Extended lymph node resection versus standard resection for pancreatic and periampullary adenocarcinoma

Staerkle, Ralph F ; Vuille-Dit-Bille, Raphael Nicolas ; Soll, Christopher ; Troller, Rebekka ; Samra, Jaswinder ; Puhan, Milo A ; Breitenstein, Stefan

Abstract: **BACKGROUND** Pancreatic and periampullary adenocarcinomas account for some of the most aggressive malignancies, and the leading causes of cancer-related mortalities. Partial pancreaticoduodenectomy (PD) with negative resection margins is the only potentially curative therapy. The high prevalence of lymph node metastases has led to the hypothesis that wider excision with the removal of more lymphatic tissue could result in an improvement of survival, and higher rates of negative resection margins. **OBJECTIVES** To compare overall survival following standard (SLA) versus extended lymph lymphadenectomy (ELA) for pancreatic head and periampullary adenocarcinoma. We also compared secondary outcomes, such as morbidity, mortality, and tumour involvement of the resection margins between the two procedures. **SEARCH METHODS** We searched CENTRAL, MEDLINE, PubMed, and Embase from 1973 to September 2020; we applied no language restrictions. **SELECTION CRITERIA** Randomised controlled trials (RCT) comparing PD with SLA versus PD with ELA, including participants with pancreatic head and periampullary adenocarcinoma. **DATA COLLECTION AND ANALYSIS** Two review authors independently screened references and extracted data from study reports. We calculated pooled risk ratios (RR) for most binary outcomes except for postoperative mortality, for which we estimated a Peto odds ratio (Peto OR), and mean differences (MD) for continuous outcomes. We used a fixed-effect model in the absence of substantial heterogeneity ($I^2 < 25\%$), and a random-effects model in cases of substantial heterogeneity ($I^2 > 25\%$). Two review authors independently assessed risk of bias, and we used GRADE to assess the quality of the evidence for important outcomes. **MAIN RESULTS** We included seven studies with 843 participants (421 ELA and 422 SLA). All seven studies included Kaplan-Meier curves for overall survival. There was little or no difference in survival between groups (log hazard ratio (log HR) 0.12, 95% confidence interval (CI) -3.06 to 3.31; $P = 0.94$; seven studies, 843 participants; very low-quality evidence). There was little or no difference in postoperative mortality between the groups (Peto odds ratio (OR) 1.20, 95% CI 0.51 to 2.80; seven studies, 843 participants; low-quality evidence). Operating time was probably longer for ELA (mean difference (MD) 50.13 minutes, 95% CI 19.19 to 81.06 minutes; five studies, 670 participants; moderate-quality evidence). There was substantial heterogeneity between the studies ($I^2 = 88\%$; $P < 0.00001$). There may have been more blood loss during ELA (MD 137.43 mL, 95% CI 11.55 to 263.30 mL; two studies, 463 participants; very low-quality evidence). There was substantial heterogeneity between the studies ($I^2 = 81\%$, $P = 0.02$). There may have been more lymph nodes retrieved during ELA (MD 11.09 nodes, 95% CI 7.16 to 15.02; five studies, 670 participants; moderate-quality evidence). There was substantial heterogeneity between the studies ($I^2 = 81\%$, $P < 0.00001$). There was little or no difference in the incidence of positive resection margins between groups (RR 0.81, 95% CI 0.58 to 1.13; six studies, 783 participants; very low-quality evidence). **AUTHORS' CONCLUSIONS** There is no evidence of an impact on survival with extended versus standard lymph node resection. However, the operating time may have been longer and blood loss greater in the extended resection group. In conclusion, current evidence neither supports nor refutes the effect of extended lymph lymphadenectomy in people with adenocarcinoma of the head of the pancreas.

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(Review)

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[Intervention Review]

Extended lymph node resection versus standard resection for pancreatic and periampullary adenocarcinoma

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ABSTRACT

Background

Pancreatic and periampullary adenocarcinomas account for some of the most aggressive malignancies, and the leading causes of cancer-related mortalities. Partial pancreaticoduodenectomy (PD) with negative resection margins is the only potentially curative therapy. The high prevalence of lymph node metastases has led to the hypothesis that wider excision with the removal of more lymphatic tissue could result in an improvement of survival, and higher rates of negative resection margins.

Objectives

To compare overall survival following standard (SLA) versus extended lymph lymphadenectomy (ELA) for pancreatic head and periampullary adenocarcinoma. We also compared secondary outcomes, such as morbidity, mortality, and tumour involvement of the resection margins between the two procedures.

Search methods

We searched CENTRAL, MEDLINE, PubMed, and Embase from 1973 to September 2020; we applied no language restrictions.

Selection criteria

Randomised controlled trials (RCT) comparing PD with SLA versus PD with ELA, including participants with pancreatic head and periampullary adenocarcinoma.

Data collection and analysis

Two review authors independently screened references and extracted data from study reports. We calculated pooled risk ratios (RR) for most binary outcomes except for postoperative mortality, for which we estimated a Peto odds ratio (Peto OR), and mean differences (MD) for continuous outcomes. We used a fixed-effect model in the absence of substantial heterogeneity ($I^2 < 25\%$), and a random-effects model in cases of substantial heterogeneity ($I^2 > 25\%$). Two review authors independently assessed risk of bias, and we used GRADE to assess the quality of the evidence for important outcomes.

Main results

We included seven studies with 843 participants (421 ELA and 422 SLA).

All seven studies included Kaplan-Meier curves for overall survival. There was little or no difference in survival between groups (log hazard ratio (log HR) 0.12, 95% confidence interval (CI) -3.06 to 3.31; $P = 0.94$; seven studies, 843 participants; very low-quality evidence).

There was little or no difference in postoperative mortality between the groups (Peto odds ratio (OR) 1.20, 95% CI 0.51 to 2.80; seven studies, 843 participants; low-quality evidence).

Operating time was probably longer for ELA (mean difference (MD) 50.13 minutes, 95% CI 19.19 to 81.06 minutes; five studies, 670 participants; moderate-quality evidence). There was substantial heterogeneity between the studies ($I^2 = 88\%$; $P < 0.00001$).

There may have been more blood loss during ELA (MD 137.43 mL, 95% CI 11.55 to 263.30 mL; two studies, 463 participants; very low-quality evidence). There was substantial heterogeneity between the studies ($I^2 = 81\%$, $P = 0.02$).

There may have been more lymph nodes retrieved during ELA (MD 11.09 nodes, 95% CI 7.16 to 15.02; five studies, 670 participants; moderate-quality evidence). There was substantial heterogeneity between the studies ($I^2 = 81\%$, $P < 0.00001$).

There was little or no difference in the incidence of positive resection margins between groups (RR 0.81, 95% CI 0.58 to 1.13; six studies, 783 participants; very low-quality evidence).

Authors' conclusions

There is no evidence of an impact on survival with extended versus standard lymph node resection. However, the operating time may have been longer and blood loss greater in the extended resection group. In conclusion, current evidence neither supports nor refutes the effect of extended lymph lymphadenectomy in people with adenocarcinoma of the head of the pancreas.

PLAIN LANGUAGE SUMMARY

Comparing standard and extended lymph node removal in people with cancer of the head of the pancreas and the periampullary region

Review question

We attempted to find out whether more extensive surgical removal of lymph nodes had a positive effect on survival, recurrence, and eventual complications, and how their removal may affect the person's quality of life.

Background

Pancreatic and periampullary adenocarcinomas reflect the most common and aggressive among pancreatic cancers. Most common symptoms include pain, jaundice (yellowing of the skin and whites of the eyes), and weight loss. Unfortunately, these symptoms often do not present during early stages of the disease, thereby delaying diagnosis. This delay means that only about 15% to 25% of people with pancreatic cancer are eligible for potentially curative therapy. Partial pancreaticoduodenectomy (PD) is the treatment of choice. This includes the removal of the head of the pancreas (a large gland that produces insulin and secretions that aid digestion), the duodenum (first part of the small intestine), the gallbladder (an organ that stores bile, which aids digestion), the far end of the bile duct (carries bile from the liver or gallbladder to the duodenum), lymph nodes close to the affected area (structures that act as filters to prevent foreign particles from entering the bloodstream), and sometimes, the far end of the stomach.

However, controversy remains as to whether it is potentially beneficial to remove more lymph nodes. In general, about 5% of people die from pancreatic surgery, and 18% to 52% face complications. These include delayed emptying of the stomach after eating, development of a pancreatic fistula (an abnormal connection between the pancreas and the abdominal cavity or other organs), the collection of pus in the abdomen, and excessive bleeding from the stomach, intestine, or abdominal cavity.

Study characteristics

We included seven randomised controlled trials (type of study in which participants are randomly assigned to the treatment groups), published before 10 September 2020, with a total of 843 adult participants who had undergone PD with either standard or extended lymph node removal. There were differences in sample size, treatments, and quality of the research between the studies.

Key results

We found little or no difference in overall survival between the two groups. It was likely that the operating time was longer, there was more blood loss, and more lymph nodes were removed in the group that underwent extended lymph node resection. However, there was little or no difference in the rate of negative resection margins (i.e. no detectable tumour cells at the cutting surface of the specimen) between the two groups.

We conclude that at present, a more extensive removal of lymph nodes does not improve survival in people with pancreatic and periampullary adenocarcinomas.

Quality of the evidence

Overall, we found low-quality evidence. The studies used different treatment regimens and different definitions of standard and extended lymph node resection; lack of blinding of the surgeons and other caregivers introduced a risk of performance bias for all outcomes; the use of chemotherapy and other co-interventions was different between studies, and between groups in individual studies. Therefore, we have limited confidence in the estimate of the effect, and the true effect may be substantially different from what we found.

SUMMARY OF FINDINGS

Summary of findings 1. Extended compared to standard lymph node resection for pancreatic and periampullary adenocarcinoma

Extended compared to standard lymph node resection for pancreatic and periampullary adenocarcinoma

Participant or population: people with pancreatic and periampullary adenocarcinoma

Setting: hospital

Intervention: extended lymph node resection

Comparison: standard lymph node resection

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard lymph node resection	Risk with extended lymph node resection				
Overall survival (1-year follow-up)	Study population		log HR 0.12 (-3.06 to 3.31)	823 (7 RCTs)	⊕⊕⊕⊕ Very low ^{a,b,c}	
	700 per 1000	670 per 1000 (0 to 980)				
Overall survival (3-year follow-up)	Study population		log HR 0.12 (-3.06 to 3.31)	823 (7 RCTs)	⊕⊕⊕⊕ Very low ^{a,b,c}	
	300 per 1000	260 per 1000 (0 to 930)				
Postoperative mortality (duration of follow-up not specified)	Study population		Peto OR 1.20 (0.51 to 2.80)	843 (7 RCTs)	⊕⊕⊕⊕ Low ^{a,b,d}	
	24 per 1000	28 per 1000 (12 to 64)				
Operating time	The mean operating times for standard resection were 205.7 to 371.9 minutes	The mean operating time for extended resection was 50.13 minutes more (19.19 more to 81.06 more)	-	670 (5 RCTs)	⊕⊕⊕⊕ Moderate ^{a,b,e,f}	
Blood loss	The mean blood losses during standard resection were 372.3 to 740 mL	The mean blood loss during extended resection was 137.43 mL more (11.55 more to 263.30 more)	-	463 (2 RCTs)	⊕⊕⊕⊕ Very low ^{a,b,c,g}	
Lymph nodes re-retrieved	The mean numbers of lymph nodes retrieved during stan-	The mean number of lymph nodes re-retrieved during extended resection was 11.09 more (7.16 more to 15.02 more)	-	670 (5 RCTs)	⊕⊕⊕⊕ Moderate ^c	

	Standard resection were 13.3 to 18.5			
Positive resection margins (R1 + R2)	Study population	RR 0.81 (0.58 to 1.13)	783 (6 RCTs)	⊕⊕⊕⊕ Very low ^{a,b,c,h}
	161 per 1000 133 per 1000 (95 to 186)			

***The risk in the intervention group** (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; **RR:** risk ratio; **Peto OR:** Peto odds ratio; **log HR:** log hazard ratio

GRADE Working Group grades of evidence

High certainty. We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty. We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty. Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect

Very low certainty. We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

^aAll included outcomes are at risk of bias because of lack of blinding of the surgeon, the other caregivers, or both.

