



Cochrane
Library

Cochrane Database of Systematic Reviews

Minimally invasive versus open pancreatoduodenectomy in benign, premalignant, and malignant disease. (Protocol)

Riviere D, van den Boezem PB, Besselink MG, van Laarhoven CJHM, Kooby DA, Vollmer CM, Davidson BR, Gurusamy KS

Riviere D, van den Boezem PB, Besselink MG, van Laarhoven CJHM, Kooby DA, Vollmer CM, Davidson BR, Gurusamy KS. Minimally invasive versus open pancreatoduodenectomy in benign, premalignant, and malignant disease. (Protocol). *Cochrane Database of Systematic Reviews* 2024, Issue 7. Art. No.: CD014017. DOI: [10.1002/14651858.CD014017](https://doi.org/10.1002/14651858.CD014017).

www.cochranelibrary.com

Minimally invasive versus open pancreatoduodenectomy in benign, premalignant, and malignant disease. (Protocol)

Copyright © 2024 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

WILEY

TABLE OF CONTENTS

ABSTRACT	1
BACKGROUND	2
OBJECTIVES	3
METHODS	3
ACKNOWLEDGEMENTS	7
REFERENCES	8
APPENDICES	10
CONTRIBUTIONS OF AUTHORS	15
DECLARATIONS OF INTEREST	15
SOURCES OF SUPPORT	15

[Intervention Protocol]

Minimally invasive versus open pancreatoduodenectomy in benign, premalignant, and malignant disease.

Deniece Riviere¹, Peter B van den Boezem², Marc G Besselink³, Cornelis JHM van Laarhoven², David A Kooby⁴, Charles M Vollmer⁵, Brian R Davidson⁶, Kurinchi Selvan Gurusamy⁶

¹Department of Medical Imaging, Radboud University Medical Center Nijmegen, Nijmegen, Netherlands. ²Department of Surgery, Radboud University Medical Center, Nijmegen, Netherlands. ³Department of Surgery, Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands. ⁴Department of Surgery, Emory University School of Medicine, Atlanta, GA, USA. ⁵Department of Gastrointestinal Surgery, University of Pennsylvania, Philadelphia, PA, USA. ⁶Division of Surgery and Interventional Science, University College London, London, UK

Contact: Deniece Riviere, d.riviere@radboudumc.nl.

Editorial group: Cochrane Z_INACTIVE_Gut Group.

Publication status and date: New, published in Issue 7, 2024.

Citation: Riviere D, van den Boezem PB, Besselink MG, van Laarhoven CJHM, Kooby DA, Vollmer CM, Davidson BR, Gurusamy KS. Minimally invasive versus open pancreatoduodenectomy in benign, premalignant, and malignant disease. (Protocol). *Cochrane Database of Systematic Reviews* 2024, Issue 7. Art. No.: CD014017. DOI: [10.1002/14651858.CD014017](https://doi.org/10.1002/14651858.CD014017).

Copyright © 2024 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the benefits and harms of laparoscopic or robot-assisted pancreatoduodenectomy versus open pancreatoduodenectomy for people with benign, premalignant, and malignant disease.

BACKGROUND

Description of the condition

Pancreatoduodenectomy is the most common surgery to remove premalignant and malignant neoplasms that involve the head of the pancreas, duodenum, periampullary region, or distal common bile duct (CBD; [Johnson 2008](#)).

Cystic pancreatic lesions are very common in the general population, with reported prevalences of up to 50% ([Komrey 2018](#)). Cystic lesions that may be malignant include cystic neuroendocrine neoplasms and mucinous neoplasms, such as intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm. Solid pseudopapillary neoplasm has a low risk for malignancy ([Stark 2016](#)). IPMN is the most common cystic pancreatic neoplasm. It is defined as a grossly visible noninvasive epithelial neoplasm made of mucin-producing cells that could arise from the main pancreatic duct (IPMN-MD) or, more commonly, from the branch ducts (IPMN-BD). IPMN-BD is associated with a relatively low risk of neoplastic transformation, estimated at 0% to 7% per year ([Crippa 2016](#)). In contrast, IPMN-MD and mixed-type IPMN are indications for surgical resection due to the high malignancy rate ([ESGCT 2018](#)).

Neuroendocrine tumours (NETs) are neoplasms arising from neuroendocrine cells. Functional NETs are capable of hormone production and are therefore associated with distinct clinical syndromes (i.e. Whipple's triad, Zollinger-Ellison syndrome). Nonfunctional NETs secrete minimal quantities of hormones or none at all, or they secrete peptides that do not result in an obvious syndrome ([Scott 2019](#)). A substantial proportion of pancreatic NETs (PNETs) are nonfunctional, and the most common functional PNETs are insulinomas, followed by gastrinomas. Most PNETs are malignant, and up to 60% of patients present with metastatic disease ([Halfdanarson 2008](#)). Although most PNETs are sporadic, they can also occur as part of an inherited syndrome such as multiple endocrine neoplasia type 1, Von Hippel-Lindau syndrome (VHL), tuberous sclerosis complex, and neurofibromatosis type 1 ([Jensen 2008](#)). Functional tumours and nonfunctional PNETs larger than 2 cm should be resected ([Falconi 2016](#)).

Chronic pancreatitis (CP) is a complex inflammatory disease with pain as the most dominant symptom. The most common indication for CP surgery is intractable pain, when medical or endoscopic management fails to provide pain relief. Other indications are a suspicion of neoplasm and local complications in adjacent organs, such as duodenal or common bile duct stenosis, pseudoaneurysm (most commonly of the splenic artery) or erosion of the large vessels producing gastrointestinal haemorrhage, large pancreatic pseudocysts, and internal pancreatic fistula. Surgical procedures for CP can be categorised into three major groups: drainage procedures (e.g. pancreaticojejunostomy), procedures combining drainage and resection (Frey or Beger procedure), and resection (e.g. pancreatoduodenectomy or pylorus-preserving pancreatoduodenectomy; [Kempeneers 2020](#)). One recent randomised controlled trial (RCT) demonstrated that pancreatoduodenectomy for CP is associated with similar outcomes as a surgical drainage procedure ([Diener 2017](#)).

Periampullary carcinomas arise within the vicinity of the ampulla of Vater and can originate from the ampulla of Vater, the distal common bile duct, the head of the pancreas, and the duodenum. Pancreatic ductal adenocarcinoma is the most common type and

has the worst prognosis. In 2022, there were 510,566 new cases and 467,005 deaths from pancreatic cancer globally. This disease ranks as the sixth leading cause of cancer mortality for both sexes combined, accounting for nearly 5% of all cancer deaths worldwide. Incidence rates are approximately four times higher in countries with a high Human Development Index (HDI) compared to those with a lower HDI, with the highest rates observed in Europe, North America, and Australia/New Zealand ([Cancer Statistics 2024](#)).

