ClinicalEvidence

Pancreatic cancer

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ABSTRACT

INTRODUCTION: Pancreatic cancer is the fourth most common cause of cancer death in higher-income countries, with 5-year survival only 10% even in people presenting with early-stage cancer. Risk factors include smoking, high alcohol intake, and dietary factors, while diabetes mellitus and previous pancreatitis may also increase the risk. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of surgical treatments in people with pancreatic cancer considered suitable for complete tumour resection? What are the effects of interventions to prevent pancreatic leak after pancreaticoduodenectomy in people with pancreatic cancer considered suitable for complete tumour resection? What are the effects of adjuvant treatments in people with completely resected pancreatic cancer? What are the effects of interventions in people with non-resectable (locally advanced or advanced) pancreatic cancer? We searched: Medline, Embase, The Cochrane Library, and other important databases up to August 2009 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 46 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: chemoradiotherapy; chemoradiotherapy for non-resectable pancreatic cancer; chemoradiotherapy for resected pancreatic cancer; fibrin glue; fluorouracil-based chemotherapy (adjuvant) for resected pancreatic cancer (with or without surgery); fluorouracil-based chemotherapy for non-resectable pancreatic cancer; fluorouracil-based chemotherapy (systemic); fluorouracil-based combination chemotherapy; fluorouracil-based monotherapy for non-resectable pancreatic cancer; gemcitabine-based chemotherapy (adjuvant) for resected pancreatic cancer; gemcitabine-based chemotherapy (systemic); gemcitabine-based combination chemotherapy; gemcitabine-based monotherapy for non-resectable pancreatic cancer; lymphadenectomy (extended [radical], or standard) in people having pancreaticoduodenectomy; pancreatic duct occlusion; pancreaticoduodenectomy (pylorus-preserving); pancreaticoduodenectomy (Whipple's procedure); pancreaticogastrostomy reconstruction; pancreaticojejunostomy; and somatostatin and somatostatin analogues.

QUESTIONS

INTERVENTIONS

SURGICAL TREATMENTS

Unknown effectiveness

PREVENTING PANCREATIC LEAK

Likely to be beneficial

Unknown effectiveness

Likely to be ineffective or harmful

ADJUVANT TREATMENTS

Beneficial

Unknown effectiveness

NON-RESECTABLE CANCER

Beneficial

Likely to be beneficial

Footnote

*RCTs comparing surgery versus no surgery may be considered unethical in people with pancreatic cancer considered suitable for complete tumour resection.

Key points

- Pancreatic cancer is the fourth most common cause of cancer death in higher-income countries, with 5-year survival only 10% (range 7%–25%), even in people presenting with early-stage cancer.

  Risk factors include age, smoking, chronic pancreatitis, a family history, and dietary factors. Diabetes mellitus may also increase the risk.

- In people with pancreatic cancer considered suitable for complete tumour resection, pancreaticoduodenectomy (Kausch–Whipple procedure) or pylorus-preserving pancreaticoduodenectomy (Traverso–Longmire procedure) may prolong survival compared with non-surgical treatment, although no large RCTs have been found.

  Pylorus-preserving pancreaticoduodenectomy may lead to similar quality of life and survival compared with Kausch–Whipple pancreaticoduodenectomy.

  Extended lymphadenectomy is associated with increases in adverse effects compared with standard lymphadenectomy, without conferring any survival benefit.

- Somatostatin and its analogues, particularly octreotide, prevent complications (pancreatic leak and intra-abdominal collections) of pancreatic surgery but do not reduce mortality.

  We don't know which anastomosis (pancreaticogastrostomy or pancreaticojejunostomy) is more effective for preventing pancreatic leak.

  Pancreatic duct occlusion does not assist in preventing complications associated with pancreatic leak when added to anastomosis. When used alone, duct occlusion increases pancreatic fistula and pancreatic endocrine and exocrine insufficiency, and cannot therefore be recommended.

  We don't know whether fibrin glue is effective for preventing pancreatic leak.

- Adjuvant fluorouracil-based chemotherapy increases median and 5-year survival in people with completely resected pancreatic cancer compared with no chemotherapy.

  Adjuvant chemoradiotherapy does not seem to improve survival in people with resected pancreatic cancer.

  We don't know whether adjuvant gemcitabine-based chemotherapy increases survival compared with no chemotherapy in people with resected pancreatic cancer. Trials are under way and we await their results.

- In people with non-resectable pancreatic cancer, gemcitabine or fluorouracil monotherapy seem preferable to combination chemotherapy based on either drug.

  We found insufficient evidence to recommend chemoradiation over chemotherapy alone in people with non-resectable pancreatic cancer.

Clinical context

DEFINITION

In this review, the term "pancreatic cancer" refers to primary ductal adenocarcinoma of the pancreas. Other pancreatic malignancies such as neuroendocrine and serous cystic tumours of the pancreas are not considered. Symptoms of pancreatic cancer include pain, jaundice, nausea, weight loss, anorexia, and symptoms associated with GI obstruction and diabetes. Pancreatic cancer is staged using the tumour, node, metastasis (TNM) and American Joint Committee on Cancer (AJCC) [1] classification systems (see table 1, p 16 and table 2, p 16). A pancreatic tumour is considered resectable if the tumour appears to be localised to the pancreas, without invasion into major blood vessels or distant spread to liver, lungs, or bone. Earlier detection of tumours increases the possibility of resection. Other factors that influence resectability include perceived perioperative risk based on other comorbidities.

INCIDENCE/ PREVALENCE

Pancreatic cancer is the eighth most common cancer in the UK, with an annual incidence in England and Wales of about 12/100,000. [2] It is the fourth most common cause of cancer death in higher-

income countries, responsible for about 30,000 deaths each year in the USA. [3] Prevalence is similar in men and women, with 5% to 10% presenting with resectable disease.

AETIOLOGY/ RISK FACTORS

Pancreatic cancer is more likely to develop in people who smoke and have high alcohol intake. Dietary factors, such as lack of fruit and vegetables, are also reported risk factors. [4] One population-based cohort study of more than 2000 people suggested that there was a 1% chance of developing pancreatic cancer within 3 years of diagnosis in people diagnosed with new-onset diabetes mellitus. [5] However, estimates of the magnitude of increased risk of pancreatic cancer in people with diabetes vary. Additional risk factors include chronic sporadic pancreatitis — which carries a five-fold increased risk of developing pancreatic cancer — and, in some cases, a family history of pancreatic cancer. [6]

PROGNOSIS

Prognosis in people with pancreatic cancer is poor. The overall median survival worldwide is less than 6 months, with an overall 5-year survival rate of 0.4% to 5.0%. The surgical resection rate worldwide is between 2.6% and 9.0%, with a median survival of 11 to 20 months and a 5-year survival of rate of 7% to 25%, with few long-term survivors. [6] Tumour resection is graded from R0 to R2, with R0 meaning that no tumour remains after surgery (confirmed by histology); R1 meaning that the surgeon believes no tumour remains but histology demonstrates positive margins; and R2 meaning that the surgeon was unable to remove all macroscopic tumour completely.

AIMS OF INTERVENTION

To prolong survival, and improve symptoms and quality of life, with minimal adverse effects of treatment.

OUTCOMES

Mortality, improvement in symptoms and quality of life, completeness of surgery (number of lymph nodes retrieved during surgery), **treatment success (including progression-free survival, time to progression, relapse rates), adverse effects of treatment, including perioperative and postoperative complications.**

METHODS

Clinical Evidence search and appraisal August 2009. The following databases were used to identify studies for this review: Medline 1966 to August 2009, Embase 1980 to August 2009, and The Cochrane Library and Cochrane Central Register of Controlled Clinical Trials, Issue 4, 2009. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and National Institute for Health and Clinical Excellence (NICE). Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributors for additional assessment, using pre-determined criteria to identify relevant studies. The contributors also performed their own search and appraisal for the question on interventions to prevent pancreatic leak using Medline, Embase, and The Cochrane Library and Cochrane Central Register of Controlled Clinical Trials, plus hand searches of reference lists of articles retrieved. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language, at least single-blinded, and containing more than 20 individuals, of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible (as it is for surgical interventions, for example). In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 33).

QUESTION **What are the effects of surgical treatments in people with pancreatic cancer considered suitable for complete tumour resection?**

OPTION **PANCREATICODUODENECTOMY VERSUS NON-SURGICAL TREATMENT**

Mortality

Compared with non-surgical treatment Pancreaticoduodenectomy (primarily Kausch–Whipple or pylorus-preserving) may be more effective at increasing survival in people with resectable pancreatic cancer (moderate-quality evidence).

Quality of life
Compared with non-surgical treatment Pancreaticoduodenectomy (primarily Kausch–Whipple or pylorus-preserving) may be no more effective at improving quality of life in people with resectable pancreatic cancer (low-quality evidence).

For GRADE evaluation of interventions for pancreatic cancer, see table, p 33 .

Benefits: **Pancreaticoduodenectomy versus non-surgical treatment:**
We found one RCT reported in two papers: interim and long-term follow-up comparing surgery (primarily Kausch–Whipple or pylorus-preserving pancreaticoduodenectomy) versus non-surgical treatment in people with resectable pancreatic cancer. [7] [8] The initial report found that surgery significantly increased mean survival compared with chemoradiotherapy (see table 3, p 17). [7] There was no significant difference in patient satisfaction, pain scores, or performance status (see table 3, p 17). [7] The long-term follow-up found that surgery significantly increased mean survival compared with chemoradiotherapy at 5 years' follow-up (mean survival: 22.6 months with surgery *v* 10.8 months with chemoradiotherapy; mean difference 11.8 months; HR 0.46, 95% CI 0.22 to 0.92; P = 0.025) and increased the proportion of people who survived at 3 years (20% with surgery *v* 0% with chemoradiotherapy; P = 0.025, absolute numbers not reported). [8]

Harms: The RCT found that surgery was associated with increased diarrhoea (see table 3, p 17). [7] [8]

Comment: **Clinical guide:**
The results of the RCT are supported by a large-cohort study (100,313 people with pancreatic cancer), which found that people having pancreaticoduodenectomy lived longer than people not treated surgically (5-year survival: 23% with surgery *v* 5% without surgery). [9] However, results may have been confounded by differences in disease stage between those having surgery and those treated without surgery.

OPTION PYLORUS-PRESERVING PANCREATICODUODENECTOMY VERSUS KAUSCH–WHIPPLE PANCREATICODUODENECTOMY

Mortality
Compared with Kausch–Whipple pancreaticoduodenectomy Pylorus-preserving pancreaticoduodenectomy may be more effective at increasing overall survival, and decreasing perioperative mortality in people with resectable pancreatic cancer (low-quality evidence).

Quality of life
Compared with Kausch–Whipple pancreaticoduodenectomy Pylorus-preserving pancreaticoduodenectomy may be no more effective at improving quality of life in people with resectable pancreatic cancer (moderate-quality evidence).

Complications
Compared with Kausch–Whipple pancreaticoduodenectomy We don't know whether pylorus-preserving pancreaticoduodenectomy reduces the risk of postoperative complications (low-quality evidence).

For GRADE evaluation of interventions for pancreatic cancer, see table, p 33 .

Benefits: We found one systematic review [10] and one subsequent RCT. [11]

The review (search date 2006; 32 studies, including 5 RCTs, 12 prospective non-randomised trials, and 15 retrospective reports; 2822 people) compared pylorus-preserving pancreaticoduodenectomy (PPPD) versus Kausch–Whipple pancreaticoduodenectomy (KW). It found that PPPD significantly improved overall survival for all resected malignant lesions at 5 years, and reduced perioperative mortality, compared with KW (see table 4, p 18). [10] However, a subgroup of RCT data found no significant difference in either 5-year overall mortality or perioperative mortality between groups (no further data reported). Two RCTs included in the review found similar global quality-of-life assessments with PPPD and KW (see table 4, p 18). [12] [13]

The subsequent RCT (67 people) compared PPPD versus standard pancreaticoduodenectomy in people who survived for 3 years after surgery. [11] The RCT found no significant difference between groups in quality of life (Global Health Status: P = 0.138).