^bUse or no use of chemotherapy (and other co-interventions) differed among studies and was not random.

^cWide 95% CI, making it difficult to infer the true effect.

^dRare outcome and a 95% CI that is too wide to make a confident inference of the true effect.

^eAlthough the I^2 is high, the point estimates point all in the same direction, and 3/4 have narrow 95% CI. We did not downgrade since the heterogeneity does not impact on the interpretation of the results.

^fAlthough the 95% CI is rather wide, it does not impact the interpretation.

^gHeterogeneity difficult to judge with just two studies, but the direction of estimates is different for unclear reasons.

^hThe I^2 is low, but this is rather misleading since the 95% CI of each study is wide. We downgraded because the point estimates are too different to make a confident inference on the true effect

BACKGROUND

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

Description of the condition

Pancreatic head and periampullary adenocarcinoma are terms that are widely used to define a heterogeneous group of neoplasms arising from the head of the pancreas, the distal common bile duct, and the duodenum. They reflect some of the most aggressive malignancies, and a leading causes of cancer-related mortalities in Western countries ([Siegel 2012](#)). Worldwide, pancreatic head and periampullary adenocarcinoma are the ninth leading cause of cancer-related death in women, and eighth leading cause of cancer-related death men ([Jemal 2011](#)). They are more common in people living in Western or industrialised parts of the world. India and Nigeria show the lowest incidence for pancreatic head and periampullary adenocarcinoma in the world, whereas the highest incidence is observed among Maoris in New Zealand, native Hawaiians, and Black American populations ([Boyle 1989](#); [Hariharan 2008](#)). Pancreatic cancer is rare before the age of 45, thereafter, the incidence rises sharply and is higher in men than in women (1.3:1; ([Zhang 2008](#))).

Pain, jaundice, and weight loss are the most common presenting symptoms in people with pancreatic head and periampullary adenocarcinoma ([Porta 2005](#)). However, in the early stage of the disease, people may only complain of some vague upper abdominal pain, which can lead to a delayed diagnosis. At primary diagnosis, only about 15% to 25% of people are eligible for curative resection ([Jang 2014](#)). About 60% to 70% of these tumours are localised in the head of the pancreas, while 20% to 25% are in the body or tail, and the remainder involve the whole organ ([Modolell 1999](#)). Abdominal computer tomography (CT) provides an assessment of the extent of local and regional disease, and also evaluates the possibility of distant metastatic spread. The sensitivity of CT for pancreatic head and periampullary adenocarcinoma is highest (89% to 97%) when using a triple-phase helical multidetector row CT ([Valls 2002](#)).

Partial pancreaticoduodenectomy (PD) with negative resection margins (referred to as 'R0' resection) is the only potentially curative therapy, and hence, the treatment of choice for resectable pancreatic head and periampullary adenocarcinoma. PD may include the removal of the duodenum, the head of the pancreas, the gallbladder, the distal bile duct, and sometimes the distal part of the stomach. Surgery-related mortality following pancreatic surgery has decreased to less than 5% in high-volume centres ([Buchler 2003](#)). In contrast, the morbidity burden remains high, ranging from 18% to 52%. The most frequent complications after pancreatic surgery are delayed gastric emptying (19% to 23%), pancreatic fistula (9% to 18%), intra-abdominal abscess (9% to 10%), and gastrointestinal or intra-abdominal haemorrhage (1% to 10%; ([Yeo 1997](#))).

The five-year overall survival of people with pancreatic head and periampullary adenocarcinoma is less than 6%; it has not increased in the last 10 years ([Siegel 2012](#)). The five-year survival rate after surgery varies from around 7% to 32% ([Alexakis 2004](#); [Nitecki 1995](#)). This dismal prognosis is based on early metastatic spread, and high local recurrence rates.

Description of the intervention

Standard partial pancreaticoduodenectomy

Standard PD is either conducted as a pylorus-preserving PD, as described by Traverso and Longmire ([Traverso 1980](#)), or as a classic 'Whipple' operation, as described by Kausch and Whipple ([Kausch 1912](#); [Whipple 1935](#)). Lymphadenectomy for partial PD is well defined, and has been the subject of national guidelines and international consensus statements ([Adler 2007](#); [Bilimoria 2009](#)). In 2014, the International Study Group on Pancreatic Surgery (ISGPS) published a consensus statement about the extent of standard lymphadenectomy (SLA) in PD. It includes the resection of lymph node stations numbers 5, 6, 8a, 12b1, 12b2, 12c, 13a, 13b, 14a, 14b, 17a, and 17b ([Tol 2014](#)).

Partial pancreaticoduodenectomy with extended lymphadenectomy

Partial PD with extended lymph lymphadenectomy (ELA) is defined as a wide en bloc PD (classical Whipple or pylorus-preserving operation) with a vast soft-tissue resection margin, combined with an extended lymphadenectomy (i.e. interaortocaval space, left side of the celiac trunk, and superior mesenteric artery). However, there is no consensus about the exact extent of lymphadenectomy in an extended lymph node resection ([Hackert 2011](#); [Michalski 2007](#)). Intraoperatively, it is usually impossible to distinguish between tumour-involved and uninvolved lymph nodes. Therefore, the lymphadenectomy usually follows a protocol that defines the extent of the lymphadenectomy. Apart from the more radical lymph node resection mentioned above, the surgical procedure is basically the same as a standard PD.

How the intervention might work

About three decades ago, Fortner introduced the term 'regional pancreatectomy' ([Fortner 1984](#)). The term refers to the en bloc removal of the tumour with an adequate soft-tissue margin with its regional lymphatic drainage. Pancreatic head and periampullary adenocarcinoma are very aggressive tumours that show an early tendency for neuronal and vascular invasion, with an overall five-year survival rate of less than 6% ([Siegel 2012](#)). Lymph node involvement is the main prognostic factor, with a reported prevalence of 65% to 86% for people undergoing resection ([Schwarz 2014](#)). The high prevalence of neural invasion in pancreatic head and periampullary adenocarcinoma, reaching to 100% ([Ceyhan 2008](#)), and its strong association with local tumour recurrence after curative tumour resection ([Ceyhan 2006](#); [Kameda 1999](#)), together with the high prevalence of lymph node metastases, even in the early stages, has led to the hypothesis that wider excision, with the removal of more lymphatic tissue, could result in improved survival, a higher resectability, and higher rates of negative resection margins (R0).

On the downside, there are concerns that morbidity may be negatively affected by a more extensive lymphadenectomy. One major concern after extended lymph node resection is the increased rate of postoperative diarrhoea. This complication depends on the extent of retroperitoneal tissue dissection, and especially on the extent of nerve dissection around the superior mesenteric artery (SMA; ([Nimura 2012](#))).

Why it is important to do this review

At present, there is no clear evidence on whether to conduct PD with a standard or extended lymph lymphadenectomy for pancreatic head and periampullary adenocarcinoma (Riall 2005). Unfortunately, different studies comparing standard and extended lymph lymphadenectomy have applied different extents of clearance of retroperitoneal tissue, nerve plexus, and lymph nodes (Jang 2014).

ELA has been used most extensively in Japan (Manabe 1989); some non-randomised studies have proposed better survival rates for people undergoing ELA (Kayahara 1995; Nagakawa 1996). Despite lack of evidence favouring either therapy, many surgeons prefer ELD (Jang 2014).

OBJECTIVES

To compare overall survival following standard versus extended lymph lymphadenectomy for pancreatic head and periampullary adenocarcinoma. We also compared secondary outcomes, such as morbidity, mortality, and tumour involvement of the resection margins between the two procedures.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCT), regardless of publication status or language.

Types of participants

We included studies with people aged 18 years and older, who were undergoing an elective partial pancreaticoduodenectomy with standard or extended lymph lymphadenectomy for pancreatic or periampullary adenocarcinoma. We excluded people with tumours arising from the distal bile duct or the duodenum.

Types of interventions

We included studies comparing any type of partial pancreaticoduodenectomy (PD) with extended lymph lymphadenectomy (ELA) versus any type of PD with standard lymph lymphadenectomy (SLA). The addition of adjuvant therapies or neoadjuvant therapies were not exclusion criteria.

Types of outcome measures

collect data on the following outcomes.

Primary outcomes

Overall survival (log hazard ratio)

Secondary outcomes

1. postoperative mortality (total number and percentage)
2. operating time (mean and standard deviation)
3. blood loss (mean and standard deviation)
4. transfusion requirements (total number and percentage)
5. number of lymph nodes retrieved (mean and standard deviation)

6. positive resection margins (R1 and R2 resections; (total number and percentage))
7. quality of life (mean and standard deviation)
8. locoregional recurrence (total number and percentage)
9. systemic recurrence (total number and percentage)
10. pancreatic fistula (total number and percentage)
11. delayed gastric emptying (total number and percentage)
12. postoperative haemorrhage (total number and percentage)

The main reason to justify extended resections is the assumption that it will improve long-term survival after pancreatic resections for pancreatic head and periampullary adenocarcinoma, and that it can be done with similar mortality and morbidity rates.

The secondary outcomes are important in order to compare the time to tumour recurrence, the complication rate, and the intraoperative outcomes. More extensive resection may also lead to a higher rate of negative resection margins (R0).

Reporting of the outcomes listed here were not an inclusion criteria for the review.

Search methods for identification of studies

We placed no language restrictions when searching electronic databases, or reviewing reference lists from identified studies.

Electronic searches

We searched the following databases to identify all published and unpublished randomised controlled trials. We did not search earlier than 1973, as the first extended PD was described in that year (Fortner 1973).