Pancreatic adenocarcinoma is a biologically aggressive cancer that is relatively resistant to chemotherapy and radiotherapy. In the minority of cases that are resectable at presentation, there is a high rate of local and systemic recurrence ([Abrams 2009](#); [Ghaneh 2007](#); [Orr 2010](#)). 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 in people likely to withstand major surgery. However, about half of people with pancreatic cancer have metastatic disease at presentation, and one-third have locally advanced unresectable disease, leaving only about 10% to 20% of cases suitable for resection ([Tucker 2008](#)). Neoadjuvant therapy may improve survival compared with upfront surgery in people with resectable and borderline resectable pancreatic cancer ([van Dam 2021](#)). Adjuvant therapy has been shown to significantly improve outcomes and is standard care in people with resected pancreatic cancer ([Pancreatic Cancer ESMO](#)).

See [Appendix 1](#) for a glossary of terms.

Description of the intervention

Surgical resection is the current standard therapy for resectable periampullary tumours and is performed by an en-bloc resection of the head of the pancreas, gallbladder with the common bile duct, duodenum, proximal jejunum, and loco-regional lymph nodes ([Lillemoe 2000](#)). The standard treatment for resectable tumours consists of a classic Whipple's operation ([Whipple 1935](#)), a pylorus-resecting pancreatoduodenectomy (PRPD; [Kawai 2011](#)), or a pylorus-preserving pancreatoduodenectomy (PPPD; [Traverso 1980](#)). The classic Whipple's operation involves resection of the stomach antrum. In PRPD, the proximal side of the pyloric ring and most of the stomach is preserved, whereas in PPPD, the whole pyloric ring is preserved.

In open surgery, access to the abdomen can be achieved by an upper midline incision or a bilateral subcostal incision (rooftop or Chevron incision). In laparoscopy, surgical access to the abdominal cavity is by a number of trocars through which laparoscopic instruments can be inserted after the abdomen is insufflated using carbon-dioxide pneumoperitoneum. The robotic surgical system consists of a three- or four-armed robot operated by the surgeon, who sits at a separate console. The robotic approach affords the surgeon a three-dimensional stereoscopic view of the operating field and restores hand-eye co-ordination, which is often lost in traditional laparoscopy when the camera is offset to the plane of dissection. The instrumentation replicates the movements of the human hand with seven degrees of freedom and eliminates hand tremor ([Joyce 2014](#)). Classic Whipple's operation, PRPD, and PPPD can all be performed through open or minimally invasive approaches ([Cameron 2015](#); [Croome 2014](#); [Mesleh 2013](#)).

Improvements in surgical techniques and centralisation of pancreatic surgery have led to mortality rates of less than 5% ([de](#)

Wilde 2012; Buchler 2003; Cameron 2015). Nevertheless, operative morbidity remains high at 30% to 45%, from causes including sepsis, pancreatic fistula, intra-abdominal abscess, and delayed gastric emptying (Bassi 2001; Cameron 2015; Gouma 2000).

How the intervention might work

For many surgical procedures – including cholecystectomy (removal of gallbladder), colon cancer operations, and hysterectomy – minimally invasive surgery is currently preferred to open surgery (Bijen 2009; Keus 2006; Reza 2006; Talseth 2014; Walsh 2009). The advantages of minimally invasive surgery include decreased pain, decreased blood loss, shorter hospital stay, earlier postoperative recovery, better cosmesis (physical appearance), and decreased costs (Bijen 2009; Keus 2006; Reza 2006; Talseth 2014; Walsh 2009).

Why it is important to do this review

Laparoscopic pancreatoduodenectomy is feasible and performed in several centres (Croome 2014; Mesleh 2013). The smaller incisions may reduce pain and result in earlier postoperative recovery. However, as pancreatoduodenectomy has a high complication rate and mandates adequate cancer clearance, the laparoscopic approach must be proven safe before it can be widely recommended (van Hilst 2019).

Another issue with laparoscopy is the adequacy of cancer clearance in terms of resection margins and the extent of lymph nodes removed. In open surgery, tactile sensibility helps the surgeon determine whether the tissue being cut is cancerous, but this is largely lost in laparoscopy (Al-Taan 2010). Other concerns related to cancer clearance are the risk of port-site metastases (recurrence of cancer at the laparoscopic port site), reported in less than 2% of a small cohort of people who underwent pancreatic and periampullary cancer surgery (Kauffmann 2016). In addition, studies have reported prolonged operating times for laparoscopic pancreatoduodenectomy (Mesleh 2013). Robot-assisted surgery has features that help overcome some of the difficulties of conventional laparoscopy, and there are increasing reports of robotic pancreatoduodenectomy (Joyce 2014).

To date, there have been no Cochrane reviews on minimally invasive versus open pancreatoduodenectomy in benign, premalignant, and malignant disease.

OBJECTIVES

To assess the benefits and harms of laparoscopic or robot-assisted pancreatoduodenectomy versus open pancreatoduodenectomy for people with benign, premalignant, and malignant disease.

METHODS

Criteria for considering studies for this review

Types of studies

We will include only RCTs, including cluster-RCTs. We will include studies reported as full text or abstract only, as well as unpublished data. A single RCT can provide a better estimate of the effect than multiple observational studies (even if they show consistent and precise results) in this particular situation. Clearly, multiple RCTs with consistent effect estimates are more reliable than a single RCT. We consider that non-randomised studies would have significant

selection bias, as low-risk participants are more likely to receive laparoscopic surgery, while high-risk participants (those with more advanced disease) are more likely to undergo open surgery. A meta-analysis of such observational studies could produce misleading effect estimates.

Types of participants

We will include adults undergoing pancreatoduodenectomy for benign, premalignant, and malignant periampullary disease. Periampullary tumours are tumours that arise from the region around the ampulla of Vater. We will exclude adults undergoing other pancreatic surgeries (e.g. metastasectomies, distal pancreatectomy, pancreatic pseudocyst drainage, pancreatic drainage procedures for CP, or pancreatic enucleation for benign neuroendocrine tumours) as the issues surrounding minimally invasive versus open surgery for these procedures are different from those surrounding minimally invasive versus open pancreatoduodenectomy.

We will include studies that enrol only a subset of participants of interest for this review if separate data are available for the eligible participants, or if most study participants are eligible for inclusion in this review. We will evaluate the impact of this decision in a sensitivity analysis, removing studies with a subset of eligible participants. In addition, we will reach out to the authors of these studies to request additional information or data on the broader eligible population.

Types of interventions

We will include trials that compare laparoscopic or robot-assisted pancreatoduodenectomy (minimally invasive) versus open pancreatoduodenectomy, provided the only difference between the randomised groups is the use of a minimally invasive or open method of access to the pancreas.

We will exclude trials comparing different methods of minimally invasive pancreatoduodenectomy (e.g. minimally invasive classical Whipple versus minimally invasive PPPD) or different methods of open pancreatoduodenectomy. We will exclude studies that plan hybrid procedures at the outset. However, if participants are randomised to one procedure but then receive another (e.g. robotic procedure converted to laparoscopic procedure or laparoscopic procedure converted to open procedure), we will include the studies and perform intention-to-treat analysis (i.e. analysing participants in the group to which they were randomised). Conversion to other procedures is one of our secondary outcomes.

Types of outcome measures

Our choice of clinical outcomes is based on the need to assess whether minimally invasive surgery is safe, results in adequate cancer clearance and survival, and is beneficial in terms of decreased blood transfusion requirements, earlier postoperative recovery, and improved health-related quality of life. To be included in this review, studies must report at least one of our primary outcomes. The primary outcomes are significant for clinical decision-making and addressing the benefits and harms of laparoscopic, robot-assisted, and open pancreatoduodenectomy for people with benign, premalignant, and malignant diseases.

