5 Recurrence at maximal follow-up

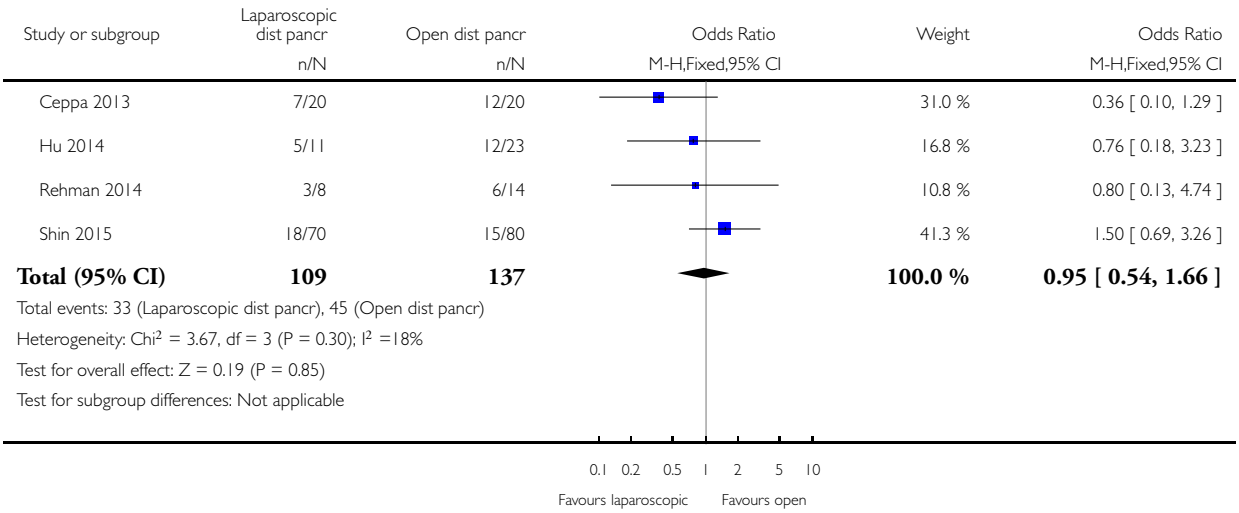


Analysis 1.6. Comparison 1 Laparoscopic distal pancreatectomy versus open distal pancreatectomy, Outcome 6 Adverse events (proportion).

Review: Laparoscopic versus open distal pancreatectomy for pancreatic cancer

Comparison: 1 Laparoscopic distal pancreatectomy versus open distal pancreatectomy

Outcome: 6 Adverse events (proportion)



Analysis 1.7. Comparison 1 Laparoscopic distal pancreatectomy versus open distal pancreatectomy, Outcome 7 Length of hospital stay.

Review: Laparoscopic versus open distal pancreatectomy for pancreatic cancer

Comparison: 1 Laparoscopic distal pancreatectomy versus open distal pancreatectomy

Outcome: 7 Length of hospital stay

Study or subgroup	Laparoscopic dist pancr N	Mean(SD)[days]	Open dist pancr N	Mean(SD)[days]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Hu 2014	11	5.2 (2.5)	23	8.6 (3.9)		10.5 %	-3.40 [-5.57, -1.23]
Kooby 2010	23	7.4 (3.4)	70	9.4 (4.7)		15.7 %	-2.00 [-3.77, -0.23]
Rehman 2014	8	8 (4.3)	14	12 (4.3)		3.5 %	-4.00 [-7.74, -0.26]
Sharpe 2015	144	6.8 (4.6)	625	8.9 (7.5)		54.3 %	-2.10 [-3.05, -1.15]
Shin 2015	70	9 (5.5)	80	12 (5.5)		15.9 %	-3.00 [-4.76, -1.24]
Total (95% CI)	**256**		**812**			**100.0 %**	**-2.43 [-3.13, -1.73]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.53$, df = 4 (P = 0.64); $I^2 = 0.0\%$

Test for overall effect: Z = 6.77 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 1.8. Comparison 1 Laparoscopic distal pancreatectomy versus open distal pancreatectomy, Outcome 8 Positive resection margins.