- the Cochrane Central Register of Controlled Trials (CENTRAL, 2020, Issue 8) in the Cochrane Library (searched on 10 September 2020; see Appendix 2);
- MEDLINE Ovid (1973 to 10 September 2020; see Appendix 3);
- PubMed (1973 to 10 September 2020; see Appendix 4);
- Embase (1973 to 10 September 2020; see Appendix 5)

Searching other resources

We checked reference lists of all included studies, and of reviews that were identified in the course of the database search, for additional references. We searched for errata or retractions from eligible studies on www.ncbi.nlm.nih.gov/pubmed, and for ongoing studies on the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 10 September 2020).

Data collection and analysis

We collected data on the following outcomes.

Selection of studies

Two review authors (RFS and RT) independently screened the titles and abstracts of all the potentially eligible studies, identified through the electronic search, for inclusion. They coded them as 'retrieve' (eligible or potentially eligible or unclear) or 'do not retrieve'. They made decisions on retrieval by consensus. We retrieved the full-text study reports or publication, and two review authors (RFS and RNV) independently screened the full

text to identify studies for inclusion. They recorded reasons for excluding ineligible studies. Disagreement between two review authors, when required, was resolved by a third person (SB). We identified and excluded duplicates, and collated multiple reports of the same study, so that each study, rather than each report, became the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table.

Data extraction and management

We used a standard data collection form for study characteristics and outcome data, which was piloted on at least one included study. One review author (RFS) independently extracted study characteristics from the selected study, and another review author (RNV) checked the extracted data.

We extracted data for the following study characteristics.

1. Methods: study design, total duration study and run-in, number of study centres and location, study setting, withdrawals, date of study
2. Participants: inclusion criteria, exclusion criteria, total number per treatment arm, mean age, age range, gender, severity of condition, diagnostic criteria
3. Interventions: description of experimental (extended) and control (standard) intervention, concomitant interventions (e.g. adjuvant or neoadjuvant therapies, or both)
4. Outcomes: primary and secondary outcome definitions, time points reported
5. Notes: funding for study, notable conflicts of interest of study authors

Two review authors (RFS and CS) independently extracted outcome data from all included studies. We noted in the 'Characteristics of included studies' table if outcome data were reported in an unusable way. We resolved disagreements by consensus, or by involving a third review author (RNV). One review author (RFS) entered the data from the data collection form into the Review Manager 5 file ([Review Manager 2014](#)). A second review author (CS) double-checked that the data were entered correctly, by comparing the study reports with the data presented in the Review Manager 5 file. Another review author (RNV) spot-checked study characteristics for accuracy against the study report. Finally, we extracted the hazard ratios and standard errors given in the systematic review by [Dasari 2015](#), and checked their data for accuracy.

Assessment of risk of bias in included studies

Two review authors (RFS, RNV) independently assessed risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). Any disagreement was resolved by discussion, or by involving a third assessor (MP). We assessed the risk of bias according to the following domains.

1. random sequence generation;
2. allocation concealment;
3. blinding of participants and personnel;
4. blinding of outcome assessment;
5. incomplete outcome data;

6. selective outcome reporting;
7. other bias.

For each study, we classified each potential bias domain as high, low, or unclear, and provided a quote from the study report together with a justification for our judgment in the 'Risk of bias' table. We summarised the 'Risk of bias' judgments across different studies for each of the domains listed. We judged blinding as 'adequate', if the study was described as blinded to participants or personnel, and the method of blinding was described. We judged blinding 'unclear' if the study was described as 'blinded', but the method of blinding was not described. When our judgment on risk of bias was based on unpublished data or correspondence with a trialist, we noted this in the 'Risk of bias' table.

Assessment of bias in conducting the systematic review

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

Measures of treatment effect

We analysed dichotomous data as risk ratio, and continuous data as mean difference or standardised mean difference. We ensured that higher scores for continuous outcomes had the same meaning for the particular outcome, explained the directions to the reader, and reported this in case the directions needed to be reversed for consistency.

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

We did not identify any studies with multiple treatment arms. If we identify any in future updates, we will include only data from the relevant treatment arms, and combine treatment arms, if appropriate. If two comparisons (e.g. two different types of extended pancreaticoduodenectomy) are entered into the same meta-analysis, we will half the control group (standard pancreaticoduodenectomy) to avoid double counting data from this group.

Unit of analysis issues

Given the nature of the intervention, individuals were the only unit of analysis.

Dealing with missing data

We contacted investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data, when possible (e.g. when searching for a study for which only an abstract was available).

Assessment of heterogeneity

We used the χ^2 test and I^2 statistic to explore heterogeneity among the studies in each meta-analysis. When we identified substantial heterogeneity ($I^2 > 25\%$), we explored sources of heterogeneity, and used a random-effects model if a substantial amount still remained.

Assessment of reporting biases

When necessary, we contacted study authors, requesting missing outcome data. When this was not possible, and we thought the missing data could cause serious bias, we explored the impact of including such studies in the overall assessment of results by a sensitivity analysis.

We were not able to include more than 10 studies. Hence, we did not create a funnel plot to explore the possibility of publication bias.

Data synthesis

We compared binary outcomes using risk ratios (RRs), and continuous outcomes using mean differences (MDs). We used a fixed-effect model in the absence of substantial heterogeneity ($I^2 < 25\%$), and a random-effects model if there was substantial heterogeneity ($I^2 \geq 25\%$). In the case of rare outcomes (postoperative mortality), we used Peto's odds ratio (Peto OR).

Subgroup analysis and investigation of heterogeneity

We had planned to carry out the following subgroup analyses.

1. adenocarcinoma of the head of the pancreas versus periampullary adenocarcinomas
2. surgery with any neoadjuvant treatment versus surgery without neoadjuvant treatment
3. surgery with any adjuvant treatment versus surgery without adjuvant treatment

We were unable to conduct the latter two subgroup analyses; see Subgroup analysis results.

Sensitivity analysis

We explored whether the results changed if studies (i) with high risk of bias, or (ii) with high or unclear risk of bias were excluded. We also conducted sensitivity analyses by excluding studies from the meta-analysis in the following situations:

- results appeared to be heavily determined by a single study, with effect estimates that were very different from the other studies;
- study was of uncertain eligibility for the systematic review.

Summary of findings and assessment of the certainty of the evidence

We created a 'Summary of findings' table using the following outcomes: overall survival at one and three years, postoperative mortality, operating time, blood loss, lymph nodes retrieved, and positive resection margins (R1 + R2). We used the five GRADE considerations (i.e. study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of the body of evidence. We used the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and used GRADEpro software (GRADEpro GDT). We justified all decisions to downgrade or upgrade the quality of the evidence using footnotes, and made comments to aid readers' understanding of the review, where necessary. We considered whether there was any additional outcome information that could not be incorporated into meta-analyses, noted this in the comments, and stated if it supported or contradicted the information from the meta-analyses.

Reaching conclusions

We based our conclusions only on findings from the quantitative or narrative synthesis of included studies. We avoided making recommendations for practice. In the 'Implications for research' section, we aimed to give the reader a clear sense of what the remaining uncertainties were, and where the focus of any future research in the area should be.

RESULTS

Description of studies

See: Characteristics of included studies and Characteristics of excluded studies.

Results of the search

We retrieved 2634 abstracts from the search in September 2020. We deleted 822 abstracts because they were duplicates. We checked 1812 records for eligibility. After reading the abstracts, we excluded 1790 records because they did not match the inclusion criteria. After assessing the full text, we excluded 10 studies. We included 12 studies in qualitative synthesis. Seven studies were included in the quantitative synthesis, four randomised controlled trials (RCT) reported updates of previously published RCTs, and one study was still ongoing (see Figure 1).

Figure 1. Study flow diagram

Included studies

We included seven RCTs, in 11 reports, which included 843 participants (421 extended lymph lymphadenectomy (ELA) and 422 standard lymph lymphadenectomy (SLA)). See characteristics of included studies for details ([Farnell 2005](#); [Ignjatovic 2017](#); [Jang 2014](#); [Nimura 2012](#); [Pedrazzoli 1998](#); [Riall 2005](#); [Sperling 2016](#)).

Sample sizes ranged from 60 ([Ignjatovic 2017](#)), to 294 participants ([Riall 2005](#)). All analysed participants were included because of resectable pancreatic or periampullary cancer. Only three of the seven RCTs reported comorbidities ([Ignjatovic 2017](#); [Nimura 2012](#); [Sperling 2016](#)). Two RCTs reported stratification according to tumour size ([Farnell 2005](#); [Pedrazzoli 1998](#)). Three RCTs randomised participants by random number generation ([Jang 2014](#); [Pedrazzoli 1998](#); [Riall 2005](#)), while four RCTs did not report the method of randomisation ([Farnell 2005](#); [Ignjatovic 2017](#); [Nimura 2012](#); [Sperling 2016](#)). Four RCTs conducted Intention-to-treat analysis ([Jang 2014](#); [Nimura 2012](#); [Riall 2005](#); [Sperling 2016](#)). Two studies were terminated after an interim analysis ([Farnell 2005](#); [Nimura 2012](#)). Definition of extended lymphadenectomy was not uniform among RCTs.

Neoadjuvant treatment was not part of the management strategy for any of the participants in any of the included studies.

The data about adjuvant therapy varied across the various studies: two RCTs gave no adjuvant therapy ([Nimura 2012](#); [Ignjatovic 2017](#)), one RCT administered intraoperative radiation to a subset

of participants ([Pedrazzoli 1998](#)), one administered postoperative chemotherapy ([Sperling 2016](#)), and three gave chemoradiation to a subset of patients ([Farnell 2005](#); [Jang 2014](#); [Riall 2005](#)).

Two studies assessed quality of life after surgery, but used different methods ([Farnell 2005](#); [Riall 2005](#)).

[Farnell 2005](#) collected data preoperatively and four months after surgery, and presented the difference over time. They used the Uniscale Global quality of life, and the Functional Assessment of Cancer Therapy Pancreas quality of life survey score (FACT-PA), which consists of the Functional Assessment of response to Cancer Therapy - General (FACT-G) score combined with the FACT-Pa subscale. [Riall 2005](#) used the Functional Assessment of Cancer Therapy - Hepatobiliary QOL survey (FACT-Hep) score once after surgery, and presented the absolute values.

Excluded studies

During the first phase of study selection, we screened and excluded 1790 abstracts. Ten of the remaining 22 studies did not fulfil the inclusion criteria. Most of the excluded studies did not compare the outcomes between SLA and ELA, were not randomised control trials, or both. See characteristics of excluded studies for details.

Risk of bias in included studies

Summaries of the risk of bias for each domain and as percentages across all studies are presented in [Figure 2](#) and [Figure 3](#).

Figure 2. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study

	Allocation concealment (selection bias)	Random sequence generation (selection bias)	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)	Other bias	Blinding of participants and personnel (performance bias): All outcomes	Blinding of outcome assessment (detection bias): All outcomes
Farnell 2005	?	?	+	?	?	?	?
Ignjatovic 2017	?	?	?	?	?	?	?
Jang 2014	+	+	+	?	+	+	?
Nimura 2012	?	?	+	?	+	?	?
Pedrazzoli 1998	+	+	?	?	?	?	?
Riall 2005	+	+	+	?	?	?	?
Sperling 2016	?	?	?	?	?	?	?