Primary outcomes

1. Mortality

- a. Short-term mortality (in-hospital mortality or mortality within three months; dichotomous outcome)
- b. Long-term mortality (from one year after randomisation to latest available time point; time-to-event outcome)
2. Serious adverse events (within three months of the operation; continuous outcome). We will record the total number of serious adverse events using the following definitions.
 - a. Clavien-Dindo classification grade III or greater: any adverse events requiring surgical, endoscopic, or radiological intervention; life-threatening complications requiring intensive care; or adverse events leading to death ([Clavien 2009](#); [Dindo 2004](#))
 - b. International Conference on Harmonisation - Good Clinical Practice (ICH-GCP) guideline: 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 ([ICH-GCP 1996](#))
 - c. 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, such as postpancreatectomy haemorrhage, delayed gastric emptying, and reintervention
 - d. Clinically significant pancreatic fistulas (type B or type C according to the International Study Group on Pancreatic Fistula (ISGPF) definition; [Bassi 2005](#))
3. Health-related quality of life (latest available time point, using any validated scale)
 - a. Short term (four weeks to three months)
 - b. Medium term (longer than three months to one year)
5. Surgical duration
6. Conversion
 - a. Conversion to laparoscopic procedures
 - b. Conversion to open procedures
7. Measures of postoperative recovery
 - a. Length of hospital stay (including the index admission for pancreatoduodenectomy and any readmissions related to surgical complications)
 - b. Time to return to normal activity (return to preoperative mobility without any additional carer support)
 - c. Time to return to work (in people who were employed previously)
 - d. Number of readmissions

Search methods for identification of studies

We will conduct a literature search to identify all published and unpublished RCTs, with no restrictions on the language of publication. We will translate any non-English language papers and fully assess them for potential inclusion in the review as necessary.

Electronic searches

We will search the following electronic databases to identify potential studies.

- Cochrane Central Register of Controlled Trials (CENTRAL; [Appendix 2](#))
- MEDLINE (1966 to present; [Appendix 3](#))
- Embase (1988 to present; [Appendix 4](#))

Searching other resources

We will check the reference lists of all primary studies and relevant review articles for additional references. We will contact authors of included trials to ask if they are aware of other published or unpublished studies.

We will search for errata or retractions from eligible trials on [PubMed](#) and report the date of this search in the review.

We will also search the following grey literature databases.

1. Health Management Information Consortium (HMIC) database (www.ovid.com/site/catalog/DataBase/99.jsp)
2. National Technical Information Service (NTIS) library (ntrl.ntis.gov/NTRL)
3. OpenGrey (www.opengrey.eu)

We will also search the following clinical trial registers.

1. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov; [Appendix 5](#))
2. World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal (trialsearch.who.int; [Appendix 6](#))

Data collection and analysis

Selection of studies

Two review authors (DR, PB) will independently screen the titles and abstracts of all records identified in the searches and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not

Secondary outcomes

1. Any adverse events (within three months; continuous outcome). We will record the total number of adverse events reported by the study authors irrespective of severity.
2. Recurrence (local recurrence, surgical wound recurrence (also called port-site metastases in the laparoscopic or robotic group) or distant metastases)
 - a. Short-term recurrence (within six months; time-to-event outcome)
 - b. Long-term recurrence (more than six months after randomisation; time-to-event outcome)
3. Oncological clearance in malignant diseases
 - a. Positive resection margins (presence of macroscopic or microscopic cancer tissue at the plane of resection) at histopathological examination after surgery
 - b. Tumour size at histopathological examination after surgery
 - c. Total number of harvested lymph nodes and number of positive lymph nodes at histopathological examination after surgery
 - d. Perineural invasion and lymphovascular invasion at histopathological examination after surgery
4. Perioperative blood loss
 - a. Quantity of blood loss
 - b. Proportion of people requiring blood transfusion during surgery or within one week after surgery (whole blood or red cell transfusion)
 - c. Quantity of blood transfusion

retrieve'. We will retrieve the full-text study reports/publications of all studies in the first category, and two review authors (DR, PB) will independently assess them against our eligibility criteria to determine which studies to include. They will record reasons for exclusion of all ineligible studies at this stage. We will resolve any disagreement through discussion or, if required, by consulting a third review author (KG). We will identify and exclude duplicates and collate multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram (Page 2021).

Data extraction and management

We will extract study characteristics and outcome data to a standard data collection form that has been piloted on at least one study in the review. Two review authors (DR, PB) will extract the following study characteristics from the included studies.

1. Methods: study design, total duration of study and run-in period, number of study centres and location, study setting, withdrawals, date of study
2. Participants: number, mean age, age range, sex, American Society of Anesthesiologists (ASA) status (ASA 2014), body mass index (BMI), inclusion and exclusion criteria, tumour size, tumour stage, histological diagnosis
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 (DR, PB) will independently extract outcome data from the included studies. If outcomes are reported multiple times in the same time period (e.g. short-term health-related quality of life reported at six weeks and three months), we will choose the later time point for data extraction. For time-to-event outcomes, we will extract data to calculate the hazard ratio (HR) and its standard error (SE) using the methods suggested by Parmar and colleagues (Parmar 1998). We will include all randomised participants for medium-term and long-term outcomes (e.g. mortality or quality of life), and this will not be conditional upon the short-term outcomes (e.g. being alive at three months or having a low or high quality of life index at three months). We will note in the 'Characteristics of included studies' table if outcome data were reported in an unusable way. We will resolve disagreements by consensus or by involving a third review author (KG). One review author (DR) will copy the data from the collection form to the Review Manager (RevMan) file (RevMan 2024). We will double-check that the data are entered correctly by comparing the study reports with how the data are presented in the systematic review. A second review author will spot-check study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (PB, DR) will independently assess risk of bias using Cochrane's risk of bias tool RoB 2 (Sterne 2019). We will assess the risk of bias according to the effect of assignment (the intention-to-treat effect). Our risk of bias assessments will focus on our primary outcomes (mortality, serious adverse events, and health-related quality of life), which we will present in a summary

of findings table. Any disagreements will be resolved by discussion or by involving a third review author (KG). We will assess risk of bias according to the following domains.

1. Bias arising from the randomisation process
2. Bias due to deviations from intended interventions
3. Bias due to missing outcome data
4. Bias in measurement of the outcome
5. Bias in selection of the reported result

For cluster-RCTs, we also plan to consider 'bias arising from the timing of identification and recruitment of individual participants within clusters in relation to timing of randomisation' (RoB 2 Domain 1b; Elridge 2021).

We will grade each potential source of bias as 'high risk of bias', 'some concerns', or 'low risk of bias' based on the answers to signalling questions. To implement the risk of bias assessment, we will use the RoB 2 excel tool (available at riskofbiasinfo.org), which comprises the following sections.