Harms: The review found no significant difference in overall morbidity or individual complications including delayed gastric emptying, haemorrhage, pancreatic leak, pancreatic fistula, biliary leak, biliary fistula, and wound infections between PPPD and KW (see table 4, p 18). [10]

The subsequent RCT found no significant difference for steatorrhoea (6/44 [14%] with PPPD *v* 2/23 [13%] with standard pancreaticoduodenectomy; P = 0.63) or other postoperative GI symptoms (including abdominal pain, heartburn, regurgitation, sucking sensation, nausea/vomiting, borborygmus, distension, eructation, decreased stool, increased stool, loose stool, hard stool, urgency, and incompleteness) between groups. However, the RCT reported that PPPD significantly decreased the incidence of flatus compared with standard pancreaticoduodenectomy (23/32 [72%] with PPPD *v* 20/20 [100%] with standard pancreaticoduodenectomy; P = 0.009). [11]

Comment: None.

OPTION EXTENDED (RADICAL) VERSUS STANDARD LYMPHADENECTOMY IN PEOPLE HAVING PANCREATICODUODENECTOMY

Mortality
Compared with standard lymphadenectomy Extended (radical) lymphadenectomy may be no more effective at increasing survival in people having pancreaticoduodenectomy (very low-quality evidence).

Quality of life
Compared with standard lymphadenectomy Extended (radical) lymphadenectomy may be no more effective at 2 years at improving quality of life in people having pancreaticoduodenectomy (very low-quality evidence).

Complications
Compared with standard lymphadenectomy Extended (radical) lymphadenectomy may increase postoperative complications, wound infections, and rates of delayed gastric emptying in people having pancreaticoduodenectomy (very low-quality evidence).

For GRADE evaluation of interventions for pancreatic cancer, see table, p 33 .

Benefits: We found one systematic review [14] and one additional RCT [15] comparing extended versus standard lymphadenectomy in people having pancreaticoduodenectomy.

The review (search date 2006; 3 RCTs; 3 prospective non-randomised trials and 9 retrospective reviews; 1909 people) found no significant difference in mean survival between extended and standard lymphadenectomy; this finding was supported by a subgroup analysis of the included RCTs (no further data reported). [14] The review also found that extended lymphadenectomy significantly increased the number of lymph nodes retrieved compared with standard lymphadenectomy. However, there was significant heterogeneity among studies; therefore, these results should be considered with caution (see table 5, p 19). [14] The additional RCT (294 people with pancreatic adenocarcinoma or peri-ampullary cancer; mean age 65.7 years; mean tumour size 2.5 cm) found no significant difference in quality of life at 2 years between the two groups (see table 5, p 19). [15]

Harms: The review found no significant difference in postoperative mortality or complications, between extended and standard lymphadenectomy except for delayed gastric emptying, which was seen more in the extended lymphadenectomy group (see table 5, p 19). [14] The additional RCT found that extended lymphadenectomy significantly increased the risk of overall postoperative complications, wound infection, and delayed gastric emptying (see table 5, p 19). [15]

Comment: None.

QUESTION What are the effects of interventions to prevent pancreatic leak after pancreaticoduodenectomy in people with pancreatic cancer considered suitable for complete tumour resection?

OPTION SOMATOSTATIN AND SOMATOSTATIN ANALOGUES

Mortality
Compared with placebo/control Somatostatin and its analogues (octreotide) may be no more effective at reducing mortality rates after pancreaticoduodenectomy (very low-quality evidence).

Complications
Compared with placebo/control Somatostatin and its analogues (octreotide) may be more effective at reducing overall pancreas-related complications (leaks, fistula, abscess, and intra-abdominal collection) after pancreatic surgery, but may be no more effective after pancreaticoduodenectomy (very low-quality evidence).

For GRADE evaluation of interventions for pancreatic cancer, see table, p 33 .

Benefits: We found one large systematic review (search date not reported) comparing somatostatin and its analogues (primarily octreotide) versus placebo or control. The review found that somatostatin and its analogues (primarily octreotide) significantly reduced overall and pancreas-related complications (leak, fistula, abscess, and intra-abdominal collection) in people with pancreatic cancer or pancreatitis having surgery (see table 6, p 20). [16] However, there was no significant difference in overall complications after pancreaticoduodenectomy, or in mortality, between somatostatin and its analogues and placebo or control (see table 6, p 20).

We found one subsequent RCT (50 people with benign or malignant pancreatic tumours requiring pancreaticoduodenectomy) comparing somatostatin versus octreotide. [17] The RCT found no significant difference between groups in mortality or postoperative complications (see table 6, p 20). [17]

Harms: The review gave no information on adverse effects associated with somatostatin or somatostatin analogues. [16] As somatostatin aims to reduce adverse effects of pancreaticoduodenectomy, all other outcomes are discussed in the benefits section above. [17]

Comment: **Clinical guide:**
The mortality associated with pancreaticoduodenectomy is less than 5% in high-volume specialist centres. However, morbidity ranges from 30% to 60%. [18] One of the major complications and causes of death after pancreaticoduodenectomy is leakage from the residual pancreatic stump. As a result, numerous attempts, both pharmacological and technical, have been made to prevent pancreatic stump-related complications. Although the review included surgery in people both with and without pancreatic cancer, results will be generalisable to people with pancreatic cancer.

OPTION DIFFERENT TYPES OF PANCREATIC-ENTERIC ANASTOMOSIS VERSUS EACH OTHER

Mortality
Pancreaticojejunostomy compared with pancreaticogastrostomy Pancreaticojejunostomy and pancreaticogastrostomy seems to be equally effective at decreasing mortality (low-quality evidence).

Complications
Pancreaticojejunostomy compared with pancreaticogastrostomy Pancreaticojejunostomy and pancreaticogastrostomy seem to be associated with similar rates of overall complications, pancreatic fistula, intra-abdominal fluid collection, and bile leak (low-quality evidence).

For GRADE evaluation of interventions for pancreatic cancer, see table, p 33 .

Benefits: **Pancreaticojejunostomy versus pancreaticogastrostomy reconstruction:**
We found one systematic review (search date 2006; 3 RCTs; 445 people) comparing pancreaticogastrostomy and pancreaticojejunostomy. [19] The review found no significant difference between groups in mortality (see table 7, p 22).

Harms: **Pancreaticojejunostomy versus pancreaticogastrostomy reconstruction:**
The review found no significant difference between pancreaticogastrostomy and pancreaticojejunostomy groups in terms of overall postoperative complications, pancreatic fistula, intra-abdominal fluid collection, or bile leak (see table 7, p 22).

Comment: **Clinical guide:**
The mortality associated with pancreaticoduodenectomy is less than 5% in high-volume specialist centres. However, morbidity ranges from 30% to 60%. [18] One of the major complications and causes of death after pancreaticoduodenectomy is leakage from the residual pancreatic stump. As a result, numerous attempts, both pharmacological and technical, have been made to prevent pancreatic stump-related complications.

OPTION FIBRIN GLUE

Symptom severity
Compared with no glue Fibrin glue may be no more effective at preventing pancreatic leak in people who have had pancreatic surgery for neoplasms or inflammatory disease (low-quality evidence).

For GRADE evaluation of interventions for pancreatic cancer, see table, p 33 .

Benefits: We found one RCT comparing fibrin glue versus no glue after a variety of types of pancreatic surgery for pancreatic neoplasms or inflammatory disease. [20] It found no significant difference in pancreatic fistula between fibrin glue and no glue (see table 8, p 22).

Harms: The RCT reported that "no complication could be directly related to the [fibrin] glue". [20] As fibrin glue aims to reduce adverse effects of pancreaticoduodenectomy, all other outcomes are discussed in the benefits section above.

Comment: **Clinical guide:**
The mortality associated with pancreaticoduodenectomy is less than 5% in high-volume specialist centres. However, morbidity ranges from 30% to 60%. [18] One of the major complications and causes of death after pancreaticoduodenectomy is leakage from the residual pancreatic stump. As a result, numerous attempts, both pharmacological and technical, have been made to prevent pancreatic stump-related complications.

OPTION PANCREATIC DUCT OCCLUSION

Mortality
Compared with anastomosis alone Adding temporary occlusion of the main pancreatic duct to enteric anastomosis may be no more effective at reducing perioperative mortality or increasing survival at 1 year (low-quality evidence).

Complications
Compared with anastomosis alone Adding temporary occlusion of the main pancreatic duct to enteric anastomosis may be no more effective at decreasing intra-abdominal collections, but we don't know whether duct occlusion may be more effective at decreasing pancreatic fistulas (very low-quality evidence).

Compared with anastomosis alone Adding temporary occlusion of the main pancreatic duct to enteric anastomosis may increase endocrine and exocrine insufficiency at 3 months to 1 year (very low-quality evidence).

For GRADE evaluation of interventions for pancreatic cancer, see table, p 33 .

Benefits: We found no systematic review but found two RCTs. [21] [22] The first RCT found no significant difference between adding duct occlusion to anastomosis and anastomosis alone in perioperative mortality, pancreatic fistula, and intra-abdominal collections (see table 9, p 23). [21] The second RCT found similar survival at 1 year between duct occlusion and anastomosis. [22] It also found no significant difference between groups in overall complications or intra-abdominal collections. However, it found that duct occlusion significantly increased pancreatic fistula, and exocrine and endocrine insufficiency (measured by need for enzyme replacement), on discharge from hospital and at 3 months, and incidence of diabetes mellitus at 1 year (see table 9, p 23).

Harms: The RCTs found no significant difference in blood loss between adding duct occlusion to anastomosis and anastomosis alone (see table 9, p 23). [21] [22] As pancreatic duct occlusion aims to reduce adverse effects of pancreaticoduodenectomy, all other outcomes are discussed in the benefits section above.

Comment: **Clinical guide:**
The mortality associated with pancreaticoduodenectomy is less than 5% in high-volume specialist centres. However, morbidity ranges from 30% to 60%. [18] One of the major complications and causes of death after pancreaticoduodenectomy is leakage from the residual pancreatic stump. As a result, numerous attempts, both pharmacological and technical, have been made to prevent pancreatic stump-related complications. The sealants assessed in these RCTs are used both to manage anastomoses (reconstructions) after pancreaticoduodenectomy and to manage the pancreatic stump after left-sided pancreatic resections (see table 9, p 23).

QUESTION What are the effects of adjuvant treatments in people with completely resected pancreatic cancer?

OPTION FLUOROURACIL-BASED CHEMOTHERAPY (ADJUVANT) FOR RESECTED PANCREATIC CANCER

Mortality
Compared with no adjuvant chemotherapy Fluorouracil-based adjuvant chemotherapy may increase survival in people with resected pancreatic adenocarcinoma compared with surgery alone (low-quality evidence).

Relapse rates
Compared with no adjuvant chemotherapy Adjuvant chemotherapy may reduce relapse rates in people with resected pancreatic cancer compared with surgery alone (low-quality evidence).

For GRADE evaluation of interventions for pancreatic cancer, see table, p 33 .

Benefits:

Fluorouracil-based chemotherapy (adjuvant) versus no adjuvant chemotherapy:
We found one systematic review (search date 2003; 4 RCTs; 1119 people with resected pancreatic adenocarcinoma), [23] [24] [25] [26] [27] which meta-analysed individual patient data comparing adjuvant chemotherapy versus surgery alone. We also found one subsequent RCT. [28] The review found that adjuvant chemotherapy significantly increased survival compared with surgery alone (see table 10, p 25). [23] The subsequent RCT found no significant difference in median survival or recurrence between adjuvant chemotherapy and surgery alone, but it may have been underpowered to detect clinically important differences in these outcomes (see table 10, p 25). [28]

Harms:

Fluorouracil-based chemotherapy (adjuvant) versus no adjuvant chemotherapy:
The review gave no information on adverse effects. [23] The first RCT (61 people) identified by the review found that chemotherapy significantly increased nausea and vomiting at 3 months compared with surgery alone (4/18 [22%] with adjuvant chemotherapy *v* 0/18 [0%] with surgery alone; P = 0.06). [24] One person having chemotherapy died from sepsis. Chemotherapy was also associated with non-fatal sepsis (4 people), alopecia (11 people), cardiotoxicity (2 people), and nephrotoxicity (2 people). The second RCT identified by the review (508 people) found that chemotherapy significantly increased leukopenia, anorexia, and nausea or vomiting compared with no chemotherapy (grade 2 or greater leukopenia: 13% with chemotherapy *v* 3% with no chemotherapy; grade 2 or greater anorexia: 22% with chemotherapy *v* 14% with no chemotherapy; grade 2 or greater nausea/vomiting: 13% with chemotherapy *v* 7% with no chemotherapy; P less than or equal to 0.05 for each comparison). [25] The other two RCTs identified by the review assessed both chemotherapy and chemoradiotherapy versus surgery alone, and did not report results separately for each group. [26] [27] The subsequent RCT did not directly compare adverse effects between adjuvant chemotherapy and surgery alone; 82% of participants completed the two cycles of chemotherapy, with the most common adverse effect being nausea and vomiting. [28]

Comment: None.