Figure 3. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item, presented as percentages across all included studies

Our analysis of the individual studies revealed heterogeneity in study design. Four studies described the underlying sample size calculation (Farnell 2005; Jang 2014; Nimura 2012; Sperling 2016). Only two studies conducted intention-to-treat statistical analysis (Jang 2014; Nimura 2012).

Allocation

Three of the seven RCTs described a valid way of generating the random sequence (Jang 2014; Pedrazzoli 1998; Riall 2005). Four studies demonstrated a valid way to conceal random allocation (Jang 2014; Nimura 2012; Pedrazzoli 1998; Riall 2005).

Blinding

Three of the seven RCTs reported blinding of the participants or outcome assessors (Jang 2014; Riall 2005; Sperling 2016).

Incomplete outcome data

Four of the seven RCTs gave information about the length of follow-up (Farnell 2005; Jang 2014; Riall 2005; Sperling 2016). Two of the seven RCTs reported losses to follow-up (Jang 2014; Riall 2005).

We evaluated quality of the follow-up by assessing the length of follow-up, and whether follow-up was well described. Riall 2005 described a median follow-up of 64 months in detail. Jang 2014 reported a mean follow-up of 18.8 months, but did not report how they conducted the follow-up. Pedrazzoli 1998 described the follow-up in detail, but only provided data to a 77-month follow-up. Nimura 2012 was stopped after an interim analysis by the study safety committee. Ignjatovic 2017 reported no information about the length of follow-up.

Selective reporting

A study protocol was not available for any of the included RCTs. Definitions for outcomes, such as delayed gastric emptying and pancreatic fistula were not given by most RCTs. Most studies did not report time ranges for postoperative hemorrhage and postoperative mortality. None of the studies reported outcomes, such as blood loss, transfusion requirements, positive resection margins, local recurrence, pancreatic fistula, delayed gastric emptying, postoperative hemorrhage, bile leak, or disease-free survival.

Other potential sources of bias

Two of the seven RCTs were sponsored by non-commercial grants (National Institute of Health or other national cancer control programs; (Jang 2014; Nimura 2012)). The other studies gave no information about funding or potential conflict of interests.

Three of the seven RCTs reported comorbidities; there were no differences between groups (Ignjatovic 2017; Nimura 2012; Sperling 2016).

Two RCTs reported stratification according to tumour size (Farnell 2005; Pedrazzoli 1998).

Effects of interventions

See: [Summary of findings 1](#) Extended compared to standard lymph node resection for pancreatic and periampullary adenocarcinoma

We included seven studies with 823 participants (410 participants received SLA, and 413 participants received ELA; (Farnell 2005; Ignjatovic 2017; Jang 2014; Nimura 2012; Pedrazzoli 1998; Riall 2005; Sperling 2016)).

Primary outcome

Survival

All seven included studies reported Kaplan-Meier curves for overall survival (Kaplan 1958); however, none reported hazard ratios (HR). To obtain the needed hazard ratios (Higgins 2011), we digitally extracted the reported Kaplan-Meier curves using the R digitize package (Poisot 2011). We then determined the overall survival estimates at six-month intervals (i.e. 0, 6, 12, . . . , 60 months) from the extracted values. Using the spreadsheet accompanying Tierney 2007, we estimated the log hazard ratios and their variances. Because this procedure has an inherent error, due to the manual process of digitising the Kaplan-Meier curves, we repeated it twice for each study to confirm that the estimated hazard ratios did not vary too much. The estimated log hazard ratios were generally within a range of ± 0.01 , and estimated variances were quite similar.

There was little or no difference in survival between the two procedures (log HR 0.12, 95% confidence interval (CI) -3.06 to 3.31; $P = 0.94$; seven studies, 823 participants; very low-quality evidence; [Analysis 1.1](#); [Figure 4](#)). There was no heterogeneity ($I^2 = 0\%$, $Q =$

0.013, $P = 1.0$). Taken together, overall survival was almost identical between SLA and ELA.

Figure 4. Forest plot of comparison: 1 Extended vs standard lymph node resection, outcome: 1.1 Overall survival.

The percentages of participants surviving for one (70%) and three years (30%) after standard resection were derived from large registries (Huang 2018). We calculated the proportions of participants surviving after extended resection from the included studies (see above). Overall survival after extended resection was 67% (95% CI 0 to 98%) at one year, and 26% (95% CI 0 to 93%) at three years.

Secondary outcomes

Postoperative mortality

One study provided 30-day mortality; it was 0% in both groups (Farnell 2005).

Five studies reported In-hospital mortality (Farnell 2005; Ignjatovic 2017; Jang 2014; Nimura 2012; Sperling 2016). It ranged from 0% (Farnell 2005), to 6.67% (Ignjatovic 2017) in the ELA groups, and from 0% (Farnell 2005; Jang 2014; Nimura 2012), to 3.33% (Ignjatovic 2017) in the SLA groups.

All seven studies reported postoperative mortality (not further specified). It was 24 per 1000 following standard resection versus 28 per 1000 after extended resection. There was little or no difference between the groups (odds ratio (OR) 1.20, 95% CI 0.51 to 2.80; $P = 0.67$; low-quality evidence; Analysis 1.2; Figure 5).

Figure 5. Forest plot of comparison: 1 Extended vs standard lymph node resection, outcome: 1.2 Postoperative mortality.

Postoperative morbidity**Pancreatic fistula**

Four studies reported the development of a pancreatic fistula (Farnell 2005; Jang 2014; Pedrazzoli 1998; Riall 2005). There was little or no difference between the SLA and ELA groups (risk ratio (RR) 1.34, 95% CI 0.85 to 2.10; $P = 0.21$; four studies, 610 participants; Analysis 1.3).

None of the studies that measured pancreatic fistula provided a definition, and pancreatic fistula was not differentiated from pancreatic leakage. Although the I^2 statistic showed no substantial heterogeneity ($I^2 = 9\%$; $\text{Chi}^2 = 3.31$, $P = 0.35$), pooled results must be regarded with caution owing to the variety of definitions used.

Delayed gastric emptying

Three studies provided information about delayed gastric emptying (Ignjatovic 2017; Jang 2014; Riall 2005). There was little or no difference between groups (RR 1.66, 95% CI 0.60 to 4.60; $P = 0.33$; three studies, 523 participants; Analysis 1.4). None of the studies provided a definition of delayed gastric emptying, and the I^2 statistic showed substantial heterogeneity ($I^2 = 63\%$; $\text{Chi}^2 = 5.44$, $P = 0.07$).

Postoperative intraperitoneal bleeding

Four studies assessed postoperative intraperitoneal bleeding (Ignjatovic 2017; Jang 2014; Pedrazzoli 1998; Sperling 2016). One study divided postoperative bleeding further, into early (versus late) intraperitoneal bleeding (Ignjatovic 2017). Postoperative intraperitoneal bleeding was little or not different between SLA and ELA (RR 1.48, 95% CI 0.61 to 3.64; $P = 0.39$; four studies, 376 participants; Analysis 1.5).

Bile leak

Only one study reported the incidence of bile leak; it was 2.05% in the SLA group and 4.73% in the ELA group (Riall 2005).

Operating time

Five RCTs reported operating time (Ignjatovic 2017; Jang 2014; Pedrazzoli 1998; Riall 2005; Sperling 2016). Operating time was probably longer for ELA than for SLA (mean difference (MD) 50.13 min, 95% CI 19.19 to 81.06 min; $P = 0.001$; five studies, 670 participants; moderate-quality evidence; Analysis 1.6; Figure 6). The I^2 statistic showed substantial heterogeneity ($I^2 = 82\%$; $\text{Chi}^2 = 17.07$, $P < 0.00001$).

Figure 6. Forest plot of comparison: 1 Extended vs standard lymph node resection, outcome: 1.6 Operating time.

Blood loss

Two studies assessed the amount of blood loss during surgery (Jang 2014; Riall 2005). There may have been more blood loss with ELA than with SLA (MD 137.43 mL, 95% CI 11.55 to 263.30 mL; $P = 0.03$; two studies, 463 participants; very low-quality evidence; Analysis 1.7). There was substantial heterogeneity ($I^2 = 81\%$, $P = 0.02$).

Transfusion requirements

Four studies assessed transfusion requirements (Jang 2014; Pedrazzoli 1998; Riall 2005; Sperling 2016). Transfusion requirements may have been higher in the ELA group compared to the SLA group (MD 0.15 units, 95% CI 0.13 to 0.17 units; $P < 0.00001$; four studies, 610 participants; Analysis 1.8). It is noteworthy that the results of one study accounted for 99.2% of the data in this analysis (Jang 2014).

Number of lymph nodes retrieved

Five studies reported the number of lymph nodes retrieved (Ignjatovic 2017; Jang 2014; Pedrazzoli 1998; Riall 2005; Sperling 2016). Probably more lymph nodes were retrieved in participants

undergoing an ELA compared to participants undergoing a SLA (MD 11.09 nodes, 95% CI 7.16 to 15.02 nodes; $P < 0.00001$; five studies, 670 participants; moderate-quality evidence; Analysis 1.9). There was substantial heterogeneity ($I^2 = 81\%$, $P < 0.00001$).

Positive resection margins

Six studies reported on positive resection margins (both microscopic (R1) and macroscopic (R2) positive margins; (Farnell 2005; Jang 2014; Nimura 2012; Pedrazzoli 1998; Riall 2005; Sperling 2016). The risk of having a positive resection margin was little or not different between the procedures (RR 0.81, 95% CI 0.58 to 1.13; $P = 0.20$; six studies, 783 participants; very low-quality evidence; Analysis 1.10).

Quality of life

Two studies assessed quality of life after surgery, using different methods (Farnell 2005; Riall 2005).

The changes in the Uniscale Global Quality of Life and the FACT-G total scores were similar for both groups. There was less of a change in the FACT-Pa subscale after ELA, which was most apparent for bowel control ($P = 0.038$), diarrhoea ($P = 0.002$), and overall

appearance ($P = 0.005$; (Farnell 2005)). Riall 2005 reported no significant differences between groups, using the FACT-Hep score.

Locoregional and systemic recurrence

Only one study reported recurrence (locoregional and systemic; (Jang 2014)). There were no differences in the pattern and time of recurrence. During follow-up, peritoneal seeding was more frequently seen in the ELA group than in the SLA group (25.9% versus 8.3%; $P = 0.011$).

Subgroup analysis

Adenocarcinoma of the head of the pancreas versus periampullary adenocarcinomas

Five studies (483 patients) only included participants with adenocarcinoma of the head of the pancreas (Farnell 2005; Ignjatovic 2017; Jang 2014; Nimura 2012; Pedrazzoli 1998).

Perioperative mortality in participants with adenocarcinoma of the head of the pancreas

Five RCTs (483 participants) reported perioperative mortality (not further specified; (Farnell 2005; Ignjatovic 2017; Jang 2014; Nimura 2012; Pedrazzoli 1998)); there was little or no difference between groups (OR 2.24, 95% CI 0.64 to 7.87; $P = 0.21$).