Review: Laparoscopic versus open distal pancreatectomy for pancreatic cancer

Comparison: 1 Laparoscopic distal pancreatectomy versus open distal pancreatectomy

Outcome: 8 Positive resection margins

Study or subgroup	Laparoscopic dist pancr n/N	Open dist pancr n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Braga 2015	8/30	11/34		13.2 %	0.76 [0.26, 2.24]
Dancea 2012	0/4	1/10		1.4 %	0.70 [0.02, 20.91]
Hu 2014	0/11	0/23			Not estimable
Kooby 2010	6/23	24/70		13.8 %	0.68 [0.24, 1.94]
Lee 2015	0/19	30/249		2.0 %	0.18 [0.01, 3.13]
Rehman 2014	1/8	2/14		2.4 %	0.86 [0.07, 11.26]
Sharpe 2015	17/144	127/625		44.5 %	0.52 [0.31, 0.90]
Shin 2015	17/70	13/80		22.6 %	1.65 [0.74, 3.71]
Vijan 2010	0/20	0/21			Not estimable
Zhang 2014	0/4	0/7			Not estimable
Total (95% CI)	**333**	**1133**		**100.0 %**	**0.74 [0.49, 1.10]**

Total events: 49 (Laparoscopic dist pancr), 208 (Open dist pancr)

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 6.36$, df = 6 (P = 0.38); $I^2 = 6\%$

Test for overall effect: Z = 1.49 (P = 0.14)

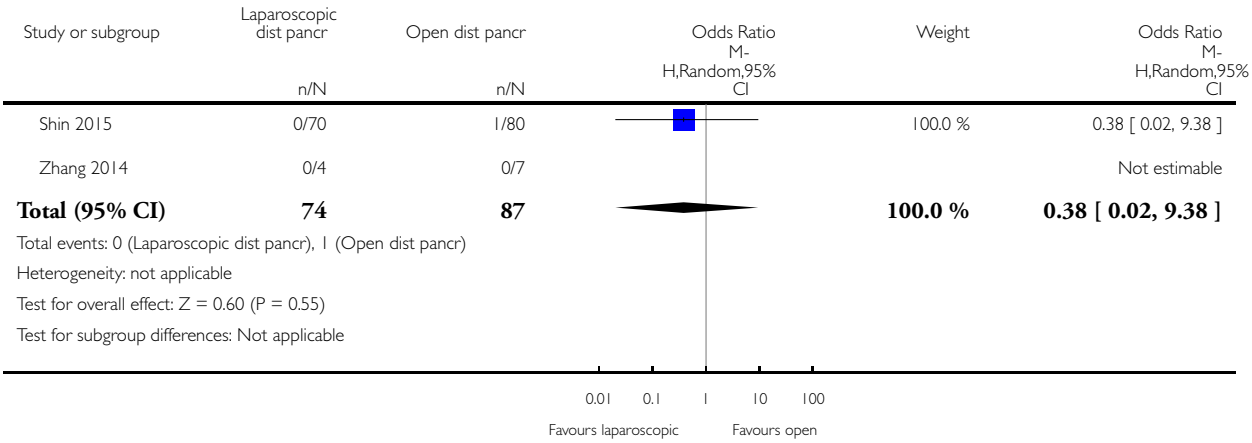
Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 Subgroup analysis (stapler only), Outcome 1 Short-term mortality.