OPTION CHEMORADIOTHERAPY FOR RESECTED PANCREATIC CANCER New

Mortality
Compared with surgery Adjuvant chemoradiotherapy is no more effective than surgery alone at decreasing mortality in people with resected pancreatic adenocarcinoma or peri-ampullary cancers (very low-quality evidence).

For GRADE evaluation of interventions for pancreatic cancer, see table, p 33 .

Benefits:

Adjuvant chemoradiotherapy versus surgery alone:
We found one systematic review (search date 2003; [23] 4 RCTs) [27] [28] [29] [30] and one long-term follow-up report of one RCT included in the review [31] comparing adjuvant chemoradiotherapy with surgery alone. The review found no significant difference in mortality between adjuvant chemoradiotherapy and surgery alone (see table 11, p 26). [23] The long-term follow-up report (218 people with histologically confirmed T1-3, N0-N1a M0 pancreatic cancer or T1-3 N0-N1 M0 peri-ampullary cancers, post-surgery) compared postoperative chemoradiation (40 Gy plus 5-fluorouracil) versus no further adjuvant treatment. [31] It found no significant difference in overall survival or progression-free survival between groups after 11.7 years' follow-up (see table 11, p 26). [31]

Harms:

Adjuvant chemoradiotherapy versus surgery alone:
The review gave no information on adverse effects. [23] The first RCT (43 people) did not directly compare adverse effects between adjuvant chemoradiotherapy and surgery alone; it found that chemotherapy was associated with leukopenia in 3/21 (14%) people. [29] The second RCT (207 people) also did not directly compare adverse effects between adjuvant chemoradiotherapy and surgery alone, and reported adverse effects of chemoradiotherapy in 81/104 (78%) people having treatment. It reported that 35/81 (44%) people received only 3 days of fluorouracil during the second course of radiotherapy owing to minor or moderate toxicity, usually nausea and vomiting. One person withdrew from treatment because of adverse effects. [30] The long-term follow-up of this RCT reported no leukopenia or thrombocytopenia worse than grade 2 with adjuvant treatment. [31] It also reported that one person developed a duodenal ulcer and other complications (maximum grade 3) including nausea/vomiting and diarrhoea. No direct comparisons were made between groups. The study also reported that 35 people (44%) only received 3 days of 5-fluorouracil during the second course due to grade 1 or 2 toxicities. [31] The other two RCTs identified by the review assessed chemotherapy or chemoradiotherapy versus surgery alone, and did not report results separately for each group. [27] [28]

Comment: None.

Clinical guide:
Adjuvant chemoradiotherapy seems to prolong survival only in incompletely excised (R1/R2) cancers, and may be detrimental to completely excised cancers of the pancreas.

OPTION GEMCITABINE-BASED CHEMOTHERAPY (ADJUVANT) FOR RESECTED PANCREATIC CANCER

Mortality
Compared with no adjuvant therapy We don't know whether adjuvant gemcitabine improves overall survival in people with resected pancreatic cancer (moderate-quality evidence).

Treatment success
Compared with no adjuvant therapy Adjuvant gemcitabine may improve disease-free survival in people with resected pancreatic cancer (moderate-quality evidence).

Quality of life
Compared with no adjuvant therapy We don't know if adjuvant gemcitabine improves quality of life in people with resected pancreatic cancer (moderate-quality evidence).

For GRADE evaluation of interventions for pancreatic cancer, see table, p 33 .

Benefits:

Systemic gemcitabine-based chemotherapy versus no adjuvant chemotherapy:
We found one systematic review (search date 2000) examining the effects of gemcitabine-based chemotherapy in people with resected pancreatic cancer. [32] It identified no RCTs comparing adjuvant gemcitabine versus no adjuvant chemotherapy or placebo. We found one subsequent RCT (368 people with gross complete (R0 or R1) resection of pancreatic cancer and no prior radiation or chemotherapy treatment) comparing adjuvant chemotherapy (6 cycles of gemcitabine on days 1, 8, and 15 every 4 weeks) versus observation. [33] The RCT found that gemcitabine significantly improved disease-free survival compared with observation (median: 13.4 months with gemcitabine *v* 6.9 months with observation; P less than 0.001) over 53 months' median follow-up. However, there was no significant difference for overall survival between groups (median 22.1 months, estimated survival 34% at 3 years and 22.5% at 5 years with gemcitabine *v* median 20.2 months, estimated survival 20.5% at 3 years and 11.5% at 5 years; P = 0.06). The RCT also found no significant difference between groups for quality of life or the median Karnofsky performance status (reported as not significant; P value not reported). [33]

Harms:

Systemic gemcitabine-based chemotherapy versus no adjuvant chemotherapy:
The review identified two studies that assessed harms of gemcitabine from both controlled and uncontrolled clinical trials. [32] Both studies included people with non-pancreatic tumours. The studies found that gemcitabine was associated with the following grade 3 to 4 toxicities: anaemia (about 7%), leukopenia (about 9%), neutropenia (about 25%), and thrombocytopenia (5%–7%). The subsequent RCT reported that grade 3 to 4 toxicities occurred infrequently with gemcitabine (no further data reported). The RCT reported 62 serious adverse events in 41 people (26/179 [15%] with gemcitabine *v* 15/175 [9%] with control), including leukopenia, nausea and vomiting, anaemia, thrombocytopenia, infection, oedema, and raised liver enzymes. [33]

Comment:

The results of larger trials investigating the role of adjuvant gemcitabine-based chemotherapy, such as ESPAC-3 (European Study Group for Pancreatic Cancer Trial 3), are still awaited. [34]

QUESTION What are the effects of interventions in people with non-resectable (locally advanced or advanced) pancreatic cancer?

OPTION CHEMOTHERAPY VERSUS SUPPORTIVE CARE FOR NON-RESECTABLE PANCREATIC CANCER

Mortality
Chemotherapy compared with supportive care Fluorouracil-based chemotherapy reduces mortality in people with non-resectable pancreatic cancer (high-quality evidence).

Note
We found no clinically important results from RCTs about other chemotherapy regimens compared with supportive care.

For GRADE evaluation of interventions for pancreatic cancer, see table, p 33 .

Benefits: We found two systematic reviews comparing fluorouracil-based chemotherapy versus supportive care. The first review (search date 2005; 7 RCTs) found that fluorouracil-based chemotherapy significantly reduced mortality at 1 year compared with supportive care (see table 12, p 26). [35] The review found no RCTs comparing other chemotherapy regimens versus supportive care. [35]

The second review (search date not reported; 7 RCTs also reported in the first review; 432 people) found fluorouracil-based chemotherapy significantly improved overall survival (defined as time of randomisation to death) compared with best supportive care (see table 12, p 26). However one trial was not included in the meta-analysis. The review reported that the published data for the excluded trial were inadequate to derive a summary estimate for overall survival. [36]

Harms: The first review gave little information on adverse effects, reporting only that one of the RCTs found that chemotherapy increased nausea compared with supportive care. [35] The second review gave no information on adverse effects. [36]

Comment: None.

OPTION FLUOROURACIL MONOTHERAPY VERSUS OTHER CHEMOTHERAPY REGIMENS FOR NON-RESECTABLE PANCREATIC CANCER

Mortality

Fluorouracil monotherapy compared with gemcitabine monotherapy Fluorouracil monotherapy and gemcitabine monotherapy seem equally effective at reducing mortality at 1 year in people with non-resectable pancreatic cancer (high-quality evidence).

Fluorouracil monotherapy compared with fluorouracil combination chemotherapy (cisplatin, oxaliplatin, and Mallinson regimen [cyclophosphamide plus methotrexate plus vincristine plus mitomycin]) Fluorouracil monotherapy is as effective as combination fluorouracil-based regimens at reducing mortality at 1 year in people with non-resectable pancreatic cancer (high-quality evidence).

Fluorouracil plus gemcitabine compared with gemcitabine monotherapy Fluorouracil plus gemcitabine combination chemotherapy is no more effective at 1 year at reducing mortality in people with non-resectable pancreatic cancer (high-quality evidence).

Treatment success

Fluorouracil monotherapy compared with fluorouracil combination chemotherapy (cisplatin, oxaliplatin, and Mallinson regimen [cyclophosphamide plus methotrexate plus vincristine plus mitomycin]) Fluorouracil monotherapy is as effective as combination fluorouracil-based regimens at increasing overall survival or time to progression of disease, although combination treatment has higher response rates and progression-free survival in people with non-resectable pancreatic cancer (high-quality evidence).

Fluorouracil plus gemcitabine compared with gemcitabine monotherapy Fluorouracil plus gemcitabine combination chemotherapy is no more effective at 1 year at reducing time to progression of disease in people with non-resectable pancreatic cancer (high-quality evidence).

Adverse effects

Fluorouracil combination chemotherapy is associated with higher rates of neutropenia and thrombocytopenia than fluorouracil monotherapy.

For GRADE evaluation of interventions for pancreatic cancer, see table, p 33 .

Benefits: **Fluorouracil monotherapy versus gemcitabine monotherapy:**
See benefits of gemcitabine-based chemotherapy, p 11 .

Fluorouracil monotherapy versus fluorouracil-based combination chemotherapy including cisplatin, oxaliplatin, and the Mallinson regimen (cyclophosphamide plus methotrexate plus vincristine plus mitomycin):
We found three systematic reviews comparing fluorouracil monotherapy versus fluorouracil-based combination therapy. [35] [36] [37] All three reviews included the same five RCTs, but reported different outcomes, so all three are reported here.

The first review (search date 2005; 8 RCTs) found no significant difference in mortality at 1 year between fluorouracil alone and fluorouracil combination chemotherapy (see table 13, p 27). [35] The second review (search date not reported; 5 RCTs; 700 people) found no significant difference between groups in overall survival (see table 13, p 27). [36] The third review (search date not reported; 5 RCTs; 700 people) found that combination therapy significantly increased progression-

free survival and overall response rates compared with monotherapy, but found no difference between groups for time to progression of disease (see table 13, p 27). [37]

Fluorouracil plus gemcitabine combination versus gemcitabine alone:
See benefits of gemcitabine-based chemotherapy, p 11 .

Harms:

Fluorouracil monotherapy versus gemcitabine monotherapy:
See harms of gemcitabine-based chemotherapy, p 11 .

Fluorouracil monotherapy versus fluorouracil-based combination chemotherapy including cisplatin, oxaliplatin, and the Mallinson regimen (cyclophosphamide plus methotrexate plus vincristine plus mitomycin):
The first two reviews gave no information on adverse effects. [35] [36] The third review found that fluorouracil combination chemotherapy increased grade 3 and 4 leukopenia, grade 3 and 4 nausea, and grade 3 and 4 vomiting compared with monotherapy. However, there was no significant difference between groups for grade 3 and 4 diarrhoea, stomatitis, thrombocytopenia, or anaemia (see table 13, p 27). [37]

Fluorouracil plus gemcitabine combination versus gemcitabine alone:
See harms of gemcitabine-based chemotherapy, p 11 .

Comment: None.