Pancreatic fistula in participants with adenocarcinoma of the head of the pancreas

Two RCTs (250 participants) reported the incidence of pancreatic fistula in participants with adenocarcinoma of the head of the pancreas (Jang 2014; Pedrazzoli 1998); there was little or no difference between groups (RR 1.04, 95% CI 0.51 to 2.13; $P = 0.91$).

Delayed gastric emptying in participants with adenocarcinoma of the head of the pancreas

Two RCTs (229 participants) provided information about delayed gastric emptying (Ignjatovic 2017; Jang 2014); there was little or no difference between groups (RR 1.23, 95% CI 0.26 to 5.86; $P = 0.80$).

Postoperative intraperitoneal bleeding in participants with adenocarcinoma of the head of the pancreas

Three RCTs (310 participant) provided information about postoperative intraperitoneal bleeding (Ignjatovic 2017; Jang 2014; Pedrazzoli 1998); there was little or no difference between groups (RR 1.42, 95% CI 0.54 to 3.75; $P = 0.48$).

Surgery with any neoadjuvant treatment versus surgery without neoadjuvant treatment

Neoadjuvant treatment was not part of the management strategy for any of the included participants in any of the included studies. Therefore, we could not conduct a subgroup analysis.

Surgery with any adjuvant treatment versus surgery with no adjuvant treatment

The data about adjuvant therapy varied across the various studies.

In Pedrazzoli 1998, 19 out of 81 participants received intraoperative beam therapy but no adjuvant therapy. The authors reported that these 19 participants were equally allocated to the two groups, as beam therapy was part of an overlapping protocol. They did not report outcome data separately for these 19 participants.

Jang 2014 reported that 122 out of 167 participants received adjuvant chemoradiotherapy. The median overall survival was longer for the 122 participants who received chemoradiation (20.8 months) than for the 45 participants who did not (14.0 months). The treatment benefit was especially prominent in the SLA group ($P = 0.016$).

In Farnell 2005, 30 out of 38 participants in the ELA group and 26 out of 34 participants in the SLA group received adjuvant chemotherapy. They did not report specific outcome data for these participants.

In Sperling 2016, 16 out of 32 participants in the ELA group and 11 out of 34 participants in the SLA group underwent adjuvant chemotherapy, without differences in overall survival.

Riall 2005 did not provide the number of participants receiving chemoradiation.

DISCUSSION

Summary of main results

It likely took longer to complete extended lymph lymphadenectomy (ELA) than standard lymph lymphadenectomy (SLA). ELA likely resulted in higher blood loss, required more transfusions of red blood cells, and resulted in little or no difference in overall survival. There seemed to be little or no difference between the groups in the development of complications (pancreatic fistula, delayed gastric emptying, and postoperative intraperitoneal haemorrhage).

There was very low-quality evidence of little or no difference in overall survival between standard (SLA) and extended lymph lymphadenectomy (ELA).

There was little or no difference in postoperative morbidity between the groups, measured by the incidence of pancreatic fistula, delayed gastric emptying, and post pancreatectomy haemorrhage.

There was very low-quality evidence of little or no difference in positive resection margins between the two groups. In other words, a wider and more radical resection did not seem to lead to more negative resection margins. Moderate-quality evidence found there were likely more lymph nodes removed from the ELA group than from the SLA group.

Moderate-quality evidence found the operating time in the ELA group was likely longer, and very low-quality evidence suggested the blood loss was greater. As a consequence of more blood loss, the transfusion requirements were probably higher in the ELA group.

Overall completeness and applicability of evidence

This review included participants with adenocarcinoma of the head of the pancreas or the periampullary region undergoing PD with SLA or ELA. Thus, the results of this review are applicable to all participants undergoing this type of pancreatic resection for pancreatic cancer.

Quality of the evidence

We rated the quality of evidence for seven important outcomes. We found moderate-quality evidence for operating time and number of lymph nodes retrieved. There was low-quality evidence for postoperative mortality. Overall survival at one and three years, blood loss, and positive resection margins were supported by very low-quality evidence ([Summary of findings 1](#)).

We downgraded the certainty of evidence for overall survival at one and three years by two levels because of a very wide 95% confidence interval, making an inference on the true effect difficult. Imprecision for postoperative mortality was less pronounced, so we downgraded the certainty of the evidence by one level. We downgraded the certainty of the evidence for all outcomes assessed by one level for indirectness (i.e. use or no use of chemotherapy), and study limitations (i.e. lack of blinding of the treating caregivers) combined.

This shows that it is likely that additional high-quality studies would change the current estimates of effect. However, the feasibility of such studies must be considered.

In 2005, Pawlik and colleagues from the MD Anderson Cancer Center published a retrospective cohort study, 'Feasibility of a randomised trial of extended lymphadenectomy for pancreatic cancer' ([Pawlik 2005](#)). In this cohort of 158 participants, 10.8% had positive first and second echelon lymph nodes. At a median follow-up of 65.1 months, only four participants with second echelon lymph nodes were alive, but three of them had recurrent disease. Using a biostatistical model, they calculated that only 0.3% of participants might achieve a survival benefit from ELA. Therefore, a randomised controlled trial (RCT) would need 202,000 participants in each arm to detect such a small difference. Understandably, the authors concluded that such a RCT would not be feasible. All RCTs included in this review were underpowered. They lacked clinical standardisation regarding the extent of lymphadenectomy, and used different perioperative radiotherapy or chemotherapy protocols, or both. Finally, the treating surgeons and other caregivers were not blinded.

Potential biases in the review process

Systematic reviews provide the best method of summarising existing evidence, but the quality of such reviews depends on the quality of the primary studies ([Mulrow 1994](#)). The studies included in this review were partially marred by bias and clinical heterogeneity, and this may distort results.

The Cochrane Gut Group approved our highly sensitive literature search, but it may still be biased.

In an attempt to identify all relevant studies, we handsearched the references of all the included studies. However, this effort did not reveal additional studies. We asked all authors of the included studies to provide the complete data sets. Only one of the authors answered the email, but could not provide the data because he was retired. A potential limitation is that although we conducted a meta-analysis for a number of outcomes, one could argue that the differences in surgical and perioperative management across studies were partly unknown.

Although we explored sources of heterogeneity, the information from the study reports did not include all the details needed to clearly identify reasons for different results across studies.

We found varying, or a lack of definitions for parameters, such as delayed gastric emptying or perioperative mortality; only one study reported 30-day mortality ([Farnell 2005](#)); five studies reported in-hospital mortality ([Farnell 2005](#); [Ignjatovic 2017](#); [Jang 2014](#); [Nimura 2012](#); [Sperling 2016](#)); all studies reported perioperative mortality, although it was not further specified.

[Nimura 2012](#) and [Ignjatovic 2017](#) did not give adjuvant therapy. [Pedrazzoli 1998](#) administered intraoperative radiation to a subset of participants. Postoperative chemotherapy ([Sperling 2016](#)), or chemoradiation ([Farnell 2005](#); [Jang 2014](#); [Riall 2005](#)), was given to a subset of participants. All of the included studies reported Kaplan-Meier curves for overall survival, but none reported hazard ratios. To obtain the hazard ratios, we digitally extracted the curves using the R digitize package, and calculated survival estimates at six-month intervals ([Poisot 2011](#)). Although we calculated the log hazard ratios twice for each trial, and the estimated log hazard ratios were within a narrow range of each other (± 0.01), manual extraction of data is inherently prone to error, and may be a source of bias.

In two studies, tumours other than ductal pancreatic adenocarcinoma were included in the survival analysis ([Riall 2005](#); [Sperling 2016](#)). However, the subgroup analysis for the different histology showed no difference in survival between the SLA and ELA groups. The vast majority of tumours in this analysis were ductal adenocarcinomas (> 80%).

Agreements and disagreements with other studies or reviews

To our knowledge, six other reviews or meta-analyses analysed all or some of the following outcomes: overall survival, number of lymph nodes retrieved, postoperative morbidity and mortality, operating time, blood loss, and transfusion requirements after extended versus standard lymph node dissection in pancreatoduodenectomy for pancreatic cancer ([Dasari 2015](#); [Kang 2016](#); [Michalski 2007](#); [Orci 2015](#); [Sun 2014](#); [Svoronos 2014](#); [Xu 2013](#)). However, the meta-analyses from [Xu 2015](#) was retracted in 2015, because the peer-review process was inappropriately influenced and compromised. Therefore, we will not include this meta-analysis in the discussion.

[Michalski 2007](#) searched the literature to February 2006. They included RCTs and non-randomised controlled studies in their review, but only pooled data from the RCTs ([Farnell 2005](#); [Pedrazzoli 1998](#); [Riall 2005](#)). They assessed one-, three-, and five-year survival, postoperative morbidities, postoperative mortality, and lymph nodes assessed. They found no significant differences between extended or standard lymph lymphadenectomy, even though they assessed more lymph nodes following ELA. This finding is in line with our analysis.

[Dasari 2015](#) included RCTs published until 2014. They included five RCTs in their meta-analysis ([Farnell 2005](#); [Jang 2014](#); [Nimura 2012](#); [Pedrazzoli 1998](#); [Riall 2005](#)). They assessed the following outcomes: overall survival, survival in node-negative and node-positive disease, number of excised lymph nodes, number of excised metastatic lymph nodes, overall postoperative morbidity, different

postoperative complications (including bile leak, pancreatic leak, intraabdominal abscess or fluid collection, delayed gastric emptying, cholangitis, wound infections, and lymphocele), 30-day mortality, duration of surgery, blood transfusions, and length of hospital stay. Among all those factors, only the number of excised lymph nodes were significantly higher following ELA, as well as overall postoperative morbidity. Furthermore, operating time was longer for participants who received ELA. None of the other assessed factors were different between groups. These results are similar to our findings.

Sun 2014 included nine studies in their meta-analysis (five non-randomised studies and four RCTs (Farnell 2005; Nimura 2012; Pedrazzoli 1998; Yeo 2002)). They assessed total morbidity, mortality, one-, three-, and five-year survival rates, pancreatic leak, delayed gastric emptying, lymphatic fistula, intra-abdominal haemorrhage, intra-abdominal abscess, wound infection, gastroenteric leak, pneumonia, stump pancreatitis, obstruction, thrombosis, cholangitis, reoperation, and diarrhoea. They found no statistical significance for morbidity, mortality, or survival between groups. Their analysis showed significantly more bile and pancreatic leaks, delayed gastric emptying, and lymphatic fistulas following ELA, and no oncological benefit for the ELA group. Our analyses found little or no difference in pancreatic leaks, or delayed gastric emptying between groups. The difference in findings may have been because Sun 2014 included five non-randomised studies.

Svoronos 2014 included eleven non-randomised studies and four RCTs (Farnell 2005; Nimura 2012; Pedrazzoli 1998; Yeo 2002). They assessed the number of retrieved lymph nodes and overall survival. They analysed the overall survival in the four RCTs separately, and found no difference between groups. The number of retrieved lymph nodes was significantly higher in the ELA group. These results are in line with our findings.