Review: Laparoscopic versus open distal pancreatectomy for pancreatic cancer

Comparison: 2 Subgroup analysis (stapler only)

Outcome: 1 Short-term mortality

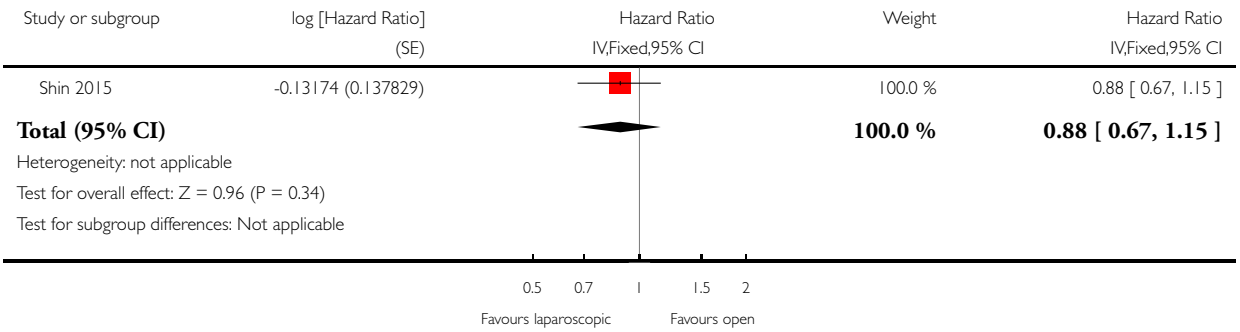


Analysis 2.2. Comparison 2 Subgroup analysis (stapler only), Outcome 2 Long-term mortality.

Review: Laparoscopic versus open distal pancreatectomy for pancreatic cancer

Comparison: 2 Subgroup analysis (stapler only)

Outcome: 2 Long-term mortality

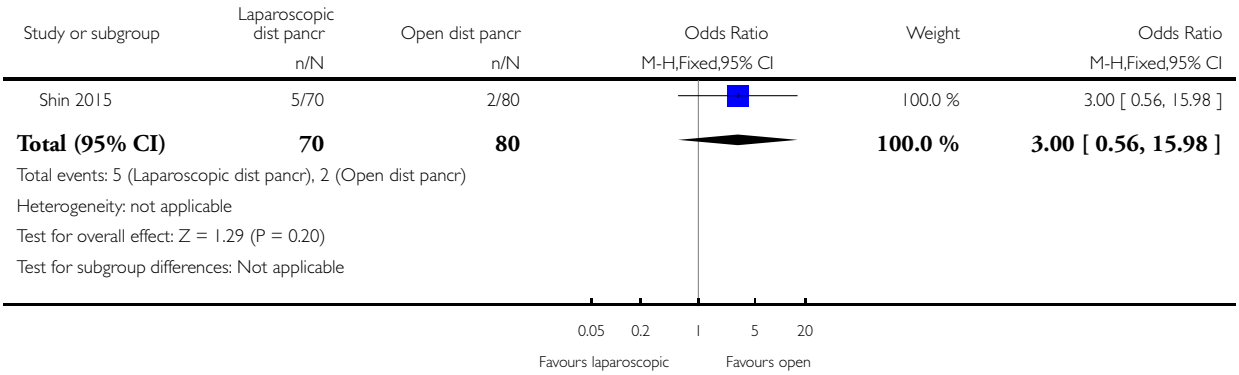


Analysis 2.3. Comparison 2 Subgroup analysis (stapler only), Outcome 3 Serious adverse events (proportion).

Review: Laparoscopic versus open distal pancreatectomy for pancreatic cancer

Comparison: 2 Subgroup analysis (stapler only)

Outcome: 3 Serious adverse events (proportion)