OPTION GEMCITABINE MONOTHERAPY VERSUS OTHER CHEMOTHERAPY REGIMENS FOR NON-RESECTABLE PANCREATIC CANCER

Mortality
Gemcitabine monotherapy compared with fluorouracil monotherapy Gemcitabine monotherapy and fluorouracil monotherapy seem equally effective at reducing mortality at 1 year in people with non-resectable pancreatic cancer (low-quality evidence).

Gemcitabine monotherapy compared with gemcitabine combination chemotherapy (cisplatin, oxaliplatin, fluorouracil, capecitabine, exatecan, or irinotecan) Gemcitabine monotherapy may be less effective at reducing mortality, although results are affected by the combination regimen used (low-quality evidence).

Treatment success
Gemcitabine monotherapy compared with fluorouracil monotherapy Gemcitabine monotherapy and fluorouracil monotherapy may be equally effective at increasing overall survival at 6, 12, or 18 months, or progression-free survival, but gemcitabine may be more effective at increasing time to progression and overall response rate in people with non-resectable pancreatic cancer (low-quality evidence).

Gemcitabine monotherapy compared with gemcitabine combination chemotherapy (cisplatin, oxaliplatin, fluorouracil, capecitabine, exatecan, or irinotecan) Gemcitabine monotherapy may be less effective at increasing overall survival, progression-free survival, time to progression, and overall response rate in people with non-resectable pancreatic cancer, although results are affected by the combination regimen used (low-quality evidence).

Symptom severity
Gemcitabine monotherapy compared with gemcitabine combination chemotherapy (cisplatin, oxaliplatin, fluorouracil, capecitabine, exatecan, or irinotecan) Gemcitabine monotherapy may be as effective at reducing pain intensity or analgesic consumption in people with non-resectable pancreatic cancer (moderate-quality evidence).

Quality of life
Gemcitabine monotherapy compared with gemcitabine combination chemotherapy (cisplatin, oxaliplatin, fluorouracil, capecitabine, exatecan, or irinotecan) Gemcitabine monotherapy may be as effective at improving quality of life in people with non-resectable pancreatic cancer (low-quality evidence).

Adverse effects
Gemcitabine monotherapy is associated with lower rates of neutropenia and thrombocytopenia than gemcitabine combination chemotherapy.

For GRADE evaluation of interventions for pancreatic cancer, see table, p 33 .

Benefits:

Gemcitabine monotherapy versus fluorouracil monotherapy:
We found three systematic reviews comparing gemcitabine monotherapy with fluorouracil monotherapy. [35] [36] [37] All three reviews included the same RCTs but reported on different outcomes, so all three are reported here.

The first review (search date 2005; 2 RCTs) found lower mortality with gemcitabine monotherapy than with fluorouracil monotherapy, but the difference between the groups was of borderline significance (see table 14, p 28). [35] The second review (search date not reported; 2 RCTs, 197 people, included in the first review) found no significant difference in overall survival between groups. [36] The third review (search date not reported; 2 RCTs also included in the first and second review) found that gemcitabine significantly increased time to progression of disease and overall response rates compared with fluorouracil, but found no significant difference between groups in progression-free survival (see table 14, p 28). [37]

Gemcitabine monotherapy versus gemcitabine in combination with cisplatin, oxaliplatin, fluorouracil, capecitabine, exatecan, or irinotecan:
We found six systematic reviews [35] [36] [37] [38] [39] [40] and two subsequent RCTs [41] [42] comparing gemcitabine monotherapy with gemcitabine combination therapy. There is significant overlap in the trials included in the reviews. However, each review does add more data to the analysis; therefore, all reviews are reported here.

The first review (search date 2005) found no significant difference in mortality at 1 year, median survival, or time to progression or treatment failure, between gemcitabine alone and gemcitabine combination chemotherapy (see table 15, p 29). [35]

The second review (search date not reported; 19 RCTs; 4694 people) found that gemcitabine monotherapy was significantly less effective than gemcitabine combination therapy at increasing overall survival (see table 15, p 29). [36]

The third review (search date not reported; 19 RCTs also included in the second review) found that gemcitabine monotherapy was significantly less effective than gemcitabine combination therapy at increasing progression-free survival, time to progression, and overall response rate (see table 15, p 29). [37]

The fourth review (search date 2006; 15 RCTs, 14 of which are also included in the second and third reviews; 4465 people) found that gemcitabine monotherapy was significantly less effective than gemcitabine combination therapy at increasing survival. However, subgroup analysis found no significant difference between groups in survival when gemcitabine was combined with irinotecan, exatecan, or pemetrexed (see table 15, p 29). [38]

The fifth review (search date 2006; 20 RCTs, 14 of which are also included in the second, third, and fourth reviews; 6296 people) found no significant difference in overall survival between gemcitabine monotherapy and gemcitabine combination therapy (see table 15, p 29). [39] However, the review also found that gemcitabine monotherapy was significantly less effective than gemcitabine combination therapy at increasing progression-free survival and overall response rate (see table 15, p 29). [39]

The sixth review (search date 2005; 23 RCTs, 20 of which are also included in the second, third, fourth, and fifth reviews; 5886 chemotherapy-naive people with advanced and metastatic pancreatic cancer) found that gemcitabine alone was significantly less effective than gemcitabine combinations at increasing overall survival at 6, 12, and 18 months (see table 15, p 29). [40]

The first subsequent RCT (319 people with advanced or metastatic pancreatic cancer) compared gemcitabine alone (1000 mg/m^2 in a 30-minute infusion weekly for 7 weeks, followed by a 1-week break, and then weekly for 3 weeks, every 4 weeks) versus gemcitabine plus capecitabine (oral Cap 650 mg/m^2 twice daily on days 1 to 14 inclusive, plus Gem 1000 mg/m^2 in a 30-minute infusion on days 1 and 8 every 3 weeks) for 24 weeks or until progression. [41] The RCT found no significant difference between groups in clinical benefit response (CBR; defined as improvement from baseline of in pain [intensity or analgesic consumption] and in Karnofsky performance status, stability in one of these parameters but improvement in the other, or stability in pain and performance status with positive improvement in weight) or quality of life (see table 15, p 29). [41]

The second subsequent RCT (104 people with histologically or cytologically confirmed stage IV-A[T4N0-1M0] or metastatic pancreatic adenocarcinoma) compared gemcitabine monotherapy versus PEFG regimen (cisplatin plus epirubicin plus 5-fluorouracil plus gemcitabine). [42] The RCT assessed quality of life outcomes using the European Organisation for Research and Treatment of Cancer QLQ-C30 and PAN 26 questionnaires completed at baseline and every second month until disease progression. The RCT found that gemcitabine alone was less effective at improving (defined as greater than 10-point scale increase from baseline) quality of life, including emotional function, fatigue, pain, and flatulence. No statistical comparisons were made between groups, but clinically important change was expressed as the percentage of people with an improved score (see table 15, p 29). [42]

Harms:

Gemcitabine monotherapy versus fluorouracil monotherapy:
The first two systematic reviews gave no information on adverse effects. [35] [36] The third systematic review reported that gemcitabine monotherapy significantly increased the risk of grade 3 and 4 neutropenia (see table 14, p 28). [37]

Gemcitabine monotherapy versus gemcitabine in combination with cisplatin, oxaliplatin, fluorouracil, capecitabine, exatecan, or irinotecan:
Five of the reviews and the subsequent RCTs gave no information on adverse effects. [35] [36] [38] [40] [39] [41] The third review reported that gemcitabine monotherapy significantly reduced the risk of thrombocytopenia, leukopenia, neutropenia, nausea, vomiting, and diarrhoea compared with gemcitabine combination therapy. [37] The review found no significant differences between groups for anaemia and stomatitis. (see table 15, p 29) [37]

Comment: None.

OPTION CHEMORADIOTHERAPY FOR NON-RESECTABLE PANCREATIC CANCER

Mortality
Compared with chemotherapy We don't know whether chemoradiotherapy increases survival at 1 year in people with non-resectable pancreatic cancer compared with chemotherapy alone (very low-quality evidence).

For GRADE evaluation of interventions for pancreatic cancer, see table, p 33 .

Benefits:

Chemoradiotherapy versus chemotherapy alone:
We identified one systematic review (search date 2005; 3 RCTs) comparing chemoradiotherapy versus chemotherapy alone. [35] Two RCTs found no significant difference in median survival between chemoradiotherapy and chemotherapy alone, whereas one RCT found that chemoradiotherapy increased survival at 1 year and median survival (see table 16, p 32).

Harms:

Chemoradiotherapy versus chemotherapy alone:
The review gave no information on adverse effects. [35]

Comment: None.

GLOSSARY

Successful surgical resection (R0 resection) Surgery is defined as successful if, after resection, no residual disease is observed macroscopically or histologically in the tumour resection margins.

Extended lymph node dissection A procedure involving retroperitoneal lymph node dissection from the inferior mesenteric artery inferiorly to the coeliac axis superiorly and laterally to include both renal hila (the extent of lymph node dissection varies among RCTs).

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Kausch–Whipple pancreaticoduodenectomy A procedure involving surgical resection of the head of the pancreas, the distal common bile duct, the duodenum, and the distal portion of the stomach, together with dissection of the adjacent lymph nodes.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Pylorus-preserving pancreaticoduodenectomy (PPPD or Traverso–Longmire procedure) A procedure involving surgical resection of the of the head of the pancreas, the duodenum, the distal common bile duct, and the duodenum distal to the pylorus, together with dissection of the adjacent lymph nodes.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Chemoradiotherapy for resected pancreatic cancer One long-term follow-up study added. [31] It found no significant difference between adjuvant chemoradiotherapy and surgery alone for overall survival or progression-free survival at 11.7 years' follow-up. [31] Categorisation unchanged (Unknown effectiveness), as the evidence is not strong enough to draw definitive conclusion.

Adjuvant systemic gemcitabine for resected pancreatic cancer One RCT added comparing adjuvant gemcitabine versus observation. [33] The RCT found that gemcitabine improved disease-free survival compared with observation, but there was no significant difference between groups in overall survival or quality of life at 53 months' follow-up.

[33] Categorisation unchanged (Unknown effectiveness), as the evidence is not strong enough to draw definitive conclusion.

Chemotherapy versus supportive care for non-resectable pancreatic cancer One systematic review added comparing fluorouracil-based chemotherapy versus supportive care. [36] It found that fluorouracil-based chemotherapy improved overall survival compared with supportive care. Categorisation unchanged (Beneficial).

Different types of pancreatic-enteric anastomosis versus each other One systematic review added comparing pancreaticogastrostomy versus pancreaticojejunostomy. [19] The review found no significant difference between groups in mortality or rates of postoperative complications. [19] Categorisation unchanged (Unknown effectiveness) as there remains insufficient evidence to assess the effects of different types of pancreatic enteric anastomosis.

Fluorouracil monotherapy versus other chemotherapy regimens for non-resectable pancreatic cancer Two systematic reviews added. [36] [37] Both of the reviews included the same RCTs but reported different outcomes. The reviews found no significant difference between fluorouracil-based monotherapy and combination therapy in overall survival or time to progression of disease. However, the reviews found that fluorouracil-based monotherapy was less effective than combination therapy and increasing progression-free survival and overall response rates. [36] [37] Categorised unchanged (Likely to be beneficial).

Gemcitabine monotherapy versus other chemotherapy regimens for non-resectable pancreatic cancer Five systematic reviews [36] [37] [38] [39] [40] and two subsequent RCTs [41] [42] added. Two reviews compared gemcitabine monotherapy versus fluorouracil monotherapy. [36] [37] The reviews found no significant difference between groups in overall survival or progression-free survival, but found that gemcitabine monotherapy increased time to progression and overall response rate compared with fluorouracil monotherapy. [36] [37] All five reviews [36] [37] [38] [39] [40] and the subsequent two RCTs [41] [42] compared gemcitabine monotherapy versus gemcitabine combination therapy.Overall, the reviews found that monotherapy was less effective than combination therapy at increasing survival. [36] [37] [38] [39] [40] The subsequent RCTs found no significant difference between groups in reduction in pain intensity, analgesic consumption, or quality of life. [41] [42] Categorisation unchanged (Likely to be beneficial).