1. A series of signalling questions
2. A judgement about risk of bias for the domain, which is facilitated by an algorithm that maps responses to the signalling questions to a proposed judgement
3. Free text boxes to justify responses to the signalling questions and risk of bias judgements
4. An option to predict (and explain) the likely direction of bias

We will include answers to signalling questions in a supplementary data file. We will summarise the risk of bias judgements across different studies for each of the domains listed. Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the risk of bias table. When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse dichotomous data as risk ratios (RRs) with 95% confidence intervals (CIs). For continuous data, we will calculate mean differences (MDs) with 95% CIs when the outcome is reported or converted to the same units in all the trials, or standardised mean differences (SMDs) with 95% CIs when different scales are used for measuring the outcome. We will ensure that higher scores for continuous outcomes have the same meaning, explain the direction to the reader, and report where we reversed the directions (if this was necessary).

We will calculate HRs for time-to-event outcomes such as long-term mortality and long-term recurrence.

We will undertake meta-analyses only where the treatments, participants, and underlying clinical question are sufficiently similar for pooling to make sense.

A common way that trialists indicate when they have skewed data is by reporting medians and interquartile ranges (IQRs). When we encounter this, we will note whether the data are skewed and consider the implications of this.

Unit of analysis issues

The unit of analysis will be the individual participant undergoing pancreatoduodenectomy. We do not anticipate finding any cluster-RCTs, but if we do, we will obtain the effect estimate adjusted for clustering. If this is not available, we will evaluate the impact of removing the trial in a sensitivity analysis, as the variance of the effect estimate unadjusted for clustering is less than the true variance, which means unadjusted cluster-RCTs have too much weight in the meta-analysis.

Where a single trial reports multiple trial arms, we will include only the relevant arms. If we have to enter two comparisons with a shared group in the same meta-analysis (e.g. laparoscopic pancreatoduodenectomy method 1 versus open pancreatoduodenectomy and laparoscopic pancreatoduodenectomy method 2 versus open pancreatoduodenectomy), we will halve the shared group to avoid double counting. An alternative way of including such a trial would be to pool the results of laparoscopic pancreatoduodenectomy method 1 and laparoscopic pancreatoduodenectomy method 2 and compare the combined group with open pancreatoduodenectomy. We will perform a sensitivity analysis to determine if the results of the two methods of dealing with multiarm trials lead to different conclusions.

We will calculate the rate ratio (RaR) for outcomes such as adverse events and serious adverse events, where it is possible for the same person to develop more than one adverse event (or serious adverse event), using the inverse variance method provided by RevMan (RevMan 2024). If the study authors have calculated the RaR of adverse events (or serious adverse events) in the intervention versus control based on Poisson regression, we will obtain the RaR by the Poisson regression method in preference to RaR calculated based on the number of adverse events (or serious adverse events) during a certain period.

Dealing with missing data

We will contact investigators or study sponsors to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as abstract only). If we are unable to obtain the information from the investigators or study sponsors, we will impute means from medians (i.e. consider median as the mean) and standard deviations (SDs) from SEs, IQRs, or P values, using methods presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2023). We will assess the impact of including these studies in a sensitivity analysis. If we are unable to calculate the SD from the SE, IQR, or P values, we will impute the SD as the highest SD in the remaining trials included in the outcome, though we understand this method of imputation will decrease the weight of the studies in the meta-analysis of MD and shift the effect towards no effect for SMD.

Assessment of heterogeneity

We will assess the presence of statistical heterogeneity by visually inspecting the forest plots and performing the Chi² test. To quantify statistical heterogeneity in each analysis, we will use the I² statistic

(Higgins 2003). If we identify substantial heterogeneity (I² value greater than 50% to 60%), we report it and investigate possible causes following the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2023).

We will assess clinical diversity in the included studies by considering differences in the participants, setting, interventions and outcomes assessed. We will also consider whether there are methodological differences in the study design or risk of bias. Diversity in these factors will impact on the decision of whether to pool data from different studies. We may also consider these sources of heterogeneity when assessing outcomes using the GRADE approach.

Assessment of reporting biases

If we are able to pool more than 10 trials, we will create and examine a funnel plot to explore possible publication biases. We will use Egger's test to determine the statistical significance of the reporting bias (Egger 1997), with the significance level set at 0.05.

Data synthesis

We will perform analyses using the random-effects model in RevMan (RevMan 2024). We plan to restrict the primary analysis to studies judged at low risk of bias and some concerns. We plan to perform sensitivity analyses to show how conclusions might be affected if studies at high risk of bias were included.

We will consider clinical and methodological differences between the studies that might account for the high heterogeneity; training and experience of surgeons may play a role.

When standard meta-analysis is not possible, we will do the following.

1. We will present the information in a table ordered by comparisons and by the sample size of studies.
2. We will perform a meta-analysis of P-values if possible.
3. If meta-analysis of P-values is not possible, we will use 'vote counting' and the 'sign test' to find out if the intervention is effective. We will not consider the statistical significance of the individual studies for the 'voting counting' method. We will present the information by harvest plot if we use the 'vote counting' method.
4. For continuous outcomes, we will also present the weighted median and quartiles of the means or medians when standard meta-analysis is not possible. If we calculate the weighted median and quartiles, we will present this information in a box plot.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses of our primary outcomes (mortality, serious adverse outcomes, and health-related quality of life).

1. Different anaesthetic risk (ASA I (healthy person) or II (person with mild systemic disease) versus ASA III or more (person with severe systemic disease or worse)), as people in lower ASA categories are more likely to undergo minimally invasive surgery.

2. Benign or premalignant disease versus malignant disease, as the probability of minimally invasive surgery being successful may be lower in malignant tumours.
3. Pancreatic ductal adenocarcinoma versus distal cholangiocarcinoma or periampullary cancer or other, as these cancer types exhibit distinct biological behaviours.
4. Pylorus preserving versus classical Whipple, as there might be differences in complication rate (such as delayed gastric emptying).
5. Tumour size (≤ 2 cm versus > 2 cm), as the probability of minimally invasive surgery being successful is higher in smaller tumours.

We will use the formal Chi² test to test for subgroup interactions, considering a P value of 0.05 as statistically significant.

Sensitivity analysis

For all outcomes, we will perform sensitivity analyses to assess the robustness of our conclusions. This will involve excluding studies with the following characteristics.

1. Some concerns or high risk of bias in one or more risk of bias domains
2. Imputed mean, SD, or both
3. Cluster RCTs without adjusted effect estimates
4. Subset of eligible participants

We will also use sensitivity analysis to evaluate the effect of using different methods of dealing with multiarm trials (see [Measures of treatment effect](#)). We will attempt to contact study authors to request missing outcome data. Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results through sensitivity analysis.

Summary of findings and assessment of the certainty of the evidence

We will create summary of findings tables according to the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Schünemann 2023a](#)), for the following comparisons and critical outcomes.

1. Comparisons
 - a. Laparoscopic versus open pancreatoduodenectomy
 - b. Robotic versus open pancreatoduodenectomy
2. Outcomes
 - a. Short-term mortality
 - b. Long-term mortality
 - c. Serious adverse events
 - d. Health-related quality of life

The overall RoB 2 judgement will feed into the GRADE assessment. We will use the five GRADE considerations (risk of bias, inconsistency, indirectness, imprecision, and publication bias) to assess the certainty of a body of evidence as it relates to the studies which contribute data to the outcomes. We will use GRADEpro for the assessment ([GRADEpro GDT](#)), following methods

and recommendations described in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Schünemann 2023b](#)). Two review authors (DR and PB) will independently assess the certainty of the evidence. Any disagreement will be resolved by discussion or by involving a third review author (KG). We will justify all decisions to downgrade or upgrade the certainty of evidence using footnotes and make comments to aid readers' understanding of the review where necessary. We will consider whether there is any additional outcome information that we could not incorporate in the meta-analyses, stating in the comments whether it supports or contradicts the information from the meta-analyses.