Orci 2015 included five RCTs, with 724 participants, in their analysis (Farnell 2005; Pedrazzoli 1998; Jang 2014; Nimura 2012; Riall 2005). They assessed the number of retrieved lymph nodes, operative time, blood transfusions, complications (pancreatic fistulas, bile leaks, lymphoceles, wound infections, cholangitis, postoperative haemorrhage, reoperation, length of hospital stay, and diarrhoea) and survival. Those in the ELA groups had more retrieved lymph nodes, longer operating time, increased need for blood transfusions, greater postoperative morbidity, and prolonged

diarrhoea after circumferential autonomic nerve dissection around major vessels. There was no difference in the oncological outcome. These results are in line with the findings of our review.

Kang 2016 included five RCTs in their review (Farnell 2005; Jang 2014; Nimura 2012; Pedrazzoli 1998; Yeo 2002). They found that ELA did not improve the oncological outcome in terms of survival. The results of this review are in line with our findings.

AUTHORS' CONCLUSIONS

Implications for practice

In conclusion, current evidence neither supports nor refutes the effect of extended lymph lymphadenectomy in people with adenocarcinoma of the head of the pancreas.

Implications for research

A randomised controlled trial with enough power to detect a difference between standard and extended lymph lymphadenectomy would have to include over 200,000 participants in each arm. In our opinion, such a study is not feasible, and hence, we do not recommend further studies comparing standard and extended lymph lymphadenectomy. We rather recommend the establishment of an international data registry to assess the impact of different treatments on survival and other outcomes in people with pancreatic and periampullary adenocarcinoma.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Farnell 2005

Study characteristics

Methods	Method of randomisation: unknown Number randomised: 80 (40 SLA, 40 ELA) Exclusion after randomisation (total and per group): 1 (0 SLA, 1 ELA) Method of allocation concealment: unknown Intention-to-treat-analysis: no Description of sample size calculation: yes
Participants	Age, years: mean 64.1 (SLA); mean 64.5 (ELA) Sex: ratio (m/f): 1:1 (SLA); 1.17:1 (ELA) Inclusion criteria: participants with adenocarcinoma, locally resectable and absent distant metastasis

Farnell 2005 (Continued)

	Exclusion criteria: participants with other periampullary tumours (ampullary, duodenal, or bile duct carcinoma), or islet-cell neoplasms
Interventions	<p>PD included a distal gastrectomy</p> <p>SLA: resection of the lymph node groups 3, 4, 6, 8A, 12B1, 12B2, 12C, 13A, 13B, 14A, 14B, 17A, and 17B</p> <p>ELA: in addition to the standard group resection of the retroperitoneal tissue from the hilum of the kidneys bilaterally, and the celiac axis superiorly to the inferior mesenteric artery inferiorly. The hepatic artery was dissected circumferentially (8P), as well as the celiac axis. The hepatoduodenal ligament was skeletonised up to the hilum of the liver (12a1, 12a2, 12p1, 12p2), and circumferential dissection of the superior mesenteric artery was conducted from the first jejunal branch inferiorly to its origin, from the aorta superiorly (14c, 14d, 14v). Para-aortic lymph nodes were harvested from the celiac axis superiorly to the inferior mesenteric artery inferiorly (16).</p> <p>Adjuvant treatment: all participants were evaluated for a standard adjuvant therapy with external beam radiotherapy and fluorouracil</p>
Outcomes	<p>Survival</p> <p>Mortality</p> <p>Pancreatic fistula</p> <p>Delayed gastric emptying</p> <p>Bile leak</p> <p>Operating time</p> <p>Transfusion requirements</p> <p>Number of lymph nodes retrieved</p> <p>Resection margins</p> <p>Quality of life</p>
Notes	<p>Country: USA, monocentric</p> <p>Time of enrolment: 76 months</p> <p>Duration of follow-up period, months: mean 49.6 SLA; mean 48.7 ELA</p> <p>Four participants in the SLA group and 3 participants in the ELA had adenocarcinoma associated with IPMN.</p> <p>One participant in the SLA group and 4 participants in the ELA group had benign disease.</p> <p>The participants without malignancy and 1 participant in each group with non-pancreatic peri-ampullary neoplasm were included in the assessment of morbidity and mortality but were excluded from survival analysis.</p> <p>The study was terminated after an interim analysis, after half of the planned number of events.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Random sequence generation was not described

Farnell 2005 (Continued)

Random sequence generation (selection bias)	Unclear risk	Allocation concealment was not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Interim analysis terminated study due to poorer survival in study group
Selective reporting (reporting bias)	Unclear risk	No study protocol available
Other bias	Unclear risk	Information about funding or conflict of interests not given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding of participants was not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment was not described

Ignjatovic 2017
Study characteristics

Methods	<p>Method of randomisation: intraoperative, details unknown</p> <p>Number randomised: 60 (30 SLA, 30 ELA)</p> <p>Exclusion after randomisation (total and per group): 0 (0 SLA; 0 ELA)</p> <p>Method of allocation concealment: unknown</p> <p>Intention-to-treat-analysis: no</p> <p>Description of sample size calculation: no</p>
Participants	<p>Age, years: mean 64.47 (SLA); mean 59.7 (ELA)</p> <p>Sex: ratio (m/f): 1.5/1 (SLA); 1/1.14 (ELA)</p> <p>Inclusion criteria: younger than 80 years, potentially resectable adenocarcinoma of the pancreatic head, written informed consent</p> <p>Exclusion criteria: mucinous cystadenocarcinoma, intraductal, papillary mucinous carcinoma, distant metastases, tumour involvement of major blood vessels, ASA score > 3, any neoadjuvant therapy</p>
Interventions	<p>Pylorus-preserving PD was defined as the standard procedure</p> <p>SLA: resection of the lymph node groups 8a, 12b1, 12b2, 12c, 13a-b, 14a-b, 17a-b</p> <p>ELA: resection of lymph node groups 8a, 8p, 9, 12a1, 12a2, 12b1, 12b2, 12c, 12p1, 12p2, 14a, 14b-c, 14d, 16a2, 16b1. Circumferential skeletonisation of the SMA.</p> <p>Adjuvant treatment: no adjuvant treatment</p>
Outcomes	<p>Survival</p> <p>Mortality</p>

Ignjatovic 2017 (Continued)

Pancreatic fistula

Delayed gastric emptying

Hemorrhage

Operating time

Number of lymph nodes retrieved

Notes

Country: Serbia, monocentric

Time of enrolment: 48 months

Duration of follow-up, months: unknown

No information about final histology and resection margins available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	The random sequence generation was not clearly reported
Random sequence generation (selection bias)	Unclear risk	Allocation concealment was not explained
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No loss to follow-up
Selective reporting (reporting bias)	Unclear risk	No study protocol available
Other bias	Unclear risk	Information about funding not given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment was not described

Jang 2014

Study characteristics

Methods

Method of randomisation: computer-generated numbers

Number randomised: 244 (101 SLA, 99 ELA)

Exclusion after randomisation (total and per group): 31 (18 SLA; 13 ELA)

Method of allocation concealment: computer-generated numbers

Intention-to-treat-analysis: yes

Jang 2014 (Continued)

	Description of sample size calculation: yes
Participants	<p>Age, years: mean 62 (SLA); mean 63.4 (ELA)</p> <p>Sex: ratio (m/f): 1.44:1 (SLA); 1.05:1 (ELA)</p> <p>Inclusion criteria: age 20 to 85 years, no history of cancer including pancreatic cancer, Karnofsky performance score above 70, potentially curable ductal adenocarcinoma of the pancreatic head, provided written informed consent</p> <p>Exclusion criteria: unresectable condition or metastasis found during surgery, surgical rule violation, inadequate case report form, pathologic diagnosis other than ductal adenocarcinoma</p>
Interventions	<p>Pylorus-preserving PD was defined as the standard procedure, although classical PD was allowed.</p> <p>SLA: resection of the lymph node groups partial 12b and 12c, 13, 17. No nerve dissection around the hepatic artery or SMA</p> <p>ELA: in addition to the standard group removal of lymph node groups 5, 6, 8, 9, 12a, 12h, 14a, 14b, 14c, 14d, 16a2, 16b1. All the soft tissues around the hepatoduodenal ligament were completely dissected and skeletonised. The nerve plexus or ganglion on the right side of the celiac axis and SMA was dissected semi-circumferentially.</p> <p>Adjuvant treatment: chemoradiation and maintenance chemotherapy were recommended for all participants except those with a T1N0 lesion and no residual tumour.</p>
Outcomes	<p>Survival</p> <p>Mortality</p> <p>Pancreatic fistula</p> <p>Delayed gastric emptying</p> <p>Haemorrhage</p> <p>Disease-free survival</p> <p>Operating time</p> <p>Blood loss</p> <p>Transfusion requirements</p> <p>Number of lymph nodes retrieved</p> <p>Resection margins</p> <p>Recurrence</p>
Notes	<p>Country: South Korea, multicentric</p> <p>Time of enrolment: 42 months</p> <p>Duration of follow-up, months: mean 18.8 SLA; mean 16.4 ELA</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Computer-generated randomisation

Jang 2014 (Continued)

Random sequence generation (selection bias)	Low risk	Computer-based concealment
Incomplete outcome data (attrition bias) All outcomes	Low risk	A flowchart described clearly the inclusion and exclusion of participants and the dropouts
Selective reporting (reporting bias)	Unclear risk	No study protocol available
Other bias	Low risk	Low risk of funding bias; study was sponsored by a national programme for cancer control
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Single-blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The blinding of the safety monitoring board was described, but not other personnel.

Nimura 2012
Study characteristics

Methods	<p>Method of randomisation: unknown</p> <p>Number randomised: 112 (56 SLA, 56 ELA)</p> <p>Exclusion after randomisation (total and per group): 11 (5 SLA; 6 ELA)</p> <p>Method of allocation concealment: central office by telephone</p> <p>Intention-to-treat-analysis: yes</p> <p>Description of sample size calculation: no</p>
Participants	<p>Age, years: mean 62.7 (SLA); mean 62.9 (ELA)</p> <p>Sex: ratio (m/f): 1.68:1 (SLA); 2.13:1 (ELA)</p> <p>Inclusion criteria: < 80 years old, potentially curable carcinoma</p> <p>Exclusion criteria: severe cardiovascular disease, severe pulmonary disease, gross metastases to the paraaortic lymph nodes, marked portal vein stenosis with collateral circulation, cystadenocarcinoma, and intraductal papillary mucinous carcinoma</p>
Interventions	<p>Pylorus-preserving PD was used as a standard procedure, however classical PD could be selected</p> <p>SLA: removal of lymph node groups 13a, 13b, 17a, 17b without nerve dissection</p> <p>ELA: in addition to the standard group removal of the lymph node groups 8a, 8p, 9, 12a, 12b, 12p, 14d, 14p, 16a2, 16b1, and nerve dissection circumferentially around the CHA and SMA, and semi-circumferentially on the right lateral aspect of the CA was carried out.</p> <p>Adjuvant treatment: no adjuvant treatment was allowed before recurrence was detected</p>
Outcomes	Survival

Extended lymph node resection versus standard resection for pancreatic and periampullary adenocarcinoma (Review)

Nimura 2012 (Continued)

Mortality

Disease-free survival

Operating time

Blood loss

Transfusion requirements

Number of lymph nodes retrieved

Resection margins

Quality of life

Recurrence

Notes

Country: Japan

Time of enrolment: 36 months

Duration of follow-up, months: no information

The study was stopped after 38 months, after an interim analysis of 112 enrolled participants. The analysis showed no survival benefit for the ELA group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	The random sequence generation was not clearly reported
Random sequence generation (selection bias)	Unclear risk	The process of allocation concealment was not clearly reported. The assignment of the participant was conducted by telephone calls.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete data collection
Selective reporting (reporting bias)	Unclear risk	No study protocol available
Other bias	Low risk	Low risk of funding bias. Study was sponsored by a national programme for cancer control.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding of participants was not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment was not described.