Pancreaticoduodenectomy versus non-surgical treatment One long-term follow-up report added to an already included RCT. [8] The report found that surgery increased mean duration of survival at 5 years' follow-up, and increased overall survival at 3 years, compared with chemoradiotherapy. [8] Categorisation unchanged (Unknown effectiveness), as there still remains one small RCT assessing the effects of surgery versus non-surgical treatment.

Pylorus-preserving pancreaticoduodenectomy versus Kausch–Whipple pancreaticoduodenectomy One systematic review [10] and one subsequent RCT [11] added. The review found that pylorus-preserving pancreaticoduodenectomy increased overall survival 5 years and reduced perioperative mortality compared with Kausch–Whipple pancreaticoduodenectomy. The subsequent RCT and two RCTs included in the review found no significant difference between groups in quality of life scores. [10] [11] Categorised as Unknown effectiveness, as there remains insufficient high-quality evidence to assess pylorus-preserving pancreaticoduodenectomy.

Somatostatin and somatostatin analogues One RCT added comparing somatostatin versus octreotide. [17] The RCT reported that there were no perioperative or postoperative deaths, and also found no difference between groups in postoperative complications. [17] Categorisation unchanged (Likely to be beneficial).

Extended (radical) versus standard lymphadenectomy in people having pancreaticoduodenectomy One systematic review added. [14] The review found no significant difference in survival, blood loss, or blood transfusions between extended and standard lymphadenectomy, but reported that extended lymphadenectomy increased the number of lymph nodes retrieved during surgery. [14] Categorisation changed from Unlikely to be beneficial to Unknown effectiveness, as the evidence shows no difference between interventions for the primary outcome of survival.

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Disclaimer

TABLE 1 **TNM staging of pancreatic cancer**

	TNM (tumour, node, metastasis)
Tumour	
Tis	Carcinoma in situ
T1	Tumour limited to the pancreas and less than 2 cm
T2	Tumour limited to the pancreas and greater than 2 cm
T3	The cancer has extended beyond the pancreas but does not involve the coeliac axis or superior mesenteric artery
T4	The cancer has extended beyond the pancreas, involving the coeliac axis or superior mesenteric artery
Node	
N0	No lymph node involvement
N1	Regional lymph node involvement
pN1a	Cancer in a single nearby lymph node
pN1b	Cancer in more than one lymph node
Metastasis	
M0	No distant metastasis
M1	Distant metastasis present

TABLE 2 **American Joint Committee on Cancer (AJCC) staging of pancreatic cancer** [1]

Stage I	T1–2	N0	M0
Stage II	T3	N0	M0
Stage III	Any T	N1	M0
Stage IV	Any T	Any N	M1

TABLE 3 **Pancreaticoduodenectomy versus non-surgical treatment**

Ref	Population	Intervention and comparison	Outcome	Comment
[7]	42 people with stage IIa or IIb pancreatic cancer invading the capsule without involvement of the superior mesenteric artery or the common hepatic artery, or without distant metastasis, mean age 65 years	Surgery (Kausch–Whipple [8 people], pylorus-preserving pancreatectomy [7 people], distal pancreatectomy [5 people]) *v* chemoradiotherapy (radiation 5040 cGy in 28 fractions plus fluorouracil 200 mg/m^2/day over 5.5 weeks followed by weekly fluorouracil 500 mg/m^2)	**Mean survival:** Surgery significantly increased mean survival compared with chemoradiotherapy (16.9 months with surgery *v* 11.0 months with chemoradiotherapy; P = 0.03) **Survival at 1 year:** Survival at 1 year was also higher with surgery compared with chemotherapy, but the difference between groups was of borderline significance (62% with surgery *v* 31% with chemoradiotherapy; P = 0.05) **Overall survival:** Surgery significantly increased overall survival (HR 0.46, 95% CI 0.22 to 0.97) **Hospital stay:** Chemotherapy was associated with significantly longer hospital stay than surgery (66 days with surgery *v* 102 days with chemoradiotherapy; P = 0.03) **QoL:** No significant difference between surgery and chemoradiotherapy in QoL at 3 months (reported as not significant, absolute results presented graphically) **Adverse effects:** Diarrhoea was significantly increased from baseline at 3 months in people having surgery (an increase from 1 to 2 bowel movements a day from baseline with surgery *v* no increase with chemoradiotherapy; P = 0.002)	81 people were initially registered for the trial, with 39 excluded after laparotomy

QoL, quality of life; Ref, reference, HR, hazard ratio.

TABLE 4 **Pylorus-preserving pancreaticoduodenectomy versus Kausch–Whipple pancreaticoduodenectomy**

Ref	Study design	Population	Intervention and comparison	Co-interventions	Outcome	Time	Comment
[10]	Systematic review (32 studies)	2822 people having PPPD or KW	PPPD *v* KW		**Perioperative mortality:** 22 studies; 2049 people; 24/1035 (2%) with PPPD *v* 44/1014 (4%) with KW; OR 1.70, 95% CI 1.02 to 2.83; P = 0.04		
					Overall survival: 9 studies; 661 people; HR 0.66, 95% CI 0.51 to 0.86; P = 0.002; Heterogeneity 0.003	5 years	
					Complications (overall morbidity): 11 studies; 999 people; OR 0.89, 95% CI 0.62 to 1.28; P = 0.53		
					Delayed gastric emptying: 18 studies; 1698 people; OR 0.69, 95% CI 0.42 to 1.14; P = 0.15		
					Haemorrhage: 10 studies; 1061 people; OR 1.17, 95% CI 0.69 to 2.00; P = 0.56		
					Pancreatic leak: 6 studies; 662 people; OR 1.05, 95% CI 0.59 to 1.87; P = 0.87		
					Pancreatic fistula: 13 studies; 1199 people; OR 0.78, 95% CI 0.52 to 1.16; P = 0.22		
					Biliary leak: 6 studies; 741 people; OR 1.32, 95% CI 0.52 to 3.38; P = 0.56		
					Biliary fistula: 6 studies; 426 people; OR 1.28, 95% CI 0.41 to 3.98; P = 0.67		
					Wound infections: 14 studies; 1196 people; OR 0.83, 95% CI 0.51 to 1.35; P = 0.46		
					Re-laparotomy: 6 studies; 715 people; OR 1.59, 95% CI 1.03 to 2.46; P = 0.04		
[12]	RCT included in review	130 people with resectable pancreatic cancer; tumour diameter 2.6–2.9 cm; 67% lymph node-positive; 82% R0 resection; mean age 65 years	PPPD *v* KW	All participants received octreotide and pancreaticojejunostomy; no-one received neoadjuvant chemoradiotherapy; no information on adjuvant treatment reported	**QoL:** Sickness impact scores (both physical and psychological) similar between PPPD and KW; P value not reported		
[13]	RCT included in review	48 people with resectable head of pancreas or peri-ampullary cancer	PPPD *v* KW	Details of anastomosis and use of octreotide not reported	**Global QOL:** No significant difference between groups at 60 weeks (measured by 100-point EORTC-QLQ-30 score); results presented graphically; score in both groups about 35; P greater than 0.05		

FACT-G QOL, Functional Assessment of Cancer Therapy — ; KW, Kausch–Whipple pancreaticoduodenectomy; PPPD, pylorus-preserving pancreaticoduodenectomy; QoL, quality of life; Ref, reference. HR, hazard ratio.

TABLE 5 **Extended (radical) versus standard lymphadenectomy in people having pancreaticoduodenectomy**

Ref	Study design	Population	Intervention and comparison	Co-interventions	Outcome	Comment
[14]	Systematic review	7 studies; 662 people	Extended (radical) *v* standard lymphadenectomy		**Mean survival:** HR 0.77, 95% CI 0.57 to 1.05; P = 0.10; absolute data not reported	Heterogeneity P = 0.006
		7 studies; 900 people			**Number of lymph nodes retrieved:** WMD –14, 95% CI –17 to –11; P less than 0.001	Heterogeneity P less than 0.001
		3 studies; 878 people			**Blood loss:** WMD +24.9 mL, 95% CI –126.0 mL to +175.7 mL; P = 0.75	Heterogeneity P less than 0.001
		4 studies; 560 people			**Blood transfusions:** WMD +0.27 units, 95% CI –0.27 units to +0.81 units; P = 0.33	Heterogeneity P = 0.004
		6 studies; 759 people			**Delayed gastric emptying:** OR 0.59, 95% CI 0.36 to 0.96; P = 0.003	
		5 studies; 467 people			**Haemorrhage:** OR 1.17, 95% CI 0.47 to 2.89; P = 0.730	
		7 studies; 945 people			**Pancreatic fistula:** OR 0.96, 95% CI 0.61 to 1.51; P = 0.86	
		5 studies; 693 people			**Biliary leak:** OR 0.47, 95% CI 0.18 to 1.26; P = 0.13	
		5 studies; 764 people			**Wound infection:** OR 0.99, 95% CI 0.49 to 1.97; P = 0.97	
		6 studies; 851 people			**Intra-abdominal abscess:** OR 0.79, 95% CI 0.38 to 1.63; P = 0.52	
[15]	RCT	294 people with pancreatic adenocarcinoma or peri-ampullary cancer; mean age 65.7 years; mean tumour size 2.5 cm	Extended (radical) *v* standard lymphadenectomy	Almost all participants received pancreaticojejunostomy; 78% of people in each group received adjuvant chemoradiotherapy	**QoL:** No significant difference between extended and standard lymphadenectomy at a mean 2.2 years (measured on scale 0–108): 147.3 with extended *v* 143.5 with standard; P = 0.45	
					Overall postoperative complications: Significantly more with extended compared with standard lymphadenectomy (43% with extended *v* 29% with standard; P = 0.01)	
					Wound infection: Significantly higher with extended compared with standard lymphadenectomy (11% with extended *v* 5% with standard; P = 0.06)	
					Delayed gastric emptying: Significantly higher with extended compared with standard lymphadenectomy (16% with extended *v* 6% with standard; P = 0.006)	

EORTC-QLQ, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; QoL, quality of life; Ref, reference.

TABLE 6 **Somatostatin and somatostatin analogues**

Ref	Study design	Population	Intervention and comparison	Outcome	Comment
[16]	SR, search date not reported, 10 RCTs	1918 people with pancreatic cancer or chronic pancreatitis (1368/1918 [71%] with malignant pathology), age not reported	Octreotide (100 microgram 3 times daily for 7 days preoperatively in 6 RCTs, intraoperatively at same dose for 10 days in 1 RCT) *v* placebo (5 RCTs) or *v* somatostatin (2 RCTs)	**Mortality:** No significant difference between somatostatin/somatostatin analogues and placebo or control (OR 1.17, 95% CI 0.70 to 1.94; absolute results presented graphically)	The trials had clinically important variations in population, timing of treatment with somatostatin or somatostatin analogues, type of pancreatic anastomosis, and use of co-intervention such as chemoradiotherapy. Therefore, we have reported random effects calculations for all ORs
			Vapreotide (0.6 mg twice daily for 7 days preoperatively) *v* placebo Somatostatin (250 microgram/hour infusion/6 mg/day for 7 days postoperatively) *v* placebo	**Overall complications:** Significantly reduced with somatostatin/somatostatin analogues compared with placebo or control (10 RCTs; OR 0.62, 95% CI 0.46 to 0.85; absolute results presented graphically) **Overall pancreas-related complications (leak, fistula, abscess, and intra-abdominal collection):** Significantly reduced with somatostatin/somatostatin analogues compared with placebo or control (10 RCTs; OR 0.56, 95% CI 0.39 to 0.81; absolute results presented graphically) **Overall pancreas-related complications following pancreaticoduodenectomy:** No significant difference between somatostatin/somatostatin analogues and placebo or control (7 RCTs; OR 0.81, 95% CI 0.52 to 1.26; absolute results presented graphically) **Pancreatic fistula:** Significantly reduced with somatostatin/somatostatin analogues compared with placebo or control (7 RCTs; OR 0.45, 95% CI 0.33 to 0.62; absolute results presented graphically) **Clinical anastomotic leak:** No significant difference between somatostatin/somatostatin analogues and placebo or control (7 RCTs; OR 0.80, 95% CI 0.44 to 1.45; absolute results presented graphically)	
[17]	RCT	50 people with benign or malignant pancreatic tumours requiring pancreaticoduodenectomy	Somatostatin (administered 15 minutes before the section of the pancreatic body and then provided by continuous infusion of 3 mg every 12 hours in 250 mL saline solution [6 mg/24 hours in 500 mL saline solution] with slow bolus of 250 microgram. The dose was reduced by half on the seventh postoperative day, then withdrawn the following day) *v* octreotide (administered about 1 hour before the section of the pancreatic body in a scheme of 3 times 100 microgram IV or SC, stopped on the seventh postoperative day)	**Mortality:** There were no perioperative or postoperative deaths	

Ref	Study design	Population	Intervention and comparison	Outcome	Comment
				Overall complications: 11/25 (44%) with somatostatin *v* 9/25 (36%) with octreotide; reported as not significant **Specific complications:** Haemorrhage: 4/25 (16%) with somatostatin *v* 2/25 (8%) with octreotide; reported as not significant Pancreatic fistula: 2/25 (8%) with somatostatin *v* 3/25 (12%) with octreotide; P = 0.52 Anastomotic non-pancreatic fistula: 3/25 (12%) with somatostatin *v* 1/25 (4%) with octreotide; P = 0.35 Biliary fistula: 2/25 (8%) with somatostatin *v* 1/25 (4%) with octreotide; P value not reported Intra-abdominal abscess: 3/25 (12%) with somatostatin *v* 1/25 (4%) with octreotide; P = 0.61	

OR, odds ratio; Ref, reference; SR, systematic review.

TABLE 7 **Different types of pancreatic-enteric anastomosis: pancreaticojejunostomy versus pancreaticogastrostomy** [19]

Ref	Study design	Population	Intervention and comparison	Co-interventions	Outcome
[19]	SR (3 RCTs)	445 people	PG *v* PJ	First RCT: octreotide was used only in participants with fistula on trial entry. Second RCT: all participants had perioperative antibiotics and preoperative and postoperative octreotide. Third RCT: all participants had perioperative antibiotics and preoperative and postoperative octreotide; 18% of people having PJ and 27% of people having PG had fibrin glue injected into the pancreatic duct; 32% of people having PJ and 27% of people having PG were treated with octreotide	**Mortality:** 3 RCTs; 10/223 (4%) with PG *v* 8/222 (4%) with PJ; OR 1.10, 95% CI 0.42 to 2.93; P = 0.51 **Overall postoperative complications:** OR 0.93, 95% CI 0.63 to 1.38; P = 0.71; absolute numbers not reported **Pancreatic fistula:** 3 RCTs; 31/223 (14%) with PG *v* 35/222 (16%) with PJ; OR 0.85, 95% CI 0.50 to 1.44; P = 0.54 **Delayed gastric emptying:** 2 RCTs; 18/142 (13%) with PG *v* 26/154 (17%) with PJ; OR 0.53, 95% CI 0.12 to 2.33; P = 0.40 **Intra-abdominal fluid collection:** 3 RCTs; 22/223 (10%) with PG *v* 40/222 (18%) with PJ; OR 0.53, 95% CI 0.23 to 1.23; P = 0.14 **Bile leakage:** 3 RCTs; 7/223 (3%) with PG *v* 12/223 (5%) with PG; OR 0.50, 95% CI 0.06 to 4.29; P = 0.53

PG, pancreaticogastrostomy; PJ, pancreaticojejunostomy; Ref, reference; SR, systematic review.

TABLE 8 **Fibrin glue** [20]

Ref	Study design	Population	Intervention and comparison	Outcome
[20]	RCT, single-centre	97 people; 51 with malignant disease, 31 with pancreatic cancer; mean age 50 years; having pancreatic surgery, 30 pancreaticoduodenectomy (technique not specified), 40 pancreaticoduodenectomy plus PJ, 23 left pancreatectomy	Fibrin glue (intra-operatively) *v* no glue	**Pancreatic fistula:** Overall: 6/43 (14%) with fibrin glue *v* 6/54 (11%) with no glue; reported as not significant; P value not reported Subgroup analysis in people with malignant disease: 3/28 (11%) with fibrin glue *v* 3/23 (13%) with no glue; significance assessment not reported

Ref, reference.

TABLE 9 **Pancreatic duct occlusion** [21] [22]

Ref	Study design	Population	Intervention and comparison	Co-interventions	Outcomes	Comment
[21]	RCT, multicentre; stratified randomisation balancing every 4 people within each stratum (type of resection, pancreaticoduodenectomy, or distal pancreatectomy; pathology; tumour or chronic pancreatitis) and at each centre	182 people having pancreaticoduodenectomy (type of surgery not reported): 65% with malignant disease; mean age 56 years	Anastomosis plus duct occlusion *v* anastomosis alone (use of PJ *v* PG was similar between groups, 60%–70% having PJ)	Significantly more people having duct occlusion also received octreotide (53% with duct occlusion *v* 26% with anastomosis alone; P less than 0.001) and had reinforcement of the anastomosis with fibrin glue (59% with duct occlusion *v* 10% with anastomosis alone; P less than 0.001)	**Perioperative mortality:** No significant difference between adding duct occlusion and anastomosis alone in perioperative mortality at 1 month (9/102 [9%] with duct occlusion *v* 4/80 [6%] with anastomosis alone; reported as not significant; P value not reported)	Significantly more participants having occlusion had fibrotic pancreatic stumps (46% with duct occlusion *v* 30% with anastomosis alone; P = 0.02); this makes the results difficult to interpret. Multivariate analysis suggested that normal pancreatic parenchyma significantly influenced the onset of intra-abdominal collections (OR 3.23, 95% CI 1.30 to 8.17)
					Intra-abdominal collections: No significant difference between adding duct occlusion and anastomosis alone (15% with duct occlusion *v* 24% with anastomosis alone; P = 0.20)	
					Pancreatic fistula: No significant difference between adding duct occlusion and anastomosis alone (9% with duct occlusion *v* 6% with anastomosis alone; reported as not significant; P value not reported)	
					Blood loss: No significant difference between adding duct occlusion and anastomosis alone (7% with duct occlusion *v* 14% with anastomosis alone; reported as not significant; P value not reported)	
[22]	RCT, single-centre	169 people having pancreaticoduodenectomy: 62% pylorus-preserving; 59% with pancreatic adenocarcinoma; 27% with periampullary cancer	Anastomosis plus duct occlusion *v* anastomosis alone (use of PJ *v* PG was similar between groups, 60%–70% having PJ)	Use of octreotide not reported	**Survival at 1 year:** Similar with duct occlusion and PJ (63% with duct occlusion *v* 69% with PJ; significance not assessed; absolute numbers not reported)	Survival was a secondary end point
					Subgroup analysis in participants with malignant disease (58% with duct occlusion *v* 66% with PJ; significance not assessed; absolute numbers not reported)	
					Overall complications: No significant difference between duct occlusion and PJ (proportion with no complications: 54/86 [64%] with duct occlusion *v* 63/83 [76%] with PJ; P = 0.07)	
					Pancreatic fistula: Significantly higher rates with duct occlusion compared with PJ (15/86 [17%] with duct occlusion *v* 4/83 [5%] with PJ; P = 0.02)	

Ref	Study design	Population	Intervention and comparison	Co-interventions	Outcomes	Comment
					Intra-abdominal abscesses: No significant difference between duct occlusion and PJ, although lower with PJ (13/86 [15%] with duct occlusion *v* 8/83 [10%] with PJ; P = 0.35)	
					Postoperative blood loss: No significant difference between duct occlusion and PJ (7/86 [8%] with duct occlusion *v* 6/83 [7%] with PJ; P = 1.00)	
					Need for enzyme replacement: Significantly higher with duct occlusion compared with PJ (77/86 [90%] with duct occlusion *v* 57/83 [67%] with PJ; P = 0.01) and at 3 months (75/86 [87%] with duct occlusion *v* 63/83 [76%] with PJ; P = 0.03) but similar at 12 months (51/86 [59%] with duct occlusion *v* 48/83 [58%] with PJ; P value not reported)	
					Diabetes mellitus: Significantly increased at 3- and 12-month follow-up in the duct occlusion group (at 12 months: 34% with duct occlusion *v* 14% with PJ; P = 0.001; follow-up of 105 people; absolute numbers not reported)	

PG, pancreaticogastrostomy; PJ, pancreaticojejunostomy; Ref, reference.

TABLE 10 **Fluorouracil-based chemotherapy (adjuvant) versus no chemotherapy for resected pancreatic cancer** [23] [24] [25] [26] [27] [28]

Ref	Study design	Population	Intervention and comparison	Outcome	Comment
[23]	SR, 4 RCTs [24] [25] [26] [27]	686 people with resected pancreatic adenocarcinoma	Adjuvant fluorouracil (alone or in combination with mytomycin or mytomycin plus doxorubicin) *v* surgery alone	**Overall mortality:** Significantly lower mortality with adjuvant chemotherapy compared with surgery alone (3 RCTs: 197/267 [74%] with adjuvant chemotherapy *v* 219/261 [84%] with surgery alone; HR 0.65, 95% CI 0.54 to 0.80; P less than 0.001; 1 RCT excluded because of significant heterogeneity; time frame not specified)	
				Analysis including the trial that had been excluded because of heterogeneity (4 RCTs: 269/348 [77%] with adjuvant chemotherapy *v* 281/338 [83%] with surgery alone; HR 0.75, 95% CI 0.64 to 0.90; P less than 0.001)	
				Median survival: 19.0 months with adjuvant chemotherapy *v* 13.5 months with surgery alone; significance not assessed	
				Survival at 2 years: 38% with adjuvant chemotherapy *v* 28% with surgery alone; significance not assessed	
				Survival at 5 years: 19% with chemotherapy *v* 12% with surgery alone; significance not assessed	
[28]	RCT, multicentre	89 people with resected pancreatic adenocarcinoma (all R0 resections)	Adjuvant fluorouracil in combination with cisplatin *v* surgery alone	**Survival at 5 years:** No significant difference between adjuvant chemotherapy and surgery alone in survival at 5 years (26% with adjuvant chemotherapy *v* 15% with surgery alone; P = 0.94)	Multivariate analysis demonstrated that nodal involvement and degree of tumour differentiation (well compared with poorly) were significant prognostic factors (nodal involvement: P = 0.001; tumour differentiation: P = 0.004)
				Median survival: No significant difference between adjuvant chemotherapy and surgery alone (12.5 months with adjuvant chemotherapy *v* 15.8 months with surgery alone; reported as not significant; P value not reported)	
				Recurrence at 5 years: No significant difference between adjuvant chemotherapy and surgery alone in recurrence at 5 years (74% with adjuvant chemotherapy *v* 81% with surgery alone; P = 0.80)	
				Median time to recurrence: No significant difference between adjuvant chemotherapy and surgery alone (8.6 months with adjuvant chemotherapy *v* 10.2 months with surgery alone; reported as not significant; P value not reported)	

Ref, reference; R0, completely resected specimen with negative margins; SR, systematic review, HR, hazard ratio.

TABLE 11 Chemoradiotherapy versus no chemotherapy for resected pancreatic cancer [23]

Ref	Study design	Population	Intervention	Outcome
[23]	SR, 4 RCTs [27] [28] [29] [30]	521 people with resected pancreatic adenocarcinoma	Fluorouracil plus radiation *v* surgery alone	**Median survival:** 15.8 months with chemoradiotherapy *v* 15.2 months with surgery alone; significance not assessed (based on 2 RCTs; unclear how many people analysed) **Survival at 2 years:** 38% with chemotherapy *v* 28% with surgery alone; significance not assessed **Survival at 5 years:** 19% with chemotherapy *v* 12% with surgery alone; significance not assessed
[31]	RCT: long-term follow-up report	218 people with histologically confirmed T1-3, N0-N1a M0 pancreatic cancer or T1-3 N0-N1 M0 peri-ampullary cancers, post-surgery	Postoperative chemoradiation (40 Gy plus 5-fluorouracil) *v* no further adjuvant treatment	**Overall survival:** HR 0.91, 95% CI 0.68 to 1.23; P = 0.54 **Progression-free survival:** 75/110 with adjuvant therapy *v* 76/108 with no adjuvant therapy; HR 0.94, 95% CI 0.7 to 1.26; P = 0.66

Ref, reference; SR, systematic review, HR, hazard ratio.

TABLE 12 Fluorouracil-based combination chemotherapy versus supportive care for non-resectable (locally advanced or advanced) pancreatic cancer

Ref	Study design	Population	Intervention and comparison	Outcome
[35]	SR, 7 RCTs	425 people with locally advanced or metastatic cancer	Fluorouracil-based combination chemotherapy *v* supportive care	**Mortality at 12 months:** Significantly reduced with chemotherapy compared with best supportive care (7 RCTs: 119/208 [57%] with chemotherapy *v* 128/217 [59%] with supportive care; RR 0.46, 95% CI 0.25 to 0.84; P = 0.011)
[36]	SR, 6 RCTs	385 people	Fluorouracil-based combination chemotherapy *v* supportive care	**Overall survival (time frame not reported):** 6 RCTs; 385 people; HR 0.64, 95% CI 9.42 to 0.98; P = 0.04; risk of death reduced by 36% with significant heterogeneity between trials. Absolute data not reported

Ref, reference; SR, systematic review, RR, relative risk.

TABLE 13 **Fluorouracil monotherapy versus fluorouracil-based combinations for non-resectable (locally advanced or advanced) pancreatic cancer** [35]

Ref	Study design	Population	Intervention and comparison	Outcome
[35]	SR, 8 RCTs	842 people with locally advanced or metastatic cancer	Fluorouracil monotherapy *v* fluorouracil-based combination chemotherapy	**Mortality at 12 months:** No significant difference in mortality between fluorouracil alone and fluorouracil-based combinations (8 RCTs: 272/476 [57%] with fluorouracil alone *v* 230/366 [78%] with fluorouracil combination; RR 0.79, 95% CI 0.59 to 1.05)
[36]	SR, 5 RCTs	700 people	Fluorouracil monotherapy *v* fluorouracil-based combination chemotherapy	**Overall survival (time frame not reported) :** HR 0.94, 95% CI 0.82 to 1.08
[37]	SR, 5 RCTs	700 people	Fluorouracil monotherapy *v* fluorouracil-based combination chemotherapy	**Time to progression:** 2 RCTs; HR 1.02, 95% CI 0.85 to 1.23
				Progression-free survival: Significantly improved with combination therapy: 2 RCTs, 416 people; HR 0.67, 95% CI 0.46 to 0.98
				Overall response rate: Significantly improved with combination therapy: 5 RCTs, 700 people; RR 0.43, 95% CI 0.25 to 0.74
				Grade 3 and 4 vomiting: 2 RCTs, 320 people; 7/164 (4%) with monotherapy *v* 25/156 (16%) with combination therapy; RR 3.76, 95% CI 1.67 to 8.44
				Diarrhoea: 2 RCTs, 406 people; 7/207 (3%) with monotherapy *v* 10/199 (5%) with combination therapy; RR 1.49, 95% CI 0.58 to 3.84
				Stomatitis: 3 RCTs, 529 people; 22/271 (8%) with monotherapy *v* 27/258 (10%) with combination therapy; RR 1.29, 95% CI 0.75 to 2.22
				Thrombocytopenia: 2 RCTs, 332 people; 6/171 (4%) with monotherapy *v* 12/161 (7%) with combination therapy; RR 2.15, 95% CI 0.83 to 5.53; P = 0.11
				Grade 3 and 4 leukopenia: 1 RCT, 123 people; 20/64 (31%) with monotherapy *v* 31/59 (53%) with combination therapy; RR 1.68, 95% CI 1.09 to 2.60; P = 0.02
				Grade 3 and 4 nausea : 1 RCT, 123 people; 3/64 (5%) with monotherapy *v* 13/59 (22%) with combination therapy; RR 4.7, 95% CI 1.41 to 15.58; P = 0.01
				Grade 3 and 4 anaemia: 1 RCT, 209 people; 9/107 (8%) with monotherapy *v* 8/102 (8%) with combination therapy; RR 0.93, 95% CI 0.37 to 2.32; P = 0.88
				Grade 3 and 4 neutropenia: 1 RCT, 209 people; 0/107 (0%) with monotherapy *v* 3/102 (3%) with combination therapy; RR 7.34, 95% CI 0.38 to 140.36; P = 0.19

Ref, reference; SR, systematic review.

TABLE 14 **Gemcitabine monotherapy versus fluorouracil monotherapy for non-resectable (locally advanced or advanced) pancreatic cancer [35]**

Ref	Study design	Population	Intervention and comparison	Outcome
[35]	SR, 2 RCTs	279 people with locally advanced or metastatic cancer	Gemcitabine monotherapy *v* fluorouracil monotherapy	**Mortality at 12 months:** Lower with gemcitabine compared with fluorouracil but of borderline significance (2 RCTs; 90/98 [92%] with gemcitabine monotherapy *v* 105/130 [81%] with fluorouracil monotherapy; RR 1.12, 95% CI 1.00 to 1.25)
[36]	SR, 2 RCTs	197 people	Gemcitabine monotherapy *v* fluorouracil monotherapy	**Overall survival:** 2 RCTs, 197 people; HR 0.75, 95% CI 0.42 to 1.31; absolute numbers not reported
[37]	SR, 2 RCTs		Gemcitabine monotherapy *v* fluorouracil monotherapy	**Time to progression:** Significantly increased with gemcitabine: 2 RCTs, 197 people; HR 0.46, 95% CI 0.31 to 0.70; absolute numbers not reported
				Progression-free survival: 2 RCTs, 197 people; HR 0.94, 95% CI 0.58 to 1.53; absolute numbers not reported
				Overall response rate: Significantly increased with gemcitabine: 1 RCT, 126 people; RR 0.14, 95% CI 0.01 to 2.66; absolute numbers not reported
				Grade 3 and 4 neutropenia: 1 RCT, 126 people; 25% with gemcitabine *v* 5% with fluorouracil; absolute numbers not reported

Ref, reference. ; SR, systematic review, HR, hazard ratio.

TABLE 15 **Gemcitabine monotherapy versus gemcitabine-based combinations for non-resectable (locally advanced or advanced) pancreatic cancer** [35] [36] [37] [39] [38] [40] [41] [42]

Ref	Study design	Population	Intervention and comparison	Outcome
[35]	SR, 5 RCTs	694 people with locally advanced or metastatic cancer	Gemcitabine monotherapy *v* gemcitabine plus cisplatin (4 RCTs) or oxaliplatin (1 RCT)	**Mortality at 12 months:** No significant difference in mortality between gemcitabine alone and gemcitabine plus cisplatin or oxaliplatin (5 RCTs: 258/346 [74%] with gemcitabine alone *v* 273/348 [78%] with gemcitabine combination; RR 0.81, 95% CI 0.57 to 1.16)
[35]	SR, 6 RCTs including 4 assessed in SR above plus 2 published only as abstracts	586 people with locally advanced or metastatic cancer	Gemcitabine monotherapy *v* gemcitabine plus cisplatin	**Grade 3 and 4 toxicities:** Higher in people having gemcitabine plus cisplatin than gemcitabine alone, but the difference between groups did not reach significance (6 RCTs; neutropenia: 82/291 [28%] with combination *v* 63/282 [22%] with monotherapy; ARI +6%, 95% CI –1% to +12%; P = 0.08; thrombocytopenia: 59/291 [20%] with combination *v* 39/292 [13%] with monotherapy; ARI +8%, 95% CI –3% to +18%; P = 0.17; vomiting/nausea: 57/270 [21%] with combination *v* 23/267 [9%] with monotherapy; ARI +11%, 95% CI –1% to +22%; P = 0.07)
[35]	SR, 5 RCTs	1539 people with locally advanced or metastatic cancer	Gemcitabine monotherapy *v* gemcitabine plus fluoropyrimidines (fluorouracil [2 RCTs], capecitabine [2 RCTs], exatecan [1 RCT])	**Mortality at 12 months:** No significant difference in mortality between gemcitabine alone and gemcitabine plus fluoropyrimidines (5 RCTs; 594/772 [77%] with gemcitabine alone *v* 597/767 [78%] with gemcitabine combination; RR 0.95, 95% CI 0.75 to 1.21)
[35]	SR, 2 RCTs	452 people with locally advanced or metastatic cancer	Gemcitabine monotherapy *v* gemcitabine plus irinotecan	**Mortality at 12 months:** No significant difference in mortality between gemcitabine alone and gemcitabine plus irinotecan (2 RCTs; 176/222 [79%] with gemcitabine alone *v* 178/230 [77%] with gemcitabine combination; RR 1.12, 95% CI 0.71 to 1.75)
[36]	SR, 19 RCTs	4697 people	Gemcitabine monotherapy *v* gemcitabine combination therapy	**Overall survival:** Significantly improved with combination therapy: 14 RCTs, 4060 people; HR 0.91, 95% CI 0.85 to 0.97
[37]	SR, 19 RCTs	4697 people	Gemcitabine monotherapy *v* gemcitabine combination therapy	**Progression-free survival:** Significantly improved with combination therapy: 4 RCTs, 864 people; HR 0.78, 95% CI 0.70 to 0.88 **Time to progression:** Significantly improved with combination therapy: 3 RCTs, 559 people; HR 0.85, 95% CI 0.72 to 0.99 **Overall response rate:** Significantly improved with combination therapy: 17 RCTs, 3577 people; RR 0.56, 95% CI 0.46 to 0.68 **Grade 3 and 4 thrombocytopenia:** 18 RCTs, 4564 people; 157/2291 (7%) with monotherapy *v* 300/2273 (13%) with combination therapy; RR 1.94, 95% CI 1.32 to 2.84; P = 0.0007 **Grade 3 and 4 leukopenia:** 8 RCTs, 1606 people; 95/808 (12%) with monotherapy *v* 138/798 (17%) with combination therapy; RR 1.46, 95% CI 1.15 to 1.86; P = 0.002 **Grade 3 and 4 neutropenia:** 15 RCTs, 3818 people; 366/1911 (19%) with monotherapy *v* 520/1907 (27%) with combination therapy; RR 1.48, 95% CI 1.07 to 2.05; P = 0.02

Ref	Study design	Population	Intervention and comparison	Outcome
				Grade 3 and 4 anaemia: 15 RCTs, 3730 people; 141/1872 (8%) with monotherapy *v* 167/1858 (9%) with combination therapy; RR 1.14, 95% CI 0.82 to 1.58; P = 0.43
				Grade 3 and 4 nausea: 9 RCTs, 3055 people; 85/1534 (6%) with monotherapy *v* 150/1521 (10%) with combination therapy; RR 1.77, 95% CI 1.37 to 2.29; P less than 0.0001
				Grade 3 and 4 vomiting: 10 RCTs, 3471 people; 75/1738 (4%) with monotherapy *v* 123/1733 (7%) with combination therapy; RR 1.64, 95% CI 1.24 to 2.16; P = 0.0005
				Grade 3 and 4 diarrhoea: 12 RCTs, 3531 people; 34/1772 (2%) with monotherapy *v* 96/1759 (5%) with combination therapy; RR 2.73, 95% CI 1.87 to 3.98; P less than 0.0001
				Grade 3 and 4 stomatitis: 6 RCTs, 2007 people; 9/1005 (0.8%) with monotherapy *v* 18/1002 (2%) with combination therapy; RR 1.84, 95% CI 0.86 to 3.92; P = 0.11
[38]	SR, 15 RCTs	4465 people	Gemcitabine monotherapy *v* any gemcitabine combination therapy	**Overall survival:** Significantly improved with combination therapy: 15 RCTs, 4465 people; HR 0.91, 95% CI 0.85 to 0.97; P = 0.004
		Subgroup analysis	Gemcitabine monotherapy *v* gemcitabine plus platinum analogue	**Overall survival:** Significantly improved with combination therapy: 5 RCTs, 1248 people; HR 0.85; P = 0.01; no further data reported
		Subgroup analysis	Gemcitabine monotherapy *v* gemcitabine plus fluoropyrimidine	**Overall survival:** Significantly improved with combination therapy: 6 RCTs, 1814 people; HR 0.90; P = 0.03; no further data reported
		Subgroup analysis	Gemcitabine monotherapy *v* gemcitabine plus other cytotoxic agent (multitarget antifolate, pemetrexed, or topoisomerase inhibitors irinotecan or exatecan)	**Overall survival:** 4 RCTs, 1404 people; HR 0.99; P = 0.80; no further data reported
[39]	SR, 20 RCTs	6296 people	Gemcitabine monotherapy *v* gemcitabine combination therapy	**Overall survival:** 20 RCTs, 6296 people; RR 0.93, 95% CI 0.84 to 1.03; P = 0.17; absolute data not reported
				Progression-free survival: Significantly improved with combination therapy: 17 RCTs, 5174 people; RR 0.91, 95% CI 0.84 to 0.98; P = 0.015; absolute data not reported
				Overall response rate: Significantly improved with combination therapy: 20 RCTs, 6296 people; RR 1.57, 95% CI 1.31 to 1.86; P less than 0.001; absolute data not reported
[40]	SR, 23 RCTs	5886 people	Gemcitabine monotherapy *v* gemcitabine combination therapy	**Overall survival at 6 months:** Significantly improved with combination therapy: 23 RCTs, 5886 people; RR 0.92, 95% CI 0.87 to 0.97; P = 0.003; absolute data not reported
				Overall survival at 12 months: Significantly improved with combination therapy: 21 RCTs; RR 0.96, 95% CI 0.93 to 0.98; P = 0.003; absolute data not reported
				Overall survival at 18 months: 16 RCTs; RR 0.97, 95% CI 0.95 to 0.99; P = 0.005

Ref	Study design	Population	Intervention and comparison	Outcome
[41]	RCT	319 people	Gemcitabine alone (1000 mg/m^2 in a 30-minute infusion weekly for 7 weeks, followed by a 1-week break and then weekly for 3 weeks, every 4 weeks) *v* gemcitabine plus capecitabine (oral Cap 650 mg/m^2 twice daily on days 1 to 14 inclusive plus Gem 1000 mg/m^2 in a 30-minute infusion on days 1 and 8 every 3 weeks) for 24 weeks or until progression	**Clinical benefit response:** 20% with gemcitabine alone *v* 19% with gemcitabine combination; median duration: 6.5 weeks with monotherapy *v* 9.5 weeks with combination therapy; P less than 0.02; no further data reported, reported as not significant **QoL:** P less than 0.05; reported as not significant
[42]	RCT	104 people	Gemcitabine *v* PEFG regimen (cisplatin plus epirubicin plus 5-fluorouracil plus gemcitabine)	**QoL:** 29% with gemcitabine *v* 55% with PEFG **Emotional function:** 18% with gemcitabine *v* 43% with PEFG **Fatigue:** 17% with gemcitabine *v* 41% with PEFG **Pain:** 41% with gemcitabine *v* 64% with PEFG **Flatulence:** 26% with gemcitabine *v* 50% with PEFG

AR, absolute risk; HR, hazard ratio; QoL, quality of life; Ref, reference; RR, relative risk; SR, systematic review.

TABLE 16 **Chemoradiotherapy versus chemotherapy alone for non-resectable (locally advanced or advanced) pancreatic cancer** [35]

Ref	Study design	Population	Intervention and comparison	Outcome	Comment
[35]	SR, 3 RCTs	59 people with gastric or pancreatic cancer, 30 with unresectable pancreatic cancer	Fluorouracil plus radiation followed by semustine *v* fluorouracil plus semustine	**Median survival:** No significant difference between chemoradiotherapy and chemotherapy alone in people with pancreatic cancer (7.8 months with chemoradiotherapy *v* 7.3 months with chemotherapy alone; reported as not significant; P value not reported)	Results assessed separately in people with pancreatic cancer
		191 people with gastric or pancreatic cancer, 91 with unresectable pancreatic cancer	Fluorouracil plus radiation *v* fluorouracil alone	**Median survival:** No significant difference between chemoradiotherapy and chemotherapy alone in people with pancreatic cancer (8.3 months with chemoradiotherapy *v* 8.2 months with chemotherapy alone; reported as not significant; P value not reported)	Results assessed separately in people with pancreatic cancer. The high loss to follow-up (22%) makes the results difficult to interpret
		42 people with gastric or pancreatic cancer, 30 with unresectable pancreatic cancer	Combined chemotherapy (using streptozotocin plus methotrexate plus fluorouracil) plus radiation combined with fluorouracil *v* combined chemotherapy (streptozotocin plus methotrexate plus fluorouracil) alone	**Survival at 1 year:** Significantly higher with chemoradiotherapy compared with chemotherapy alone (41% with chemoradiotherapy *v* 19% with chemotherapy alone; P = 0.02) **Median survival:** Higher with chemoradiotherapy compared with chemotherapy alone (10.5 months with chemoradiotherapy *v* 8.5 months with chemotherapy alone; P value not reported)	Results assessed separately in people with pancreatic cancer. The trial closed early because of lack of funding

Ref, reference; SR, systematic review.

TABLE **GRADE evaluation of interventions for pancreatic cancer**

Important outcomes	Relapse rates, treatment success (including progression-free survival, time to progression, and relapse), symptom severity, complications, quality of life, mortality, adverse effects								
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of surgical treatments in people with pancreatic cancer considered suitable for complete tumour resection?									
1 (81) [7] [8]	Mortality	Pancreaticoduodenectomy *v* non-surgical treatment	4	–2	0	0	+1	Moderate	Quality points deducted for sparse data and incomplete reporting of results. Effect-size point added for RR less than 0.5
1 (81) [7] [8]	Quality of life	Pancreaticoduodenectomy *v* non-surgical treatment	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (2822) [10]	Mortality	Pylorus-preserving pancreaticoduodenectomy *v* Kausch–Whipple pancreaticoduodenectomy	2	–1	0	0	0	Very low	Quality point deducted for incomplete reporting of results
3 (254) [12] [13] [11]	Quality of life	Pylorus-preserving pancreaticoduodenectomy *v* Kausch–Whipple pancreaticoduodenectomy	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (2889) [10] [11]	Complications	Pylorus-preserving pancreaticoduodenectomy *v* Kausch–Whipple pancreaticoduodenectomy	2	–1	0	0	0	Very low	Quality point deducted for incomplete reporting of results
1 (622) [14]	Mortality	Extended *v* standard lymphadenectomy	2	–2	0	0	0	Very low	Quality points deducted for incomplete reporting of results and uncertain follow-up
1 (294) [15]	Quality of life	Extended *v* standard lymphadenectomy	4	–1	0	–2	0	Very low	Quality point deducted for incomplete reporting of results. Directness points deducted for uncertainty about use of drug interventions and differences in type of surgery and anastomosis between groups
2 (2203) [14] [15]	Complications	Extended *v* standard lymphadenectomy	2	–1	–1	0	0	Very low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
What are the effects of interventions to prevent pancreatic leak after pancreaticoduodenectomy in people with pancreatic cancer considered suitable for complete tumour resection?									
10 (1918) [16]	Mortality	Somatostatin and analogues *v* placebo/control	4	–1	0	–3	0	Very low	Quality point deducted for incomplete reporting of results. Directness points deducted for inclusion of people with non-pancreatic cancer, variations in timing of treatment, pancreatic anastomosis, and use of other interventions
10 (1918) [16]	Complications	Somatostatin and analogues *v* placebo/control	4	–1	–1	–3	0	Very low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results. Directness points deducted for inclusion of people with non-pancreatic cancer, variations in timing of treatment, pancreatic anastomosis, and use of other interventions

Important outcomes	Relapse rates, treatment success (including progression-free survival, time to progression, and relapse), symptom severity, complications, quality of life, mortality, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
3 (445) [19]	Mortality	Pancreaticojejunostomy (PJ) *v* pancreaticogastrostomy (PG)	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for differences in co-interventions
3 (445) [19]	Complications	Pancreaticojejunostomy (PJ) *v* pancreaticogastrostomy (PG)	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for different co-interventions
1 (97) [20]	Complications	Fibrin glue *v* no glue	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
2 (357) [21] [22]	Mortality	Duct occlusion *v* anastomosis alone	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for differences in disease severity
2 (357) [21] [22]	Complications	Duct occlusion *v* anastomosis alone	4	–1	–1	–1	0	Very low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results. Directness point deducted for differences in disease severity and outcomes measured
What are the effects of adjuvant treatments in people with completely resected pancreatic cancer?									
5 (1208) [24] [25] [26] [27]	Mortality	Fluorouracil-based adjuvant chemotherapy *v* no adjuvant chemotherapy	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
1 (89) [28]	Relapse rates	Fluorouracil-based adjuvant chemotherapy *v* no adjuvant chemotherapy	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
5 (521) [26] [28] [29] [30] [31]	Mortality	Adjuvant chemoradiotherapy *v* surgery	4	–1	–1	–1	0	Very low	Quality point deducted for incomplete reporting of results. Consistency point deducted for heterogeneity between RCTs. Directness point deducted for the inclusion of people with other cancers
1 (368) [33]	Mortality	Adjuvant gemcitabine-based chemotherapy *v* no adjuvant chemotherapy	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (368) [33]	Treatment success	Adjuvant gemcitabine-based chemotherapy *v* no adjuvant chemotherapy	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (368) [33]	Quality of life	Adjuvant gemcitabine-based chemotherapy *v* no adjuvant chemotherapy	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
What are the effects of interventions in people with non-resectable (locally advanced or advanced) pancreatic cancer?									
7 (425) [35] [36]	Mortality	Chemotherapy *v* supportive care	4	0	0	0	0	High	
8 (842) [35] [36] [37]	Mortality	Fluorouracil monotherapy *v* fluorouracil combination chemotherapy	4	0	0	0	0	High	

Important outcomes	Relapse rates, treatment success (including progression-free survival, time to progression, and relapse), symptom severity, complications, quality of life, mortality, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
8 (842) [35] [36] [37]	Treatment success	Fluorouracil monotherapy *v* fluorouracil combination chemotherapy	4	0	0	0	0	High	
3 (197) [35] [36] [37]	Mortality	Gemcitabine monotherapy *v* fluorouracil monotherapy	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
23 (6296) [41] [39] [38] [36] [37] [35] [40]	Mortality	Gemcitabine monotherapy *v* gemcitabine combination chemotherapy	4	0	–1	–1	0	Low	Consistency point deducted for conflicting results. Directness point deducted for the use of different combinations
3 (197) [35] [36] [37]	Treatment success	Gemcitabine monotherapy *v* fluorouracil monotherapy	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
23 (6296) [41] [39] [38] [36] [37] [35] [40]	Treatment success	Gemcitabine monotherapy *v* gemcitabine combination chemotherapy	4	0	–1	–1	0	Low	Consistency point deducted for conflicting results. Directness point deducted for the use of different combinations
1 (319) [41]	Symptom severity	Gemcitabine monotherapy *v* gemcitabine combination chemotherapy	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (423) [41] [42]	Quality of life	Gemcitabine monotherapy *v* gemcitabine combination chemotherapy	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and no statistical comparisons between groups
3 (292) [35]	Mortality	Chemoradiotherapy *v* chemotherapy alone	4	–2	–1	–1	0	Very low	Quality points deducted for incomplete reporting of results and poor follow-up. Consistency point deducted for conflicting results. Directness points deducted for inclusion of people with non-pancreatic cancer

Type of evidence: 4 = RCT; 2 = observational; 1 = non-analytical/expert opinion.
Consistency: similarity of results across studies
Directness: generalisability of population or outcomes
Effect size: based on relative risk or odds ratio