We will base our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We will avoid making recommendations for practice, and 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 what the remaining uncertainties are.

ACKNOWLEDGEMENTS

The methods section of this protocol is based on a standard template used by Cochrane Gastrointestinal and Pancreatic Diseases Review Group.

We thank Cathy Yuan, Trials Search Co-ordinator, Cochrane Upper Gastrointestinal and Pancreatic Diseases (UGPD) Group for proving support for developing search strategies.

We acknowledge the help and support of the Cochrane Upper Gastrointestinal Diseases Review Group. The review authors would also like to thank the editors and peer referees who provided comments to improve the protocol.

Cochrane GUT Group supported the authors in the development of this systematic review protocol. The following people conducted the editorial process for this article:

- Sign-off Editor (final editorial decision): Grigorios Leontiadis, McMaster University, Canada
- Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Marwah Anas El-Wegoud, Cochrane Central Editorial Service
- Editorial Assistant (conducted editorial policy checks and supported editorial team): Lisa Wyrzynski, Cochrane Central Editorial Service
- Copy Editor (copy editing and production): Julia Turner, Cochrane Central Production Service
- Peer-reviewers (provided comments and recommended an editorial decision): Aslam Ejaz, MD, MPH, The Ohio State University (clinical review); Benedetto Ielpo HPB Unit Hospital del Mar, Pompeu Fabra University, Barcelona, Spain (clinical review); Safi Dokmak, MD PhD, Department of HPB surgery and liver transplantation, Beaujon hospital, Clichy France (clinical review); Alfretta Vanderheyden, UGPD (consumer review); Nuala Livingstone, Cochrane Evidence Production and Methods Directorate (methods review); Jo Abbott, Cochrane Information Specialist (search review)

REFERENCES

Additional references

Abrams 2009

Abrams RA, Lowy AM, O'Reilly EM, Wolff RA, Picozzi VJ, Pisters PW. Combined modality treatment of resectable and borderline resectable pancreas cancer: expert consensus statement. *Annals of Surgical Oncology* 2009;**16**(7):1751-6.

Al-Taan 2010

Al-Taan OS, Stephenson JA, Briggs C, Pollard C, Metcalfe MS, Dennison AR. Laparoscopic pancreatic surgery: a review of present results and future prospects. *HPB (Oxford)* 2010;**12**(4):239-43.

ASA 2014

American Society of Anesthesiologists. ASA physical status classification system. www.asahq.org/Home/For-Members/Clinical-Information/ASA-Physical-Status-Classification-System (accessed 13 November 2014).

Bassi 2001

Bassi C, Falconi M, Salvia R, Mascetta G, Molinari E, Pederzoli P. Management of complications after pancreaticoduodenectomy in a high volume centre: results on 150 consecutive patients. *Digestive Surgery* 2001;**18**(6):453-7.

Bassi 2005

Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery* 2005;**138**(1):8-13.

Bijen 2009

Bijen CB, Vermeulen KM, Mourits MJ, de Bock GH. Costs and effects of abdominal versus laparoscopic hysterectomy: systematic review of controlled trials. *PLoS One* 2009;**4**(10):7340.

Buchler 2003

Buchler MW, Wagner M, Schmied BM, Uhl W, Friess H, Z'graggen K. Changes in morbidity after pancreatic resection: toward the end of completion pancreatectomy. *Changes in morbidity after pancreatic resection: toward the end of completion pancreatectomy* 2003;**138**(12):1310-4.

Cameron 2015

Cameron JL, He J. Two thousand consecutive pancreaticoduodenectomies. *Journal of the American College of Surgeons* 2015;**220**(4):530-6.

Cancer Statistics 2024

Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. *CA: A Cancer Journal for Clinicians* 2024;**74**(1):12-49.

Clavien 2009

Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Annals of Surgery* 2009;**250**(2):187-96.

Crippa 2016

Crippa S, Capurso G, Cammà C, Fave GD, Castillo CF, Falconi M. Risk of pancreatic malignancy and mortality in branch-duct IPMNs undergoing surveillance: a systematic review and meta-analysis. *Digestive and Liver Disease* 2016;**48**(5):473-9.

Croome 2014

Croome KP, Farnell MB, Que FG, Reid-Lombardo KM, Truty MJ, Nagorney DM, et al. Total laparoscopic pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: oncologic advantages over open approaches? *Annals of Surgery* 2014;**260**(4):633-8.

de Wilde 2012

de Wilde RF, Besselink MG, van der Tweel I, de Hingh IH, van Eijck CH, Dejong CH, et al. Impact of nationwide centralization of pancreaticoduodenectomy on hospital mortality. *British Journal of Surgery* 2012;**99**(3):404-10.

Deeks 2023

Chapter 10: Analysing data and undertaking meta-analyses In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s) *Cochrane Handbook for Systematic Reviews of Interventions* Version 64 (updated August 2023) Cochrane, 2023. Chapter 10: Analysing data and undertaking meta-analyses. Available from training.cochrane.org/handbook.

Diener 2017

Diener MK, Hüttner FJ, Kieser M, Knebel P, Dörr-Harim C, Distler M, et al, ChroPac Trial Group. Partial pancreatoduodenectomy versus duodenum-preserving pancreatic head resection in chronic pancreatitis: the multicentre, randomised, controlled, double-blind ChroPac trial. *Lancet* 2017;**390**(10099):1027-37.

Dindo 2004

Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Annals of Surgery* 2004;**240**(2):205-13.

Egger 1997

Egger M, Davey SG, Schneider M, Minder C. Bias in meta analysis detected by a simple, graphical test. *BMJ (Clinical Research Ed.)* 1997;**315**(7109):629-34.

Elridge 2021

Elridge S, Campbell MK, Campbell MJ, Drahote AK, Giraudeau B, Reeves BC, et al. Revised Cochrane risk of bias tool for randomized trials (RoB 2) – Additional considerations for cluster-randomized trials (RoB 2 CRT). Available at www.riskofbias.info/welcome/rob-2-0-tool/rob-2-for-cluster-randomized-trials.

ESGCT 2018

European Study Group on Cystic Tumours of the Pancreas. European evidence-based guidelines on pancreatic cystic neoplasms. *Gut* 2018;**67**:789-804.

Falconi 2016

Falconi M, Eriksson B, Kaltsas G, Bartsch DK, Capdevila J, Caplin M, et al, Vienna Consensus Conference participants. Consensus guidelines update for the management of functional p-NETs (F-p-NETs) and non-functional p-NETs (NF-p-NETs). *Neuroendocrinology* 2016;**103**(2):153-71.

Ghaneh 2007

Ghaneh P, Costello E, Neoptolemos JP. Biology and management of pancreatic cancer. *Gut* 2007;**56**(8):1134-52.

Gouma 2000

Gouma DJ, van Geenen RC, van Gulik TM, de Haan RJ, de Wit LT, Busch OR, et al. Rates of complications and death after pancreaticoduodenectomy: risk factors and the impact of hospital volume. *Annals of Surgery* 2000;**232**(6):786-95.

GRADEpro GDT [Computer program]

GRADEpro Guideline Development Tool. McMaster University and Evidence Prime, 2024. Available at gradepr.org.

Halfdanarson 2008

Halfdanarson TR, Rubin J, Farnell MB, Grant CS, Petersen GM. Pancreatic endocrine neoplasms: epidemiology and prognosis of pancreatic endocrine tumors. *Endocrine-Related Cancer* 2008;**15**(2):409-27.

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60.

Higgins 2023

Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 6.4 (updated August 2023). Cochrane, 2023. Available from training.cochrane.org/handbook.

ICH-GCP 1996

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Code of Federal Regulation & ICH Guidelines. Media: Parexel Barnett 1996.

Jensen 2008

Jensen RT, Berna MJ, Bingham DB, Norton JA. Inherited pancreatic endocrine tumor syndromes: advances in molecular pathogenesis, diagnosis, management, and controversies. *Cancer* 2008;**113**:1807-43.

Johnson 2008

Johnson LB, Amin R. Pancreaticoduodenectomy. In: Evans SRT, editors(s). *Surgical Pitfalls: Prevention and Management*. Saunders Elsevier, 2009.

Joyce 2014

Joyce D, Morris-Stiff G, Falk GA, El-Hayek K, Chalikhonda S, Walsh RM. Robotic surgery of the pancreas. *World Journal of Gastroenterology* 2014;**20**(40):14726-32.

Kauffmann 2016

Kauffmann EF, Napoli N, Costa F, Menonna F, Iacopi S, De Lio N, et al. Port-site metastasis following laparoscopic robotic-assisted pancreatic resections for cancer. *HPB* 2016;**18**:e353.

Kawai 2011

Kawai M, Tani M, Hirono S, Miyazawa M, Shimizu A, Uchiyama K, et al. Pylorus ring resection reduces delayed gastric emptying in patients undergoing pancreatoduodenectomy: a prospective, randomized, controlled trial of pylorus-resecting versus pylorus-preserving pancreatoduodenectomy. *Annals of Surgery* 2011;**253**(3):495-501.

Kempeneers 2020

Kempeneers MA, Issa Y, Ali UA, Baron RD, Besselink MG, Buchler M, et al. International consensus guidelines for surgery and the timing of intervention in chronic pancreatitis. *Pancreatology* 2020;**20**:149-157.

Keus 2006

Keus F, de Jong JA, Gooszen HG, van Laarhoven CJ. Laparoscopic versus open cholecystectomy for patients with symptomatic cholelithiasis. *Cochrane Database of Systematic Reviews* 2006, Issue 4. Art. No: CD006231. [DOI: [10.1002/14651858.CD006231](https://doi.org/10.1002/14651858.CD006231)]

Komrey 2018

Kromrey ML, Bülow R, Hübner J, Paperlein C, Lerch MM, Ittermann T, et al. Prospective study on the incidence, prevalence and 5-year pancreatic-related mortality of pancreatic cysts in a population-based study. *Gut* 2018;**67**(1):138.

Lillemoe 2000

Lillemoe KD, Yeo CJ, Cameron JL. Pancreatic cancer: state-of-the-art care. *CA: A Cancer Journal for Clinicians* 2000;**50**(4):241-68.

Mesleh 2013

Mesleh MG, Stauffer JA, Bowers SP, Asbun HJ. Cost analysis of open and laparoscopic pancreaticoduodenectomy: a single institution comparison. *Surgical Endoscopy* 2013;**27**(12):4518-23.

Orr 2010

Orr RK. Outcomes in pancreatic cancer surgery. *Surgical Clinics of North America* 2010;**90**(2):219-34.

Page 2021

Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* 2021;**18**(3):e1003583.

Pancreatic Cancer ESMO

Conroy T, Pfeiffer P, Vilgrain V, Lamarca A, Seufferlein T, O'Reilly EM, et al, on behalf of the ESMO Guidelines Committee. Pancreatic cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Annals of Oncology* 2023;**34**(11):987-1002.

Parmar 1998

Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in Medicine* 1998;**17**(24):2815-34.

RevMan 2024 [Computer program]

Review Manager (RevMan). Version 7.10.1. The Cochrane Collaboration, 2024. Available at revman.cochrane.org.

Reza 2006

Reza MM, Blasco JA, Andradas E, Cantero R, Mayol JS. Systematic review of laparoscopic versus open surgery for colorectal cancer. *British Journal of Surgery* 2006;**93**(8):921-8.

Schünemann 2023a

Schünemann HJ, Vist GE, Higgins JP, Santesso N, Deeks JJ, Glasziou P, et al. Chapter 15: Interpreting results and drawing conclusions. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 6.4 (updated August 2023). Cochrane, 2023. Available from training.cochrane.org/handbook.

Schünemann 2023b

Schünemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, et al. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 6.4 (updated August 2023). Cochrane, 2023. Available from training.cochrane.org/handbook.

Scott 2019

Scott AT, Howe JR. Evaluation and management of neuroendocrine tumors of the pancreas. *Surgical Clinics of North America* 2019;**99**(4):793-814.

Stark 2016

Stark A, Donahue TR, Reber HA, Hines OJ. Pancreatic cyst disease: a review. *JAMA* 2016;**315**(17):1882-93.

Sterne 2019

Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;**366**:l4898.

Talseth 2014

Talseth A, Lydersen S, Skjedlestad F, Hveem K, Edna TH. Trends in cholecystectomy rates in a defined population during and after the period of transition from open to laparoscopic surgery. *Scandinavian Journal of Gastroenterology* 2014;**49**(1):92-8.

Traverso 1980

Traverso LW, Longmire WP Jr. Preservation of the pylorus in pancreaticoduodenectomy: a follow-up evaluation. *Annals of Surgery* 1980;**192**(3):306-10.

Tucker 2008

Tucker ON, Rela M. Controversies in the management of borderline resectable proximal pancreatic adenocarcinoma with vascular involvement. *HPB Surgery* 2008;**2008**:839503.

van Dam 2021

van Dam JL, Janssen QP, Besselink MG, Homs MY, van Santvoort HC, van Tienhoven G, et al. Neoadjuvant therapy or upfront surgery for resectable and borderline resectable pancreatic cancer: A meta-analysis of randomised controlled trials. *European Journal of Cancer* 2022;**160**:140-9.

van Hilst 2019

van Hilst J, de Rooij T, Bosscha K, Brinkman DJ, van Dieren S, Dijkgraaf MG, et al, Dutch Pancreatic Cancer Group. Laparoscopic versus open pancreatoduodenectomy for pancreatic or periampullary tumours (LEOPARD-2): a multicentre, patient-blinded, randomised controlled phase 2/3 trial. *Lancet Gastroenterology & Hepatology* 2019;**4**(3):199-207.

Walsh 2009

Walsh CA, Walsh SR, Tang TY, Slack M. Total abdominal hysterectomy versus total laparoscopic hysterectomy for benign disease: a meta-analysis. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 2009;**144**:3-7.

Whipple 1935

Whipple AO, Parsons WB, Mullins CR. Treatment of carcinoma of the ampulla of Vater. *Annals of Surgery* 1935;**102**:763-79.

APPENDICES

Appendix 1. Glossary of terms

Adenocarcinoma: a malignant tumour that forms in mucus-secreting glands.

Adjuvant: additional therapy to enhance or extend the effect of primary therapy's and prevent recurrence due to microscopic residual disease.

Antrum: a cavity within a hollow organ (e.g. stomach).

ASA: American Society of Anesthesiologists.

Benign: a condition, tumour, growth, or process that is not cancerous and does not have the potential to invade nearby tissues or spread to other parts of the body.

Bilateral: on both sides.

Minimally invasive versus open pancreatoduodenectomy in benign, premalignant, and malignant disease. (Protocol)

Copyright © 2024 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

BMI: body mass index.

CBD: common bile duct.

Chemotherapy: treatment of disease by means of chemical substances or drugs; usually used in reference to cancer.

Cholecystectomy: removal of the gallbladder.

Clavien Dindo classification: classification of surgical complications consisting of seven grades (I, II, IIIa, IIIb, IVa, IVb, V), based on the therapy used to correct the specific complication, designed to rank complications in an objective and reproducible manner.

CP: chronic pancreatitis.

Duodenum: the first section of the small intestine, connecting the stomach to the middle part of the small bowel (jejunum), where the bile duct and pancreatic duct enter, facilitating digestion with their secretions.

Endoscopic: a medical procedure or examination that involves the use of a flexible, slender tube (endoscope) with a light and a camera, inserted through natural openings or small incisions.

Enucleation: the removal of an entire structure in one piece from its supporting tissue.

Exocrine pancreas: the exocrine glands of the pancreas that produce digestive enzymes.

Fistula: an abnormal connection or passage that forms between two organs, vessels, or structures that are not normally connected.

HR: hazard ratio.

Hysterectomy: removal of the uterus.

ICH-GCP: International Conference on Harmonisation - Good Clinical Practice.

Insufflated: inflated with gas.

Intra-abdominal abscess: a collection of pus within the abdominal cavity.

Intraductal: the condition or process is occurring within a duct, a tube, or passage in the body that carries fluids.

IPMN: intraductal papillary mucinous neoplasm.

IPMN-MD: IPMD arising from the main pancreatic duct.

IPMN-BD: IPMD arising from the branch ducts.

Jejunum: the middle part of the small intestine between the duodenum and ileum.

Laparoscopy: a surgical procedure in which instruments are inserted through a hole in the abdominal wall.

Malignancy: a cancerous growth.

Metastasis: spread of cells from the original site of the cancer to another part of the body, usually through blood vessels, lymph channels, or spinal fluid.

Morbidity: illness. Complications following a surgical procedure or other treatment.

Mortality: death.

Neoplasm: abnormal mass of tissue that forms when cells divide more than they should or do not die when they should. Also known as a tumour.

NET: neuroendocrine tumour.

Neuroendocrine: cells that release a hormone into the circulating blood in response to a neural stimulus.

Pancreatic fistula: an abnormal or surgically created passage between the pancreas and the body surface, or between the pancreas and a hollow or tubular organ.

Pancreatoduodenectomy: an operation to remove part of the pancreas, small intestine, and the gallbladder. Also known as the Whipple procedure.

Minimally invasive versus open pancreatoduodenectomy in benign, premalignant, and malignant disease. (Protocol)

Copyright © 2024 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Periampullary cancers: cancers that arise from the region around the ampulla of Vater.

PNET: pancreatic NET.

Pneumoperitoneum: presence of air or gas in the abdominal cavity as a result of disease, or artificially induced to create space to perform laparoscopic surgery.

PPPD: pylorus-preserving pancreatoduodenectomy.

Premalignant: a condition, tumour, growth, or cellular change that has the potential to develop into cancer but has not yet become malignant.

Prognosis: outcome.

Proximal: situated near the central point.

PRPD: pylorus-resecting pancreatoduodenectomy.

Pseudocyst: a collection of fluid in the abdomen lacking a wall or lining normally characteristic of a true cyst.

Pylorus: the opening connecting the stomach and intestines.

Radiotherapy: treatment with radiation, especially by selective irradiation with X-rays or other ionising radiation and by ingestion of radioisotopes.

RCT: randomised controlled trial.

Resection: surgical removal.

Sepsis: harmful bacteria in the blood.

Subcostal: below a rib.

Systemic: affecting the whole body.

Transected: cut crosswise.

Trocars: sharp pointed surgical instruments used to insert instruments into the abdomen in laparoscopic surgery.

Uncinate process: a portion of the pancreas that wraps behind the superior mesenteric artery and superior mesenteric vein.

VHL: Von Hippel-Lindau syndrome.

Whipple's operation: an operation (pancreatoduodenectomy) to remove part of the pancreas, small intestine, and the gallbladder.

Appendix 2. Cochrane Central search strategy (via Ovid)

1. exp Pancreatic Neoplasms/
2. (pancreas* adj5 (neoplas* or cancer* or carcinoma* or tumor* or tumour* or malignan* or adenocarcinoma* or cystic or cyst or cysts)).tw,kw.
3. ((periampull* or peri-ampull*) adj5 (neoplas* or cancer* or carcinoma* or tumor* or tumour* or malignan* or adenocarcinoma*)).tw,kw.
4. (intraductal papillary mucinous neoplasia* or IPMN or IPMNs).tw,kw.
5. exp Duodenal Neoplasms/
6. exp Bile Duct Neoplasms/
7. (((ampulla* adj5 (hepatopancreatic or vater*)) or ampullovateric) adj5 (neoplas* or cancer* or carcinoma* or tumor* or tumour* or malignan* or adenocarcinoma*)).tw,kw.
8. ((duodenal or duodenum or bile duct or biliary or (papillar adj vater*) or choledoch* or alcholedoch* or cholangio* or gall duct) adj5 (neoplas* or cancer* or carcinoma* or tumor* or tumour* or malignan* or adenocarcinoma*)).tw,kw.
9. exp Pancreatitis, Chronic/
10. chronic pancreatitis.tw,kw.
11. or/1-10
12. exp Pancreaticoduodenectomy/ or exp pancreaticojejunostomy/
13. exp Pancreatectomy/

- 14.(pancreaticoduodenectomy* or pancreatoduodenectomy* or duodenopancreatectomy* or pancreatectomy* or hemipancreatectomy* or pancreaticojejunostomy* or pancreatojejunostomy*).tw,kw.
- 15.(pancreas* and (duodenectomy* or Whipple or PPPD or Pylorus-Preserv*)).tw,kw.
- 16.(pancrea* adj3 (surger* or surgical or operat* or resect* or remov*)).tw,kw.
- 17.or/12-16
- 18.11 and 17
- 19.exp Laparoscopy/
- 20.laparoscop*.tw,kw.
- 21.(peritoneoscop* or celioscop* or coelioscop*).tw,kw.
- 22.robot*.tw,kw.
- 23.(minimal* adj invasive).tw,kw.
- 24.exp Surgical Procedures, Minimally Invasive/
- 25.or/19-24
- 26.18 and 25

Appendix 3. Medline Search strategy (via Ovid)