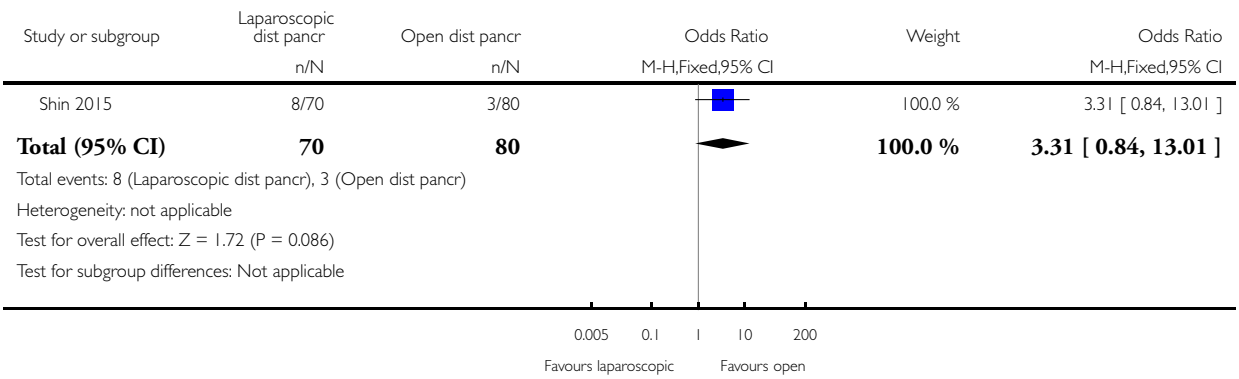


Analysis 2.4. Comparison 2 Subgroup analysis (stapler only), Outcome 4 Pancreatic fistula (grade B or C).

Review: Laparoscopic versus open distal pancreatectomy for pancreatic cancer

Comparison: 2 Subgroup analysis (stapler only)

Outcome: 4 Pancreatic fistula (grade B or C)

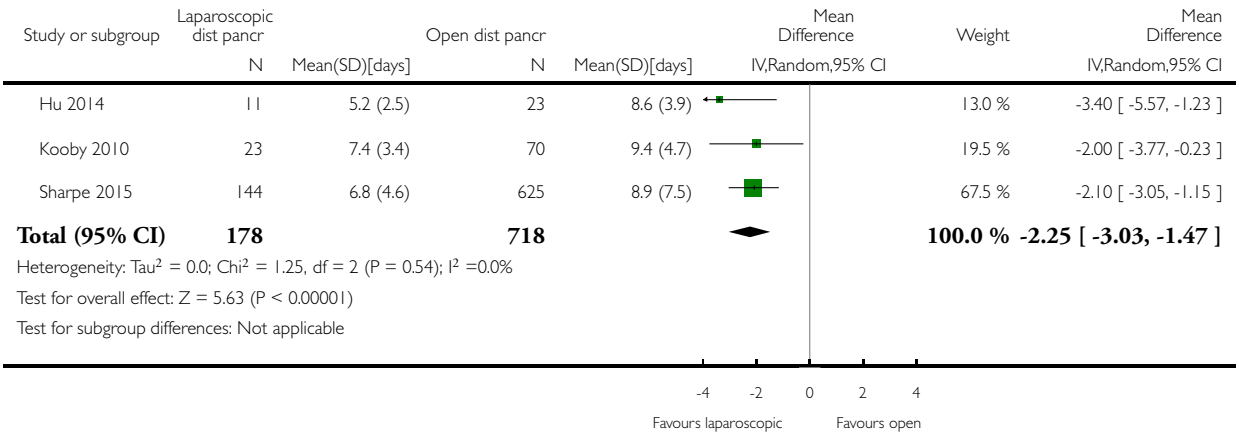


Analysis 3.1. Comparison 3 Sensitivity analysis, Outcome 1 Length of hospital stay.

Review: Laparoscopic versus open distal pancreatectomy for pancreatic cancer

Comparison: 3 Sensitivity analysis

Outcome: 1 Length of hospital stay



APPENDICES

Appendix 1. CENTRAL search strategy

#1 (pancreas)
#2 (pancrea*)
#3 MeSH descriptor: [Pancreas] explode all trees
#4 #1 or #2 or #3
#5 MeSH descriptor: [Carcinoma] this term only
#6 MeSH descriptor: [Adenocarcinoma] this term only
#7 MeSH descriptor: [Carcinoma, Ductal] this term only
#8 MeSH descriptor: [Neoplasms] explode all trees
#9 (cancer* or carcin* or neoplas* or tumo* or cyst* or growth* or adenocarcin* or malig*)
#10 #5 or #6 or #7 or #8 or #9
#11 #4 and #10
#12 Pancreatectomy
#13 MeSH descriptor: [Pancreatectomy] explode all trees
#14 #12 or #13
#15 (laparoscopy or laparoscopic)
#16 MeSH descriptor: [Laparoscopy] explode all trees
#17 #15 or #16
#18 #11 and #14 and #17