Pedrazzoli 1998

Study characteristics

Extended lymph node resection versus standard resection for pancreatic and periampullary adenocarcinoma (Review)

Pedrazzoli 1998 (Continued)

Methods	<p>Method of randomisation: computer-generated numbers</p> <p>Number randomised: 83 (42 SLA, 41 ELA)</p> <p>Exclusion after randomisation (total and per group): 2 (2 SLA, 0 ELA)</p> <p>Method of allocation concealment: computer-generated numbers</p> <p>Intention-to-treat-analysis: no</p> <p>Description of sample size calculation: no</p>
Participants	<p>Age, years: mean 62.0 (SLA); mean 59.2 (ELA)</p> <p>Sex: ratio (m/f): 2.08:1 (SLA); 1.56:1 (ELA)</p> <p>Inclusion criteria: written informed consent, adenocarcinoma of the head of the pancreas</p> <p>Exclusion criteria: unresectable tumour because of local spread, peritoneal metastases, liver metastases</p>
Interventions	<p>The choice of conducting a PD with or without pylorus preservation was left to the preference of the operating surgeon.</p> <p>SLA: removal of lymph node groups 5, 6, 8a, 8p, 12b, 13, 17, 18</p> <p>ELA: in addition to the standard group removal of the lymph node groups 9, 12a, 12c, 12p, 14a, 14b, 14c, 14d, 14v, 16a1, 16a2, 16b1, and nerve dissection circumferentially around the origin of the celiac trunk and the SMA</p> <p>Adjuvant treatment: 19 participants received intraoperative radiotherapy (equally allocated in the two groups). Neither group received postoperative adjuvant therapy.</p>
Outcomes	<p>Survival</p> <p>Mortality</p> <p>Pancreatic fistula</p> <p>Haemorrhage</p> <p>Operating time</p> <p>Transfusion requirements</p> <p>Number of lymph nodes retrieved</p> <p>Resection margins</p>
Notes	<p>Country: Italy</p> <p>Time of enrolment: 64 months</p> <p>Duration of follow-up, months: maximum follow-up 77 months</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Computer-generated randomisation.

Pedrazzoli 1998 (Continued)

Random sequence generation (selection bias)	Low risk	Computer-based concealment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No loss to follow-up
Selective reporting (reporting bias)	Unclear risk	No study protocol available
Other bias	Unclear risk	Information about funding or conflict of interests not given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding of participants was not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment was not described

Riall 2005
Study characteristics

Methods	<p>Method of randomisation: computer-generated numbers</p> <p>Number randomised: 299 (? SLA, ? ELA)</p> <p>Exclusion after randomisation (total and per group): 0 (0 SLA, 0 ELA)</p> <p>Method of allocation concealment: computer-generated numbers</p> <p>Intention-to-treat-analysis: yes</p> <p>Description of sample size calculation: yes</p>
Participants	<p>Age, years: mean 64.6 (SLA); mean 65.4 (ELA)</p> <p>Sex: ratio (m/f): 1.70:1 (SLA); 0.81:1 (ELA)</p> <p>Inclusion criteria: periampullary adenocarcinoma, written informed consent</p> <p>Exclusion criteria: preoperative chemoradiation therapy, pathology revealing tumour other than adenocarcinoma primary to the periampullary region, presence of gross tumour left behind (positive resection margin by frozen section), absence of informed consent</p>
Interventions	<p>All had clearing of lymphatic and neural tissue from the ventral and right lateral aspect of the SMA for about a 90° to 180° circumference</p> <p>SLA: pylorus preservation was preferred. The following lymph node groups were resected en bloc: 12b2, 12c, 13, 14b, 14v, 17</p> <p>ELA: in addition to the standard group, a distal gastrectomy and removal of lymph node groups 3, 4, 5, 6, 9, 16a2, 16b1</p> <p>Adjuvant treatment: approximately 75% of the participants received postoperative chemoradiation</p>
Outcomes	Survival

Extended lymph node resection versus standard resection for pancreatic and periampullary adenocarcinoma (Review)

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Riall 2005 (Continued)

Mortality

Pancreatic fistula

Delayed gastric emptying

Bile leak

Operating time

Blood loss

Transfusion requirements

Number of lymph nodes retrieved

Resection margins

Notes

Country: USA

Time of enrolment: 64 months

Duration of follow-up, months: mean 25 (SLA), mean 28 (ELA)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Computer-generated randomisation
Random sequence generation (selection bias)	Low risk	Computer-based concealment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Consistent data within several publications on the same cohort with increasing time of follow-up
Selective reporting (reporting bias)	Unclear risk	No study protocol available
Other bias	Unclear risk	Funding not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding of participants was not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment was not described

Sperling 2016

Study characteristics

Methods

Method of randomisation: unknown

Number randomised: 103 (50 SLA, 53 ELA)

Sperling 2016 (Continued)

	<p>Exclusion after randomisation (total and per group): 37 (unknown SLA, unknown ELA)</p> <p>Method of allocation concealment: unknown</p> <p>Intention-to-treat-analysis: yes</p> <p>Description of sample size calculation: yes</p>
Participants	<p>Age, years: mean 68.4 (SLA); mean 65.5 (ELA)</p> <p>Sex: ratio (m/f): unknown</p> <p>Inclusion criteria: age > 18 years, diagnosis or suspicion of periampullary adenocarcinoma, tumours of pancreatic head, distal common bile duct, ampulla of Vater, written informed consent</p> <p>Exclusion criteria: metastases, unable to resect locally</p>
Interventions	<p>Pylorus-preserving PD as standard, but classic Whipple procedure was allowed, depending on the clinical situation</p> <p>SLA: pylorus preservation was preferred. The following lymph node groups were resected: 5, 6, 8a/p, 12a, 13, 17</p> <p>ELA: in addition to the standard group removal of the lymph node groups 9, 12p/b, 14a-v, 16a1, 16a2, 16b1</p> <p>Adjuvant treatment: 11 participants in the SLA group and 16 participants in the ELA group received adjuvant chemotherapy</p>
Outcomes	<p>Survival</p> <p>Mortality</p> <p>Pancreatic fistula</p> <p>Haemorrhage</p> <p>Operating time</p> <p>Transfusion requirements</p> <p>Number of lymph nodes retrieved</p> <p>Resection margins</p> <p>Recurrence</p>
Notes	<p>Country: Germany</p> <p>Time of enrolment: 26 months</p> <p>Duration of follow-up, months: median 19.9 (SLE) and 16.7 (ELD)</p> <p>Distale bile duct carcinomas are included</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	The random sequence generation was not clearly reported

Sperling 2016 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Allocation concealment was not clearly reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No loss to follow-up
Selective reporting (reporting bias)	Unclear risk	No study protocol available
Other bias	Unclear risk	Information about funding not given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding of participants was not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment was not described

SLA: standard lymph lymphadenectomy
ELA: extended lymph lymphadenectomy
PD: partial pancreaticoduodenectomy
IPMN: intraductal papillary mucinous neoplasm
ASA: American Society of Anesthesiologists
SMA: superior mesenteric artery
CHA: common hepatic artery
CA: coeliac axis

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

Study	Reason for exclusion
Aimoto 2013	Non-randomised study design
Bottger 1997	No comparison of SLA versus ELA; retrospective study
Gazzaniga 2001	Non-randomised study design
Henne-Bruns 1998	Non-randomised study design
Henne-Burns 2000	Non-randomised study design
Iacono 2002	Non-randomised study design
Kawabata 2012	Non-randomised study design
Paiella 2017	Letter to the editor
Schniewind 2006	Non-randomised study design
Takao 2008	Non-randomised study design; retrospective study

SLA: standard lymph lymphadenectomy

ELA: extended lymph lymphadenectomy

Characteristics of ongoing studies [ordered by study ID]

NCT02928081

Study name	Standard versus extended lymphadenectomy in pancreatoduodenectomy for patients with pancreatic head adenocarcinoma
Methods	Randomized controlled trial
Participants	<p>Number: 320 participants</p> <p>Age: 18 years to 75 years</p> <p>Sexes: all</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Subject was diagnosed with pancreatic ductal adenocarcinoma supported by pathological and radiological examination preoperatively • Subject with absence of vascular invasion and metastasis • Subject with absence of prior history of cancer <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Subject was diagnosed that other pancreatic tumour types (neuroendocrine tumors, intraductal papillary mucinous neoplasm, serous cystadenoma, mucinous cystadenocarcinoma, solid pseudopapillary neoplasm and pancreatitis) • Subject was found with liver, omental, mesenteric or peritoneal metastasis intraoperatively • Subject with presence of other significant diseases (e.g., coronary heart disease)
Interventions	<p>Standard lymphadenectomy:</p> <p>Lymph node dissection includes(LN5, LN6),(LN8a, 8b),(LN12b1, 12b2, 12c),(LN13a, 13b),(LN14a, 14b),(LN17a, 17b)</p> <p>Procedure: extended lymphadenectomy:</p> <p>Extended lymphadenectomy with nerve tissues around CHA and the SMA and nodes around the celiac trunk and SMA (No.16a2, 16b1)</p>
Outcomes	<p>Primary outcome:</p> <ul style="list-style-type: none"> • 5-year overall survival <p>Secondary outcomes:</p> <ul style="list-style-type: none"> • Postoperative pancreatic fistula • Bile leakage • Delayed gastric emptying • Post-pancreatectomy haemorrhage • Intra-abdominal infection • Wound infection • Postoperative mortality (within 30 days or 60 days) • Quality of life • 5-year disease-free survival rate
Starting date	January 2016
Contact information	West China Hospital:

Extended lymph node resection versus standard resection for pancreatic and periampullary adenocarcinoma (Review)

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NCT02928081 (Continued)