1. exp Pancreatic Neoplasms/
2. (pancreas* adj5 (neoplas* or cancer* or carcinoma* or tumor* or tumour* or malignan* or adenocarcinoma* or cystic or cyst or cysts)).tw,kw.
3. ((periampull* or peri-ampull*) adj5 (neoplas* or cancer* or carcinoma* or tumor* or tumour* or malignan* or adenocarcinoma*)).tw,kw.
4. (intraductal papillary mucinous neoplasia* or IPMN or IPMNs).tw,kw.
5. exp Duodenal Neoplasms/
6. exp Bile Duct Neoplasms/
7. (((ampulla* adj5 (hepatopancreatic or vater*)) or ampullovateric) adj5 (neoplas* or cancer* or carcinoma* or tumor* or tumour* or malignan* or adenocarcinoma*)).tw,kw.
8. ((duodenal or duodenum or bile duct or biliary or (papillar adj vater*) or choledoch* or alcholedoch* or cholangio* or gall duct) adj5 (neoplas* or cancer* or carcinoma* or tumor* or tumour* or malignan* or adenocarcinoma*)).tw,kw.
9. exp Pancreatitis, Chronic/
- 10.chronic pancreatitis.tw,kw.
- 11.or/1-10
- 12.exp Pancreaticoduodenectomy/ or exp pancreaticojejunostomy/
- 13.exp Pancreatectomy/
- 14.(pancreaticoduodenectomy* or pancreatoduodenectomy* or duodenopancreatectomy* or pancreatectomy* or hemipancreatectomy* or pancreaticojejunostomy* or pancreatojejunostomy*).tw,kw.
- 15.(pancreas* and (duodenectomy* or Whipple or PPPD or Pylorus-Preserv*)).tw,kw.
- 16.(pancrea* adj3 (surger* or surgical or operat* or resect* or remov*)).tw,kw.
- 17.or/12-16
- 18.11 and 17
- 19.exp Laparoscopy/
- 20.laparoscop*.tw,kw.
- 21.(peritoneoscop* or celioscop* or coelioscop*).tw,kw.
- 22.exp Robotic Surgical Procedures/
- 23.robot*.tw,kw.
- 24.(minimal* adj invasive).tw,kw.
- 25.exp Minimally Invasive Surgical Procedures/
- 26.or/19-25
- 27.18 and 26
- 28.randomized controlled trial.pt.
- 29.controlled clinical trial.pt.
- 30.randomized.ab.
- 31.placebo.ab.
- 32.randomly.ab.
- 33.trial.ab.

- 34.groups.ab.
- 35.or/28-34
- 36.exp animals/ not humans.sh.
- 37.35 not 36
- 38.27 and 37
- 39.remove duplicates from 38

Note: lines #28-37. Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); Ovid format, excluded "drug therapy.fs."

Appendix 4. Embase search strategy (via Ovid)

1. exp pancreas tumor/
2. (pancreas* adj5 (neoplas* or cancer* or carcinoma* or tumor* or tumour* or malignan* or adenocarcinoma* or cystic or cyst or cysts)).tw,kw.
3. ((periampull* or peri-ampull*) adj5 (neoplas* or cancer* or carcinoma* or tumor* or tumour* or malignan* or adenocarcinoma*)).tw,kw.
4. (intraductal papillary mucinous neoplasia* or IPMN or IPMNs).tw,kw.
5. exp duodenum tumor/
6. exp bile duct tumor/
7. (((ampulla* adj5 (hepatopancreatic or vater*)) or ampullovateric) adj5 (neoplas* or cancer* or carcinoma* or tumor* or tumour* or malignan* or adenocarcinoma*)).tw,kw.
8. ((duodenal or duodenum or bile duct or biliary or (papillar adj vater*) or choledoch* or alcholedoch* or cholangio* or gall duct) adj5 (neoplas* or cancer* or carcinoma* or tumor* or tumour* or malignan* or adenocarcinoma*)).tw,kw.
9. chronic pancreatitis/
- 10.chronic pancreatitis.tw,kw.
- 11.or/1-10
- 12.exp pancreaticoduodenectomy/ or exp pancreaticojejunostomy/
- 13.exp pancreas resection/
- 14.(pancreaticoduodenectom* or pancreatoduodenectom* or duodenopancreatetectom* or pancreatetectom* or hemipancreatetectom* or pancreaticojejunostom* or pancreatojejunostom*).tw,kw.
- 15.(pancreas* and (duodenectom* or Whipple or PPPD or Pylorus-Preserv*)).tw,kw.
- 16.(pancrea* adj3 (surger* or surgical or operat* or resect* or remov*)).tw,kw.
- 17.or/12-16
- 18.11 and 17
- 19.exp laparoscopy/
- 20.laparoscop*.tw,kw.
- 21.(peritoneoscop* or celioscop* or coelioscop*).tw,kw.
- 22.exp robotics/
- 23.robot*.tw,kw.
- 24.(minimal* adj invasive).tw,kw.
- 25.exp minimally invasive surgery/
- 26.or/19-25
- 27.18 and 26
- 28.random:.tw.
- 29.placebo:.mp.
- 30.double-blind:.tw.
- 31.or/28-30
- 32.exp animal/ not human.sh.
- 33.31 not 32
- 34.27 and 33

Lines #28-31, Hedge Best balance of sensitivity and specificity filter for identifying randomized trials in Embase. https://hiru.mcmaster.ca/hiru/HIRU_Hedges_EMBASE_Strategies.aspx

Appendix 5. ClinicalTrials.gov search strategy

"Interventional" [STUDY-TYPES] AND pancreaticoduodenectomy [INTERVENTION]

Appendix 6. WHO ICTRP search strategy

pancrea* AND laparoscop*

pancrea* AND minimal*

pancrea* AND robot*

CONTRIBUTIONS OF AUTHORS

Conceiving the protocol: DR

Designing the protocol: DR, KG

Co-ordinating the protocol: DR

Providing general advice on methodology: PB, MB, CL, DK, CV, BD

Designing search strategies: CY

Writing - original draft of the protocol: DR, KG

Review & editing the protocol: KG, PB, MB, CL, DK, CV, BD

Performing previous work that was the foundation of the current study: KG

DECLARATIONS OF INTEREST

DR: none known.

PB: none known.

MB: received grants for investigator-initiated studies from Medtronic (DIPLOMA-1 trial), Intuitive (DIPLOMA-2 trial, LEARNBOT robot pancreas training program), Ethicon (PANDORINA trial).

CvL: none known.

DK: in 2021, DK received USD 5,922.50 from Medtronic as an educational consultant and USD 57.38 from Individual Surgical. In 2022, DK received USD 98.38 from Intuitive Surgical and USD 10.21 from Medtronic. DK has no ongoing relationships with any of the corporations.

CV: received compensation from Intuitive Surgical for consulting services as a participant in a usability study in 2024.

BD: none known.

KSG: the promotions and salary of KGS are dependent upon journal publications. KSG is a Cochrane editor and was not involved in the editorial process of this protocol.

SOURCES OF SUPPORT

Internal sources

- Internal source of support, Other

No funds, grants, or other support was received by DR or the other authors to perform this review.

External sources

- External funding, Other

No funds, grants, or other support was received by DR or the other authors to perform this review.