Appendix 2. MEDLINE search strategy

1. (pancreas or pancrea*).mp.
2. exp Pancreas/
3. 1 or 2
4. Carcinoma/
5. Adenocarcinoma/
6. Carcinoma, Ductal/
7. exp Neoplasms/
8. (cancer* or carcin* or neoplas* or tumo* or cyst* or growth* or adenocarcin* or malig*).mp.
9. 4 or 5 or 6 or 7 or 8
10. 3 and 9
11. Pancreatectomy.mp.
12. exp Pancreatectomy/
13. 11 or 12
14. (laparoscopy or laparoscopic).mp.
15. exp Laparoscopy/
16. 14 or 15
17. 13 and 16
18. 10 and 17

Appendix 3. EMBASE search strategy

1. (pancreas or pancrea*).mp.
2. exp pancreas/
3. 1 or 2
4. carcinoma/ or adenocarcinoma/ or carcinoma, ductal/
5. exp neoplasms/
6. (cancer* or carcin* or neoplas* or tumo* or cyst* or growth* or adenocarcin* or malig*).mp.
7. 4 or 5 or 6
8. 3 and 7
9. Pancreatectomy.mp.
10. exp Pancreatectomy/
11. 9 or 10
12. (laparoscopy or laparoscopic).mp.
13. exp laparoscopy/
14. 12 or 13
15. 11 and 14
16. 8 and 15

Appendix 4. Science Citation Index search strategy

#1 TS=(pancreas or pancrea*)
#2 TS=(cancer* or carcin* or neoplas* or tumo* or cyst* or growth* or adenocarcin* or malig*)
#3 TS=(Pancreatectomy)
#4 TS=(laparoscopy or laparoscopic)
#5 #4 AND #3 AND #2 AND #1

Appendix 5. ClinicalTrials.gov search strategy

"Interventional" [STUDY-TYPES] AND pancreatic cancer [DISEASE] AND laparoscopic distal pancreatectomy [TREATMENT] AND ("Phase 2" OR "Phase 3" OR "Phase 4") [PHASE]

Appendix 6. WHO ICTRP search strategy

Distal pancreatectomy AND laparoscop*

CONTRIBUTIONS OF AUTHORS

Conceiving of the review: KG.

Designing the review: KG.

Co-ordinating the review: KG, CVL.

Designing search strategies: KG.

Extracting data: DR, KG.

Analysing data: DR, KG.

Writing the review: DR, KG.

Providing critical comments on the review: DK, CV, MB, BRD, CVL.

Securing funding for the review: KG, BRD.

Performing previous work that served as the foundation of the current study: KG, BRD.

DECLARATIONS OF INTEREST

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DR: none known.

KSG: none known.

DAK: received partial sponsorship from Intuitive Surgical (makers of the da Vinci Surgical System) to attend a training course on robotic pancreatic surgery.

CMV: none known.

MGHB: none known.

BRD: none known.

CJHMvL: has written chapters for UpToDate, which are not related to this review.

SOURCES OF SUPPORT

Internal sources

- University College London, UK.

External sources

- National Institute for Health Research, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. No randomised controlled trials were identified; therefore, we included non-randomised studies to provide the current best available evidence. As a result, we made the following modifications to the protocol.

i) We did not use the filter for randomised controlled trials during electronic searches of the databases.

ii) We used 'A Cochrane Risk Of Bias Assessment Tool: for Non-Randomized Studies of Interventions' (ACROBAT-NRSI) for assessment of risk of bias, rather than the standard Cochrane 'Risk of bias' tool for randomised controlled trials.

2. We planned to calculate the risk ratio for binary outcomes. However, because case-control studies were included, we calculated the odds ratio because it is not possible to calculate the baseline risk in case-control studies.

3. We planned to calculate the hazard ratio for long-term recurrence. However, data were not available in the format required for calculating the hazard ratio. So we calculated the odds ratio.