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Notes

LN: lymph node

CHA: common hepatic artery

SMA: superior mesenteric artery

DATA AND ANALYSES

Comparison 1. Extended vs standard lymph node resection

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Overall survival	7		log Hazard Ratio (IV, Fixed, 95% CI)	0.12 [-3.06, 3.31]
1.2 Postoperative mortality	7	843	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.20 [0.51, 2.80]
1.3 Pancreatic fistula	4	610	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.85, 2.10]
1.4 Delayed gastric emptying	3	523	Risk Ratio (M-H, Random, 95% CI)	1.66 [0.60, 4.60]
1.5 Postoperative haemorrhage	4	376	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [0.61, 3.64]
1.6 Operating time	5	670	Mean Difference (IV, Random, 95% CI)	50.13 [19.19, 81.06]
1.7 Blood loss	2	463	Mean Difference (IV, Random, 95% CI)	137.43 [11.55, 263.30]
1.8 Transfusion requirements	4	610	Mean Difference (IV, Fixed, 95% CI)	0.15 [0.13, 0.17]
1.9 Lymph nodes retrieved	5	670	Mean Difference (IV, Random, 95% CI)	11.09 [7.16, 15.02]
1.10 Positive resection margins (R1 + R2)	6	783	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.58, 1.13]

Analysis 1.1. Comparison 1: Extended vs standard lymph node resection, Outcome 1: Overall survival

Analysis 1.2. Comparison 1: Extended vs standard lymph node resection, Outcome 2: Postoperative mortality

Analysis 1.3. Comparison 1: Extended vs standard lymph node resection, Outcome 3: Pancreatic fistula

Analysis 1.4. Comparison 1: Extended vs standard lymph node resection, Outcome 4: Delayed gastric emptying

Analysis 1.5. Comparison 1: Extended vs standard lymph node resection, Outcome 5: Postoperative haemorrhage

Analysis 1.6. Comparison 1: Extended vs standard lymph node resection, Outcome 6: Operating time

Analysis 1.7. Comparison 1: Extended vs standard lymph node resection, Outcome 7: Blood loss

Analysis 1.8. Comparison 1: Extended vs standard lymph node resection, Outcome 8: Tranfusion requirements

Analysis 1.9. Comparison 1: Extended vs standard lymph node resection, Outcome 9: Lymph nodes retrieved

Analysis 1.10. Comparison 1: Extended vs standard lymph node resection, Outcome 10: Positive resection margins (R1 + R2)

APPENDICES

Appendix 1. Glossary of terms

Adjuvant therapy: the addition of one or more treatments to a primary treatment in hopes of improving survival or outcome

Celiac trunk: the first artery from the abdominal aorta just below the diaphragm and branches into the left gastric artery, the splenic artery and the common hepatic artery

Common hepatic artery: a branch of the celiac trunk which runs at the superior border of the pancreas

Curative resection: surgical removal of all the tumour-bearing tissue with no residual disease at the end of the operation

Distal: at the far end of a structure

En bloc resection: removal of a tumour (and adjacent structures) as one piece

Gastric: relating to the stomach

Gastrointestinal: relating to the stomach and intestines (gut)

Haemorrhage: excessive bleeding

Hepato-duodenal ligament: a portion of the lesser omentum between the liver and the duodenum containing the proper hepatic artery, the portal vein and the common bile duct

Intra-abdominal abscess: a painful collection of pus or infected fluid within the abdomen (belly)

Intraoperatively: occurring during surgery

Kausch-Whipple: Walther Kausch and Allen Whipple conducted the first two partial pancreaticoduodenectomies (see below) described in literature

Locoregional: restricted to a localized region around the tumour

Lymphadenectomy: surgical removal of lymph nodes

Lymph nodes: structures that act as filters to prevent foreign particles from entering the bloodstream

Malignancies: forms of cancer

Metastatic: relating to the passing of cancerous cells from an original site to one or more other sites in the body

Morbidity: death

Mortality: the rate of disease within a population

Negative resection margins: no detectable tumour cells at the cutting surface of the specimen

Neurological: relating to the nervous system

Oncological: relating to the study of tumours

Pancreatic fistula: leakage of pancreatic secretions from the anastomosis between the remnant pancreas and the intestine

Partial pancreaticoduodenectomy: en bloc removal of the duodenum, the head of the pancreas, the common bile duct, the gallbladder and the distal third of the stomach

Periampullary carcinoma: a widely used term to define a heterogeneous group of neoplasms arising from the head of the pancreas, the distal common bile duct and the duodenum

Portal vein: a vein carrying blood from the digestive organs and spleen to the liver

Pylorus: the distal end of the stomach that connects to the duodenum

Pylorus-preserving partial pancreaticoduodenectomy: a partial pancreaticoduodenectomy without resection of the distal third of the stomach and with preservation of the pylorus

Superior mesenteric artery: the second major branch arising from the abdominal aorta, and supplying most of the small intestine and parts of the colon

Superior mesenteric vein: a tributary to the portal vein that drains blood from the small intestine and parts of the colon

Vascular: relating to blood vessels

Appendix 2. CENTRAL search strategy

For CENTRAL we used the following search terms:

```
((pancreatic OR pancreas OR periampullary OR peri-ampullary) NEAR/3 (adenocarcinoma OR carcinoma OR cancer OR neoplasm* OR tumor))) AND ((Pancreatoduodenectomy* OR duodenopancreatectomy OR pancreatectomy OR hemipancreatectomy OR hemipancreatectomy) OR (pancrea* NEAR/3 (duodenectomy OR resection OR dissection OR excision)) OR ((brunschwig OR whipple) NEAR/3 (operation OR resection))) AND (lymphadenectomy OR lymphadenectomy OR ('lymph node' NEAR/3 (dissect* OR excis* OR extirpate* OR resect* OR metastas* OR retriev*))) :ti,ab,kw
```

Appendix 3. MEDLINE search strategy

For MEDLINE Ovid we used the following search terms:

```
(Pancreatic Neoplasms/ OR ((pancreatic OR pancreas OR periampullary OR peri-ampullary) ADJ3 (adenocarcinoma OR carcinoma OR cancer OR neoplasm* OR tumor)).ab,ti.) AND (Pancreatoduodenectomy/ OR Pancreatectomy/ OR (Pancreatoduodenectomy* OR duodenopancreatectomy OR pancreatectomy OR hemipancreatectomy OR hemipancreatectomy).ab,ti. OR (pancrea* ADJ3 (duodenectomy OR resection OR dissection OR excision)).ab,ti. OR ((brunschwig OR whipple) ADJ3 (operation OR resection)).ab,ti.) AND (exp Lymph Node Excision/ OR lymphadenectomy.ab,ti. OR lymphadenectomy.ab,ti. OR (lymph node ADJ3 (dissect* OR excis* OR extirpate* OR resect* OR metastas* OR retriev*)).ab,ti.) NOT case report/
```

Appendix 4. PubMed search strategy

For PubMed we used the following search terms:

```
(Pancreatic Neoplasms[mh] OR ((pancreatic[tiab] OR pancreas[tiab] OR periampullary[tiab] OR peri-ampullary[tiab]) AND (adenocarcinoma[tiab] OR carcinoma[tiab] OR cancer[tiab] OR neoplasm*[tiab] OR tumor[tiab]))) AND (Pancreatoduodenectomy[mh] OR Pancreatectomy[mh] OR (Pancreatoduodenectomy*[tiab] OR duodenopancreatectomy[tiab] OR pancreatectomy[tiab] OR hemipancreatectomy[tiab] OR hemipancreatectomy[tiab]) OR (pancrea*[tiab] AND (duodenectomy[tiab] OR resection[tiab] OR dissection[tiab] OR excision[tiab]))) OR ((brunschwig[tiab] OR whipple[tiab]) AND (operation[tiab] OR resection[tiab])) AND (Lymph Node Excision[mh] OR lymphadenectomy[tiab] OR lymphadenectomy[tiab] OR ((lymph[tiab] OR node[tiab]) AND (dissect*[tiab] OR excis*[tiab] OR extirpate*[tiab] OR resect*[tiab] OR metastas*[tiab] OR retriev*[tiab]))) NOT case report[pt] AND (publisher[sb] OR inprocess[sb])
```

Appendix 5. Embase search strategy

For Embase (embase.com) we used the following search terms:

('pancreas cancer'/exp OR ((pancreatic OR pancreas OR periampullary OR peri-ampullary) NEAR/3 (adenocarcinoma OR carcinoma OR cancer OR neoplasm* OR tumor)):ab,ti) AND ('pancreaticoduodenectomy'/exp OR 'pancreas resection'/exp OR (Pancreatoduodenectom* OR duodenopancreatectomy OR pancreatectomy OR hemipancreatectomy OR hemi-pancreatectomy):ab,ti OR (pancrea* NEAR/3 (duodenectomy OR resection OR dissection OR excision)):ab,ti OR ((brunschwig OR whipple) NEAR/3 (operation OR resection)):ab,ti) AND ('lymph node dissection'/exp OR lymphadenectomy:ab,ti OR lymphoadenectomy:ab,ti OR ('lymph node' NEAR/3 (dissect* OR excis* OR extirpate* OR resect* OR metastas* OR retriev*)):ab,ti) NOT 'conference abstract'/it NOT 'case report'/de

HISTORY

Protocol first published: Issue 2, 2015

Review first published: Issue 1, 2021

CONTRIBUTIONS OF AUTHORS

- Conceiving the protocol: RFS, RNVdB
- Designing the protocol: RFS, RNVdB, MAP
- Providing general advice on the protocol: CS, JS, SB, MAP
- Co-ordinating the protocol: RFS
- Designing search strategies: RFS, RT
- Title and abstract screening: RFS, RT
- Full text screening: RFS, RT
- Data extraction: RFS, RNVdB, CS
- Writing the protocol: RFS, RNVdB, MAP, JS, SB
- Analysing data: RNVdB, MAP
- Risk of bias: CS, RFS
- GRADE assessment: MAP

DECLARATIONS OF INTEREST

- RFS: none known
- CS: none known
- RNVdB: none known
- RT: none known
- JS: none known
- MAP: none known
- SB: none known

SOURCES OF SUPPORT

Internal sources

- Cantonal Hospital of Winterthur, Department of Visceral and Thoracic Surgery, Switzerland

In-kind support

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Expressing overall survival time using mean and standard deviation, and survival at particular times points (one- to five-year survival) 'using odds ratios' was changed to 'using hazard ratios'. 'Thirty-day mortality' was renamed 'postoperative mortality'. 'Overall perioperative morbidity' was split into the single morbidities: 'pancreatic fistula', 'delayed gastric emptying', and 'postoperative haemorrhage'. 'Overall disease-free survival' was omitted, since there is accumulating evidence that this surrogate outcome often does not correlate well with overall survival.

INDEX TERMS

Medical Subject Headings (MeSH)

Adenocarcinoma [mortality] [*surgery]; Ampulla of Vater [*surgery]; Blood Loss, Surgical; Common Bile Duct Neoplasms [mortality] [*surgery]; Confidence Intervals; Gastric Emptying; Kaplan-Meier Estimate; Lymph Node Excision [*methods] [mortality]; Margins of Excision; Operative Time; Pancreatic Fistula [etiology]; Pancreatic Neoplasms [mortality] [*surgery]; Pancreaticoduodenectomy [methods]; Postoperative Complications [etiology]; Postoperative Hemorrhage [etiology]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans