National Institute for Health and Care Excellence

Final

Pancreatic cancer in adults:

diagnosis and management

Appendix F

Evidence tables

February 2018

Final

Developed by the National Guideline Alliance, hosted by the Royal College of Obstetricians and Gynaecologists

Disclaimer
The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Contents

1 Appendix F: Evidence tables

F.12 People with jaundice

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
Full citation Agarwal, B., Abu-Hamda, E., Molke, K. L., Correa, A. M., Ho, L.(2004) Endoscopic ultrasound-guided fine needle aspiration and multidetector spiral CT in the diagnosis of pancreatic cancer. American Journal of Gastroenterology, 99, 844-50, Ref Id 522817 Country/ies where the study was carried out USA Study type Retrospective single-centre study Aim of the study	Sample size N= 47 patients Characteristics M/F (n): not reported Median age (range): not reported Final diagnosis: malignant(n): 45 benign(n): 2 Inclusion criteria clinical suspicion of PC based on: Obstructive jaundice with biliary stricture seen on ERCP (n = 47). Suspected pancreatic mass on CT two or more episodes of acute pancreatitis in 6 months without predisposing factors.	Index test 1 (n=47): EUS EUS examination was performed using both radial and linear echoendoscopes. Index test 2 (n=47): EUS-FNA cytology FNA was performed whenever a suspicious “mass” lesion was identified on EUS and multiple FNA passes (1–7) were made using the Echo-tip FNA needle until the cytologist could make a preliminary diagnosis. Index test 2 (n=47): Spiral CT All scans were performed on a multidetector helical CT scanner. A multiphasic scanning technique was used with intravenous injection of 150 ml of non-ionic contrast	2x2 table EUS Disease + / Disease + / Tot. Test + 45 1 46 Test - 0 1 1 Tot. 45 2 47 Sensitivity^= 100.00% (95% CI 92.13% to 100.00%) Specificity^= 50.00 % (95% CI 1.26% to 98.74%) PPV^= 100.00% NPV^= 97.83% (95% CI 91.84% to 99.45%) ^ calculated by the NGA technical team from data EUS – FNA Disease + / Disease + / Tot. Test + 38 0 38 Test - 7 2 9 Tot. 45 2 47 Sensitivity^= 84.44% (95% CI 670.54% to 93.51%) Specificity^= 100.00% (95% CI 15.81% to 100.00%) NPV^= 22.22% (95% CI 12.64% to 36.08%) PPV^= 100.00% ^ calculated by the NGA technical team from data reported the article https://www.medcalc.org/calc/diagnostic_test.php CT Disease + / Disease + / Tot. Test + 30 0 30	Limitations QUADAS 2 checklist Patient selection Risk of bias: Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? yes Could the selection of participants have introduced bias? low risk Applicability: Is there concern that the included participants do not match the review question? Low risk Index tests Risk of bias: Were the index tests interpreted without knowledge of the

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
To evaluate the diagnostic accuracies of EUS, EUS-FNA, and newer generation multidetector spiral CT, in the evaluation of patients with suspected PC. Study dates Data collection: 2000-2001 Study publication: 2004 Source of funding: Not reported	Exclusion criteria: patients suspected of having neuroendocrine tumours prior to EUS based on abnormal endocrine evaluation (n = 2); Ampullary tumours pancreatic cysts including cystic neoplasms patients who had spiral CT without pancreatic protocol; patients without definite cytological or pathologic diagnosis who were lost to follow-up less than 1 yr. after EUS-FNA.	material delivered by a power injector at a rate of 5 ml/s. The images were interpreted by CT radiologists who specialize in body imaging. Data were obtained from the results transcribed on the online medical record. Pancreatic mass was considered present on spiral CT scan only if a definite mass lesion was identified. Reference standard: The final diagnosis was based on definitive cytology, surgical pathology, or the development of metastatic disease. Patients were finally considered not to have cancer if they did not have any evidence of cancer after 1 yr. of clinical follow-up with partial or complete resolution of suspicious lesion on follow-up CT scans (number of patients by reference standard test are not reported)	Test - 15 2 17 Tot. 45 2 47 Sensitivity^= 66.67% (95% CI 51.05% to 80.00%) Specificity^= 100.00% (95% CI 15.81% to 100.00%) NPV^= 11.76% (95% CI 8.11% to 16.77%) PPV^= 100.00 ^ calculated by the NGA technical team from data reported the article	reference standard? Unclear (no details given in the report) If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Unclear risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low risk Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear (no information given about blinding) Could the reference standard, its conduct

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
				or interpretation have introduced bias? Unclear risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low risk Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Yes Did all participants receive a reference standard? Yes Did participants receive the same reference standard? No Were all patients included in the analysis? Yes Could the participant flow have introduced bias? unclear risk Overall risk of bias: unclear risk of bias Other information

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
Full Citation Ghaneh P, Hanson R, Titman A, Lancaster G, Plumpton C, Lloyd-Williams H, et al. (2018) PET-PANC: multicentre prospective diagnostic accuracy and health economic analysis study of the impact of combined modality ^{18}fluorine-2-fluoro-2-deoxy-d-glucose positron emission tomography with computed tomography scanning in the diagnosis and management of pancreatic cancer. Health Technology Assessment 22(7) Country/ies where the study was carried out: UK Study type:	Participants N=393 patients with suspected PC Inclusion criteria Written informed consent Able to have MDCT scan and attend PET/CT scan Able to attend 12-mo FU Patients with suspected pancreatic malignancy, defined as: (1) Focal lesion in pancreas/bulky pancreas/dilated pancreatic duct (with or without metastases) detected by MDCT (without or without MRI/EUS/ultrasound), or (2) Jaundice due to distal obstruction of common bile duct or ampulla (not due to calculi) [defined as serum	Index test 1=PET/CT Index 2=MDCT Reference test=Histology (biopsy or resection) or 12-mo clinical FU TNM staging classification used: UICC 2009 (7th edition) Procedure Study comprised 18 major pancreatic centres. All participants received standard diagnosis and staging with MDCT. Patients then underwent PET/CT with reference standard diagnosis within 2 weeks following informed consent. Follow up was 12 months. For 18-F-FDG PET/CT, patients fasted for 6 hours before scan; accurate SUV measurements obtained using calibrated class III device with blood	Study flow 910 patients screened, 619 registered, 589 underwent PET/CT scan (ITT, n=583; per protocol, n=550) Jaundiced patients only (due to distal obstruction of common bile duct or ampulla), (per protocol analysis, n=148; # with PDAC=91, # without PDAC=57) MDCT Sensitivity= 90.1% (95% CI 82.1% to 94.8%) Specificity= 57.9% (95% CI 44.8% to 69.9%) PET/CT Sensitivity= 95.6% (95% CI 88.9% to 98.3%) Specificity= 52.6% (95% CI 40.0% to 65.1%) Adverse events No events related to study procedure. One case of lymphangitis carcinomatosis, related to patient's original condition.	Limitations QUADAS 2 checklist Patient selection Risk of bias: Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of participants have introduced bias? Low Applicability: Is there concern that the included participants do not match the review question? Low Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Yes If a threshold was used, was it pre-specified? N/A

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
Multicentre prospective cohort study Aim of the study: To determine incremental diagnostic accuracy and impact of PET/CT on standard diagnostic work-up in patients with suspected pancreatic cancer. Study dates: 01/2011-05/2014 Source of funding: Funded by HTA project # 08/29/02; DC funded by NIHR Biomedical Research Centre at Royal Marsden and Institute of Cancer Research.	bilirubin > 35 µmol/l] or (3) Serum CA 19-9>37 kU/l Exclusion criteria: Patients <18 years Pregnant Poorly controlled diabetes Characteristics: (ITT population, n=583) Median age (years)=66, range 21-87) Male/female=328/255 Eligibility criteria: Focal lesion=538; jaundice=159 CA 19-9 >37=127	glucose recorded using calibrated Boehringer Mannheim glucometer. Patients hydrated before scan; scan started 90 minutes after FDG injection. All PET/CT scans transferred to central reporting centre and reviewed by independent expert. Scans also additionally reviewed by 4 other centres.		Could the conduct or interpretation of the index test have introduced bias? Low Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Yes Could the reference standard, its conduct or interpretation have introduced bias? Low Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
				Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Yes Did participants receive the same reference standard? No Were all patients included in the analysis? No Could the participant flow have introduced bias? High (69 patients not included in analysis) Overall risk of bias: No serious risk of bias
Full citation Kim, J. J., Walia, S., Lee, S. H., Patel, B., Vetsa, M., Zhao, Y., Srikureja, W., Laine, L.(2015) Lower yield of endoscopic ultrasound-guided fine-needle aspiration in patients with	Sample size: N= 180 patients (105 with stent – G1; 75 without stent –G2) Characteristics: M/F (n): 108 / 72 Mean age (SD): 65 (12) years Final diagnosis: malignant(n): 172 ^ benign(n): 8	Index test 1 (n=105): EUS-FNA - no stent Index test 2 (n=75): EUS-FNA - stent All EUS-FNAs were performed by staff gastroenterologists with or without a trainee. The examinations were performed using 22Fr or 25Fr needles for	Results 2x2 table EUS – FNA cytology * Test + 144 1 145 Test - 28 7 35 Tot. 172 8 180 Sensitivity^= 83.72 % (95% CI 77.34% to 88.90%) Specificity^= 87.50 % (95% CI 47.35% to 99.68%) NPV^= 20.00 % (95% CI 14.01% to 27.73%) PPV^= 99.31% (95% CI 95.83% to 99.89%)	Limitations QUADAS 2 checklist Patient selection Risk of bias: Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
pancreatic head mass with a biliary stent. Digestive Diseases & SciencesDig Dis Sci, 60, 543-9, Ref ID 484167 Country/ies where the study was carried out: US Study type: Retrospective single-centre study Aim of the study: To compare the diagnostic accuracy of EUS-FNA in patients with obstructive jaundice due to a pancreatic head mass with or without a biliary stent. Study dates Data collection: 2005-2013 Study publication: 2015 Source of funding: None	^ PC(n)= 159 Inclusion criteria*: Patients that were aged ≥18 years, who underwent EUS-FNA for evaluation of pancreatic mass and jaundice. Exclusion criteria: Patients who had cystic lesions of the pancreas, lacked >6-month follow-up from the index procedure after a non-malignant lesion was diagnosed on initial EUS-FNA and who were unable to receive a FNA during EUS.	FNA or/and 22Fr or 25Fr Pro core needle for core biopsy. All procedures were performed with moderate sedation under the guidance of the endoscopist in the hospital GI laboratory. Onsite cytopathology review is not routinely available at our center and was arranged per the discretion of the endoscopist. Reference standard: The final diagnosis was based on histologic diagnosis of malignancy on EUS-FNA (n=166), surgically resected specimen (number not reported), and/or other tissue acquisition from endoscopic or percutaneous modalities (n=6).	* calculated by NGA staff: By trial data and error based on the total number diseased and the reported sensitivity/specificity ^ calculated by the NGA technical team from data reported the article https://www.medcalc.org/calc/diagnostic_test.php	Did the study avoid inappropriate exclusions? Yes Could the selection of participants have introduced bias? low risk Applicability: Is there concern that the included participants do not match the review question? Low risk Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Unclear (no details given in the report) If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Unclear risk Applicability: Is there concern that the index test, its conduct or interpretation differ

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
				from the review question? Low risk Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? No (Incorporation bias: as the test that is being evaluated is included in the reference standard, there can be an overestimation of test accuracy) Were the reference standard results interpreted without knowledge of the results of the index test? Unclear (no information given about blinding) Could the reference standard, its conduct or interpretation have introduced bias? High risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
				review question? Low risk Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Yes Did all participants receive a reference standard? Yes Did participants receive the same reference standard? Not Were all patients included in the analysis? Unclear (not enough information in the report to appraise this criteria) Could the participant flow have introduced bias? High risk Overall risk of bias: very serious risk of bias Other information * In cases where patients had multiple EUS-FNAs during the study period, the initial procedure that

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
				met inclusion criteria at our center was counted as the index case.
Full citation Oppong, K., Raine, D., Nayar, M., Wadehra, V., Ramakrishnan, S., Charnley, R. M.(2010) EUS-FNA versus biliary brushings and assessment of simultaneous performance in jaundiced patients with suspected malignant obstruction. Jop: Journal of the Pancreas [Electronic Resource]Jop, 11, 560-7, Ref Id 483867 Country/ies where the study was carried out UK Study type Retrospective single-centre study	Sample size N= 37 patients (39 procedures)* Characteristics: M/F (n): 21 / 17*** Mean age (range): 62.4 (26- 87) years Final diagnosis: malignant(n): 32 **,^ benign(n): 5 ^PC(n)= 29 Inclusion criteria: All the patients presented with obstructive jaundice and had either an indeterminate biliary stricture or a mass in the head of pancreas, with a requirement for biliary drainage and a formal tissue diagnosis for the purpose of planning treatment (surgical or conservative).	Index test 1 (n=39): EUS-FNA A standard technique was used. The mass was identified and after staging assessment and the use of Doppler to assess for vessels, the FNA needle was passed into the lesion under EUS control. Suction was used and the needle moved within the tumour for 6-10 throws. Index test 2 (n=39): ERCP + Brushings of biliary strictures Brushings were taken using a standard cytology brush (M0054500; Boston Scientific, St Albans, United Kingdom) and standard technique. The brush catheter was advanced over a wire and under fluoroscopic control to the lower margin of the stricture.	Results 2x2 table EUS – FNA** Disease + / Disease + / Tot. Test + 25 0 25 Test - 9 5 14 Tot. 34 5 39 Sensitivity^= 73.53 % (95% CI 55.64% to 87.12%) Specificity^= 100.00 % (95% CI 47.82% to 100.00%) NPV^= 35.71 % (95% CI 24.09% to 49.31%) PPV^= 100.00% ^ calculated by the NGA technical team from data reported the article https://www.medcalc.org/calc/diagnostic_test.php ERCP + BB** Disease + / Disease + / Tot. Test + 22 0 10 Test - 12 5 29 Tot. 34 5 39 Sensitivity^= 64.71% (95% CI 46.49% to 80.25%) Specificity^= 100.00 % (95% CI 47.82% to 100.00%) NPV^= 29.41 % (95% CI 20.91% to 39.64%) PPV^= 100.00% ^ calculated by the NGA technical team from data reported the article https://www.medcalc.org/calc/diagnostic_test.php ** Suspicious cytology considered as a malignancy	Limitations QUADAS 2 checklist Patient selection Risk of bias: Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of participants have introduced bias? Low risk Applicability: Is there concern that the included participants do not match the review question? Low risk Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Unclear

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
Aim of the study Study dates Data collection: 2004-2007 Study publication: 2010 Source of funding Not reported	In whom ERCP-BB and EUS-FNA were performed sequentially under the same sedation and those in whom the second procedure was performed prior to availability of the results of the first sampling procedure. Exclusion criteria: final diagnosis of lymphoma	The brush was then advanced and retracted a minimum of three times, the catheter removed, the brush wiped on a glass slide and the slide and brush tip sent for cytological assessment. A cytopathologist was not present in the endoscopy suite for any of the procedures. Reference standard: The final diagnosis was based on surgical histology or other biopsy methods (n=30) any + cytology result combined with clinical follow-up that provided further evidence of malignancy (n=3) clinical, biochemical and radiological follow-up until death or for at least two years if there was no pathological or radiological evidence of malignancy (n=4).		(no details given in the report) If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Unclear risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low risk Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear (no information given about blinding) Could the reference standard, its conduct or interpretation have

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
				introduced bias? Unclear risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low risk Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Yes Did all participants receive a reference standard? Yes Did participants receive the same reference standard? No Were all patients included in the analysis? Yes Could the participant flow have introduced bias? Unclear risk Overall risk of bias: unclear risk of bias Other information

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
				* 39 (two individuals had two paired procedures); **The two individuals who had two paired procedures had malignancies. *** The Study sample was initially of 38 patients, 1 was excluded (with a final diagnosis of lymphoma).
Full citation Ross, W. A., Wasan, S. M., Evans, D. B., Wolff, R. A., Trapani, L. V., Staerkel, G. A., Prindiville, T., Lee, J. H.(2008) Combined EUS with FNA and ERCP for the evaluation of patients with obstructive jaundice from presumed pancreatic malignancy. Gastrointestinal Endoscopy, 68, 461-6, Ref Id	Sample size N= 114 patients Characteristics: M/F (n): 66 / 48 Mean age (SD): 62.6 (11.8) years Final diagnosis: malignant(n): 80^ benign(n): 34 ^ PC(n)= 68 Inclusion criteria: All patients with obstructive jaundice and/or abnormal periampullary imaging that raised a concern for periampullary (including	Index test 1 (n=83): EUS-FNA By using a linear-array endoscope with or without a radial echoendoscope, an EUS evaluation was done. When a pancreatic mass or a thickened bile-duct wall was present, 2 to 4 aspirates were obtained with a fine needle. The specimens were immediately assessed for adequacy by a cytotechnician and then were stained with Papanicolaou's stain for examination by a staff cytologist to	Results 2x2 table EUS -FNA Disease + Disease + Tot. Test + 55 0 55 Test - 11 17 28 Tot. 66 17 83 Sensitivity^= 83.33 % (95% CI 72.13% to 91.38%) Specificity^= 100.00 % (95% CI 80.49% to 100.00%) NPV^= 60.71 % (95% CI 47.40% to 72.61%) PPV^= 100.00 % ^ calculated by the NGA technical team from data reported the article https://www.medcalc.org/calc/diagnostic_test.php EUS – ERCP+BB Disease + Disease + Tot. Test + 4 0 4 Test - 26 20 46 Tot. 30 20 50 Sensitivity^= 13.33 % (95% CI 3.76% to 30.72%)	Limitations QUADAS 2 checklist Patient selection Risk of bias: Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? No (suspicious aspirates are excluded from analysis and not considered as either diagnostic or false negative). Could the selection of participants have

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
456241 Country/ies where the study was carried out US Study type Retrospective single-centre study Aim of the study To determine the feasibility and outcomes of combining an EUS-FNA and a therapeutic ERCP into a single session. Study dates Data collection: 2001-2004 Study publication: 2008 Source of funding: Not reported	pancreatic) malignancy Exclusion criteria: Not reported	establish a tissue diagnosis. Tissue processing and interpretation took 5 to 30 minutes, with results being called to the endoscopy suite by the cytopathologist. Index test 2 (n=50): ERCP + Brushings of biliary strictures While the FNA specimens were being evaluated, an ERCP was performed. When the FNA specimens were adequate to establish a diagnosis, no further tissue sampling was attempted during the ERCP. However, if the initial specimens were not + for cancer or if the reporting was delayed, then additional tissue samples were obtained by brushing and/or a biopsy. If the FNA specimens were not thought to be adequate, then another FNA with the reintroduction of the linear EUS endoscope	Specificity^= 100.00 % (95% CI 83.16% to 100.00%) NPV^= 43.48 % (95% CI 40.07% to 46.95%) PPV^= 100.00 % https://www.medcalc.org/calc/diagnostic_test.php	introduced bias? Unclear risk Applicability: Is there concern that the included participants do not match the review question? Low risk Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Unclear (no details given in the report) If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Unclear risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low risk Reference standard Risk of bias:

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
		after completion of the ERCP was carried out. Reference standard: The final diagnosis was based on tissue acquisition (n=78) or clinical course (n=2).		Is the reference standard likely to correctly classify the target condition? Unclear Were the reference standard results interpreted without knowledge of the results of the index test? Unclear (no information given about blinding) Could the reference standard, its conduct or interpretation have introduced bias? unclear risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low risk Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Yes

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
				Did all participants receive a reference standard? Yes Did participants receive the same reference standard? No Were all patients included in the analysis? No Could the participant flow have introduced bias? iHgh risk Overall risk of bias: Very serious risk of bias Other information
Full citation Tummala, P., Munigala, S., Eloubeidi, M. A., Agarwal, B.(2013) Patients with obstructive jaundice and biliary stricture +/- mass lesion on imaging: prevalence of malignancy and potential role of EUS-FNA. Journal of clinical	Sample size N= 348 patients Characteristics: M/F (n): 176 / 166 Mean age (range): 68 (12.5) years Final diagnosis: malignant(n): 248^ benign(n): 9 ^ PC(n)= 210 Inclusion criteria: patients who had presented with ObJ and a stricture in the extrahepatic bile duct on	Index test 1 (n=342): EUS-FNA Whenever a suspicious "mass" lesion was identified during the radial EUS examination, FNA was performed using a linear echoendoscope. Multiple FNA passes (up to 7 passes) were made using the Echo-tip EUS-FNA needle until the cytologist was able to make a preliminary diagnosis. The cytology	Results 2x2 table EUS -FNA Disease + / Disease + / Tot. Test + 227 5 232 Test - 21 89 110 Tot. 248 94 342 Sensitivity^= 91.53 % (95% CI 87.35% to 94.68%) Specificity^= 94.68 % (95% CI 88.02% to 98.25%) NPV^= 80.91 % (95% CI 73.73% to 86.48%) PPV^= 97.84 % (95% CI 95.08% to 99.07%) ^ calculated by the NGA technical team from data reported the article https://www.medcalc.org/calc/diagnostic_test.php Adverse Events	Limitations QUADAS 2 checklist Patient selection Risk of bias: Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of participants have

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
gastroenterology, 47, 532-7, 2013 Ref Id 523027 Country/ies where the study was carried out: US Study type: Retrospective single-centre study Aim of the study: To evaluate the diagnostic accuracy, the potential benefit and limitations of EUS-FNA in the evaluation of patients with suspected pancreatobiliary cancer. Study dates: Data collection: 2002-2009 Study publication: 2013 Source of funding: Funded by an educational grant from Institute for Science and Health	ERCP± a pancreatobiliary mass lesion on contrast CT scans Exclusion criteria: CT/MRI reported unresectable lesions, the final diagnosis was unavailable, CT report was unavailable, adequate EUS examination could not be performed because of postsurgical (Bilroth II) anatomy or the patient was finally diagnosed to have biliary obstruction due to hepatocellular carcinoma.	specimens were stained by the Diff-Quik and Papanicoulou method and assessed immediately by an attending cytologist. Reference standard: The final diagnosis was based on surgical pathology or definitive cytology and clinical follow-up of >=12 months (number of patients by reference standard test are not reported).	"There were 2 complications in study patients: 1 patient had acute pancreatitis requiring hospitalization for 3 days and another patient had aspiration pneumonia requiring oral antibiotics"	introduced bias? Low risk Applicability: Is there concern that the included participants do not match the review question? Low risk Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Unclear (no details given in the report) If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Unclear risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low risk Reference standard Risk of bias:

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
				Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear (no information given about blinding) Could the reference standard, its conduct or interpretation have introduced bias? Unclear risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low risk Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Yes Did all participants receive a reference standard? Yes

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
				Did participants receive the same reference standard? No Were all patients included in the analysis? Yes Could the participant flow have introduced bias? Unclear risk Overall risk of bias: Unclear risk of bias Other information

1 *CT-computed tomography; EUS-endoscopic ultrasonography; EUS-FNA- Endoscopic ultrasound-guided fine-needle aspiration; ERCP-Endoscopic retrograde*
2 *cholangiopancreatography; PC-pancreatic cancer; MRI-magnetic resonance imaging; PET-CT-positron emission tomography- computed tomography; NPV- Negative Predictive*
3 *Value; PPV- Positive Predictive Value.*

F.24 People without jaundice but with a pancreatic abnormality

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
Full Citation Bang, J. Y., Hebert-Magee, S., Trevino, J., Ramesh, J., & Varadarajulu, S. (2012). Randomized trial comparing the 22-gauge aspiration	Sample size N=56 consecutive patients with solid pancreatic lesion and suspected PC (EUS-FNA, n=28; EUS-FNB, n=28) Characteristics of EUS-FNA group:	Index test 1=EUS-FNA Index test 2=EUS-FNB Reference test=Histology on EUS-FNA/FNB samples	Type of imaging used to identify abnormality: CT or non-diagnostic EUS-FNA Do participants have jaundice? No Methods Randomisation: Computer-generated randomization assignments to either EUS-FNA or EUS-FNB were placed in sealed envelopes and opened by the nurse during the	Malignant vs. benign lesions EUS-FNA Calculated from identification of 25 malignant and 3 benign Sens=1.0 (95%CI, 0.86-1.0)	Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of applicability See ROB section below for full details.

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
and 22-gauge biopsy needles for EUS-guided sampling of solid pancreatic mass lesions. Gastrointestinal endoscopy, 76(2), 321-327. Country/ies where the study was carried out: USA Study type: Prospective tertiary care RCT Aim of the study: (1) To assess capability of 22G EUS-FNB device to obtain cytology specimens of solid pancreatic mass lesions and to compare its performance with 22G FNA system; (2) To compare the ability of both	Mean age (years)=65.4 (11.1) Gender (M/F)=16/12 Lesion location=20 Head/uncinate process, 8 body/tail Lesion size=3.37 (0.72) Characteristics of EUS-FNB group: Mean age (years)=65 (15.4) Gender (M/F)=15/13 Lesion location=20 Head/uncinated process, 8 body/tail Lesion size=3.25 (0.9) Inclusion criteria: Previously diagnosed using CT at outside facility or previous non-diagnostic EUS-FNA Exclusion criteria: No mass lesion on EUS Mass has cystic component Abnormal coagulation parameters Final diagnosis of EUS-FNA group:		procedure when patients met criteria for study inclusion. Procedure: All procedures were performed by using a linear array echoendoscope (Olympus UCT140;), with patients in the left lateral decubitus position under conscious sedation. All pancreatic head and uncinate masses were accessed via the duodenum and all pancreatic body and tail masses via the stomach. EUS-FNA After mass punctured, the stylet removed, and needle moved to-and-fro within the lesion 12-16 times. Suction not applied, and the stylet not deployed after first pass. Tissue material expressed onto slides by advancing stylet within needle assembly. EUS-FNB After mass punctured, the stylet removed, and needle moved to-and-fro within the lesion 4 times. Suction applied using a 10-mL syringe for 20 seconds and released before needle is withdrawn from the mass lesion. The specimen is then expressed onto slides by flushing air into the needle assembly. The stylet was not used for subsequent passes. After the initial pass, the specimen was processed on site by an attending pathologist who was blinded	Sp=1.0 (95%CI, 0.89-1.0) PPV=1.0 NPV=1.0 EUS-FNB Calculated from identification of 22 malignant (TP) and 3 benign (TN) and 3 failed onsite diagnosis (FN) Sens=0.88 Sp=1.0 PPV=1.0 NPV=0.5 (95%CI, 0.26-0.74) Adverse events EUS-FNA Complication rate of 3.6% (post-procedural abdominal pain managed conservatively on OP basis) EUS-FNB Complication rate of 3.6% (mild acute pancreatitis requiring	

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
needle systems to yield histologic core tissue. Study dates: 06/2011-09/2011 Source of funding: None reported	Malignant, n=25 Benign, n=3 Final diagnosis of EUS-FNB group Malignant, n=25 Benign, n=3		to the needle type used for tissue procurement. Three maximum passes were performed by using the original needle type, and if there was diagnostic failure (=failure to obtain sufficient diagnostic material after 3 passes) or technical failure (=malfunction of needle before diagnosis reached), the patient underwent crossover to the alternative needle. However, if a definitive diagnosis was established after the initial attempt, the procedure was terminated, and the number of passes performed was documented. In the crossover cohort, 3 maximum passes were attempted by using the alternate needle until sufficient diagnostic material was obtained or the needle technically failed. If no diagnosis was established in the crossover cohort, the procedure was terminated, and the patient was rescheduled for a repeat EUS on a different day. If on-site analysis warranted more tissue for further studies, 1 or 2 additional passes were made, and the specimen was collected in Hank buffered salt solution. Also, 2 dedicated passes were carried out for histologic assessment by cell block preparation. Air-dried and alcohol-stained smears were prepared on site after individual passes. Onsite cytological analysis: Air-dried smears were stained with Diff-Quick stain and immediately reviewed by a cytopathologist to ascertain sample	hospitalisation for 2 days).	

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
			adequacy and diagnosis. Alcohol-stained smears were prepared by using Papanicolaou stain. Histological analysis: In the laboratory, a 10-mL vial of HBSS containing the collected specimen was placed into the centrifuge, counter-balanced, and spun for 5 minutes. If the specimen quantity was sufficient, the supernatant was removed, and 3 drops of plasma and thrombin were added to the sediment. On formation of a clot, the cell button was removed intact, enclosed in a Tissue-Loc HistoScreen cassette (Microm International, Walldorf, Germany), and fixed in formalin. The cassette was processed, embedded in paraffin, and then prepared in hematoxylin and eosin to be evaluated by one pathologist, who was blinded to the randomization sequence, for the presence of a histologic core. If the histologic core was present, the specimen was graded as optimal or suboptimal. Optimal specimens were those in which the procured material enabled satisfactory assessment of histologic architecture that either did not change the original diagnosis or yielded additional findings. Suboptimal specimens were those in which the quality of the histologic core was unsatisfactory for assessment of histologic architecture. When required,		

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
			immunohistochemical or special staining was performed for differentiation of morphologically challenging lesions.		
Full Citation Bournet, B., Selves, J., Grand, D., Danjoux, M., Hanoun, N., Cordelier, P., & Buscail, L. (2015). Endoscopic Ultrasound–guided Fine-Needle Aspiration Biopsy Coupled With a KRAS Mutation Assay Using Allelic Discrimination Improves the Diagnosis of Pancreatic Cancer. Journal of clinical gastroenterology, 49(1), 50-56. Country/ies where the study was carried out: France Study type: Prospective single centre cohort Aim of the study:	Sample size N=186 consecutive patients with suspected solid pancreatic mass Characteristics: Mean age (years)=62 (12) Gender (M/F)=103/83 % Lesions of head=56% (Pancreatic adenocarcinoma group)/40% (other malignant tumours)/45 (benign lesions) Lesion size=not reported Inclusion criteria: Solid pancreatic mass ≥1 EUS-FNA, Referred to centre based on abdominal US, CT or MR cholangiopancreatography (MRCP), Written informed consent Exclusion criteria:	Index test 1=EUS-FNA Index test 2=EUS-FNA with KRAS mutation assay Reference test=Clinical follow up (including subsequent imaging and surgery).	Type of imaging used to identify abnormality: Abdominal US, CT, MRCP Do participants have jaundice? No Methods: EUS performed under i.v. propofol anaesthesia using curved linear-array echoendoscope (Olympus UC140T) conned to Aloka US device. FNA performed using 22-G needle. In 20% of patients, when first EUS-FNA sample using regular 22-G needle was judged insufficient, the second (and if necessary third) FNA was performed with the EUS-Procore 22-G needle. Core-biopsy samples of the pancreatic tissues were transferred into formalin with the needle stylet for further histologic analysis. Once core biopsies were obtained, the stylet was removed and the cellular material remaining in the needle catheter was air flushed twice with a sterile 20-mL syringe. The cellular material was placed in a dry sterile 1-mL Eppendorf tube and frozen at -20◦C until DNA was extracted. Samples were then centrifuged for 10 minutes at 8000 rpm. DNA was extracted from the pellets using a QIAamp DNA micro kit. Nucleic acid quantization was carried out using a Nanovue spectrophotometer.	Malignant vs. benign lesions EUS-FNA Sens=0.77 (95%CI, 0.68-0.84) Sp=1.0 (95%CI, 0.94-1.0) PPV=1.0 (95%CI, 0.96-1.0) NPV=0.67 (95%CI, 0.57-0.77) EUS-FNA with KRAS mutation assay Sens=0.91 (95%CI, 0.83-0.95) Sp=0.99 (95%CI, 0.93-0.99) PPV=0.99 (95%CI, 0.94-0.99) NPV=0.88 (95%CI, 0.8-0.94) Adenocarcinoma vs. other malignant or benign pancreatic lesions EUS-FNA	Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of applicability See ROB/applicability section below for full details.

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
To assess whether combining cytopathology and the KRAS-mutation assay improved the diagnosis of PDAC, especially in cases where EUS-FNA samples gave inconclusive or doubtful results after a cytopathologic examination. Study dates: 01/2010-02/2013 Source of funding: None reported	Previous chemotherapy or pancreatic surgery, Contraindication for EUS. Final diagnosis: Malignant, n=126 (Adenocarcinoma=104 , other=22) Benign, n=60 (CP=35, other=25)		To identify the KRAS codon-12 mutations (c.34 G>C p.G12R; c.35 G>A p.G12D; c.35 G>T p.G12V), a mutation detection assay based on custom TaqMan MGB dual probes was performed. Each probe incorporates a 50 reporter dye (VIC/FAM)-specific of WT or SNP sequence and a 30 nonfluorescent quencher. Amplification of the probe-specific product causes cleavage of the probe and generates an increase in reporter fluorescence. The use of dual probe in each experiment makes possible the signal discrimination of WT-specific and SNP-specific fluorescence, in a single polymerase chain reaction (PCR) and closed-tube format. Each alternation is screened by a dualprobe assay set: wild-type and mutant for 1 of the 3 mutations screened. Runs were performed on ABI Prism 7300 and Roche LC480II sequence detection systems. PCR was carried out in a total of 10 mL reaction volume including 20 ng of genomic DNA and 1X final master mix custom Taqman SNP genotyping assay. Cycling conditions were carried out with a 2-step PCR as follows: 95◦C 15 minutes, and 40 cycles of 95◦C 15 seconds, and 60◦C 1 minute in 96-well plates.	Sens=0.72 (95%CI, 0.62-0.8) Sp=1.0 (95%CI, 0.95-1.0) PPV=1.0 (95%CI,0.95-1.0) NPV=0.74 (95%CI, 0.64-0.82) EUS-FNA with KRAS mutation assay Sens=0.9 (95%CI, 0.83-0.95) Sp=0.99 (95%CI, 0.93-0.99 PPV=0.99 (95%CI, 0.92-0.99) NPV=0.89 (95%CI, 0.73-0.8) Adverse events: Not reported	

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
Full Citation Bournet, B., Souque, A., Senesse, P., Assénat, E., Barthet, M., Lesavre, N., Aubert, A., O'Toole, D., Hammel, P., Ruszniewski, P., Bouisson, M., Escourrou, J., Cordelier, P.& Buscail, L. (2009). Endoscopic ultrasound-guided fine-needle aspiration biopsy coupled with KRAS mutation assay to distinguish pancreatic cancer from pseudotumoral chronic pancreatitis. Endoscopy, 41(06), 552-557. Country/ies where the study was carried out:	Sample size N=178 consecutive patients with suspected solid pancreatic mass Characteristics: Mean age (years)=64.5 (11.6) Gender (M/F)=104/74 Lesion location=not reported Lesion size=not reported Inclusion criteria: Referred for EUS-FNA due to abdominal US, CT, MRCP Informed consent. Exclusion criteria: Cystic lesions, Previous chemotherapy or pancreatic surgery, Contraindication for EUS. Final diagnosis: Malignant, n= Benign, n=135 (adenocarcnimoa=129, other=16)	Index test 1=EUS-FNA Index text 2=EUS-FNA with KRAS mutation assay Reference test=Clinical follow up (inc. subsequent imaging and cytopathology)	Type of imaging used to identify abnormality: abdominal US, CT, MRCP. Do participants have jaundice? No Methods: EUS was carried out with the patient under i.v. propofol anesthesia using curved linear array echo endoscopes, FG-36 UA Pentax or UCT140T Olympus, connected to Hitachi or Aloka ultrasound devices, respectively. EUS-FNAB was done using the EUS N1–22 gauge needle (Wilson-Cook, Limerick, Ireland). At each centre, at least two needle passes were done until sufficient tissue material was collected. Core biopsy samples of pancreatic tissues were transferred into either Dubosq-Brazil or Cytolyte medium [20] with the needle stylet, for further cytological and histological diagnosis. Once the core biopsies had been transferred, the stylet was removed and the cellular material remaining in the needle catheter was air-flushed with a sterile 20-ml syringe and put into a sterile 1-ml Eppendorf tube and immediately frozen at –20°C until DNA extraction. The EUS-FNAB samples were centrifuged for 30 minutes at 7000 r. p.m. DNA was extracted from the pellets using	Malignant vs benign lesions EUS-FNA only Sens=0.81 (95%CI, 0.75-0.88) Sp=1.0 (95%CI,0.86-1.0) PPV=1.0 (95%CI, 0.96-1.0) NPV=0.48 (95%CI, 0.41-0.7) EUS-FNA + KRAS mutation assay Sens=0.86 (95%CI, 0.78-0.9) Sp=1.0 (95%CI, 0.85-1.0) PPV=1.0 (95%CI, 0.97-1.0) NPV=0.59 (95%CI, 0.49-0.79) Adenocarcinoma vs pseudotumoural chronic pancreatitis EUS-FNA only Sens=0.83 (95%CI, 0.76-0.89) Sp=1.0 (95%CI, 0.87-1.0) PPV=1.0 (95%CI, 0.96-1.0)	Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of applicability See ROB/applicability section below for full details.

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
France Study type: Multicentre prospective cohort (4 referral centres) Aim of the study: To assess whether combining EUS-FNAB with KRAS mutation analysis might effectively distinguish between PADC and a pseudo-tumoral form of chronic pancreatitis. Study dates: 01/2005-04/2007 Source of funding: None reported	Benign, n=33 (pseudotumoural chronic pancreatitis=27, other=6)		the QIAamp DNA micro kit (Qiagen, Les Ulis, France) and eluted in 20-µl volumes. To identify KRAS codon-12 mutations, we performed a two-step nested polymerase chain reaction (PCR) amplification, followed by restriction fragment length polymorphism (RFLP) analysis, DNA sequencing using the BigDye Terminator v3.1 kit in an automatic ABI 3100 sequencer (Applied Biosystems, California, USA) allowed verification and identification of mutations of the first or second nucleotide of codon-12 and a possible mutation of codon-13 in case of a wild-type codon-12 [8]. DNA extracted from human pancreatic cancer cells Capan-1 and BxPC-3, respectively, was used as positive (mutated KRAS) and negative (wild-type KRAS) control.	NPV=0.56 (95%CI, 0.41-0.7) EUS-FNA + KRAS mutation assay Sens=0.88 (95%CI, 0.82-0.93) Sp=1.0 (95%CI, 0.87-1.0) PPV=1.0 (95%CI, 0.96-1.0) NPV=0.63 (95%CI, 0.49-0.79) Adverse events: Not reported	
Full Citation Fabbri, C., Polifemo, A. M., Luigiano, C., Cennamo, V., Baccarini, P., Collina, G., Fornelli, A., Macchia, S., Zanini, N., Jovine,	Sample Size N=50 consecutive patients with suspected malignant solid lesions Characteristics: Mean age (years)=68.2 (7.4; range 51-80)	Index test=EUS-FNA Reference test=Surgery, death from disease or clinical follow up (evaluation and imaging studies). After at least a 12 month follow-up, patients with no signs	Type of imaging used to identify abnormality: CT Do participants have jaundice? No Methods: All patients were admitted to hospital and underwent the procedure under conscious sedation with meperidine and midazolam according to the American Gastroenterological Association	Malignant vs benign lesions 22- or 25-G needle Sens=0.96 (95%CI, 0.85-0.99) Sp=1.0 (95%CI, 0.4-1.0) PPV=1.0	Quality of study assessed using QUADAS-2: Overall high risk of bias (reference/flow and timing) Overall low risk of applicability

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
E., Fiscaletti, M., Alibrandi, A. & D'Imperio, N. (2011). Endoscopic ultrasound-guided fine needle aspiration with 22- and 25-gauge needles in solid pancreatic masses: a prospective comparative study with randomisation of needle sequence. Digestive and Liver Disease, 43(8), 647-652. Country/ies where the study was carried out: Italy Study type: Prospective cohort Aim of the study: To compare the rates of technical success, diagnostic accuracy and	Gender (M/F)=30/20 Lesion location=34 head, 8 uncinate process, 8 body Lesion size (cm)=2.9 (0.07) (range 1.5-5.0) Inclusion criteria: Diagnosed or suspected pancreatic lesions according to clinical evaluation and CT-scans Written informed consent Exclusion criteria: Cystic pancreatic lesions, Lesions < 1cm, Previous stent placement, History of previous gastrectomy, Patients haemodynamically unstable or with severe coagulopathy (INR >1.5 or platelet count < 60,000/mm3, Unable to suspend anticoagulant/anti-aggregant therapy for	of disease progression, or patients with disease regression, were considered to have had pancreatic inflammation at the time of the EUS-FNA. Malignant and suspicious lesions (diagnosed by cytopathology on EUS-FNA) which were finally diagnosed as malignant were considered to be true positives (TPs) whilst those which were finally diagnosed as benign disease on follow-up were considered to be false positives (FPs). Similarly, benign aspirates which were finally diagnosed as benign were considered to be true negatives (TNs) and those aspirates which were	guidelines. After EUS-FNA, the patients were monitored for at least six hours in order to immediately detect post-procedural complications and were followed for up to 30 days in order to detect late complications; a 3 month clinical follow-up was then carried out (mean 10.2 months, range 6–27 months) for non-surgical patients. Serious adverse events were defined as oversedation requiring the administration of a reversal agent, and those events requiring emergency hospitalisation or medical examination by a physician. EUS-FNA Performed using a linear echoendoscope (Fujinon) by an experienced choendoscopist using a well-established technique. The needle system used in all cases was the 3-22 and 25 gauge Cook EUS-FNA system (EchoTip Ultra with HDFNA, Cook Endoscopy, Winston-Salem, NC), which is a disposable device with a 140 cm long stainless steel needle within a spiral steel sheath surrounded by a Teflon cover; the system has a central stylet to protect the aspiration channel of the needle which can extend for 8 cm and has a scored tip to enhance echogenicity. A transduodenal approach was used for lesions of the head or uncinated process, and a trans-gastric approach was used for lesions of the body or tail of the pancreas. The target lesion was reached	NPV=0.66 (95%CI, 0.34-0.89) (Note that 95%CIs not reported and were calculated using reported data) Adverse events: No procedure- nor sedation-related immediate or delayed complications.	See ROB/applicability section below for full details.

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
complications of EUS-FNA performed with 22-gauge and 25-gauge needles on the same solid pancreatic mass. Study dates: 09/2007-12/2008 Source of funding: None reported	at least 5 days before start of study, Pregnancy, Inability or refusal to give informed consent, Refusal to participate in study. Final diagnosis Malignant, n=46 (pancreatic adenocarcinoma=45; neuroendocrine tumour=1) Benign, n=4 (CP=2, inflammatory pseudotumoural masses=2)	finally diagnosed as malignant were considered to be false negatives (FNs). The nondiagnostic cases were considered to be FNs as the procedure failed to reach a diagnosis.	and, after morphological studies, FNA was performed under EUS guidance. After the puncture, the stylet was removed; a 10 cm3 suction syringe was applied to the hub of the FNA device, and 15 uniform to-and-fro movements were made within the lesion during each puncture session. At the end of the procedure, the needle was retracted into the catheter and removed from the echoendo-scope. The needle sequences were assigned randomly and we performed two punctures with both needles in each lesion; the number of needle passes had previously been decided upon and was not subject to change. After aspiration, the first needle was retracted into the catheter and removed; the procedure was then repeated with the second needle. The randomisation of the needle used first, 22 or 25, was carried out by a computer-generated list. Assignments were prepared in a 1:1 proportion, and the allocation sequence was concealed using an opaque envelope system. Cytology: Samples were immediately smeared onto slides, fixed in 95% ethanol solution and stained using the Papanicolaou method. Two on-site pathologists, experienced in gastrointestinal cytology viewed all the		

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
			prepared slides, blinded to the size of the needle used to obtain the specimens. The cases were stratified into 4 diagnostic categories: (a) positive for malignancy, (b) suspicious for malignancy, (c) negative for malignancy and (d) non-diagnostic.		
Full Citation Fritscher-Ravens, A., Brand, L., Knöfel, W. T., Bobrowski, C., Topalidis, T., Thonke, F., & Soehendra, N. (2002). Comparison of endoscopic ultrasound-guided fine needle aspiration for focal pancreatic lesions in patients with normal parenchyma and chronic pancreatitis. The American journal of gastroenterology, 97(11), 2768-2775.	Sample size N=207 consecutive patients with suspected focal lesion Characteristics for whole sample Age: not reported Male/female: not reported Lesion location: 153 head, 33 body, 21 tail. Lesion size: 2.6 cm (range 0.7-5.4) Inclusion criteria: Malaise, pain, weight loss or jaundice, with abnormal findings on CT, US, PET, or octreotide scintiscan, or isolated elevation of CA 19.9. Majority of lesion solid when high clinical suspicion of PC	Index test=EUS-FNA Reference test Whole sample Histology (n=108), bacteriology (n=6), clinical follow-up (n=83) Normal pancreas group Surgery=58% Follow up=32% Bacteriology=10% CP group Surgery=31% Follow up=57% Bacteriology=8% Repeat FNA=4%	Type of imaging used to identify abnormality: CT (n=132), US (n=34), ERCP for jaundice (n=29), PET (n=4) or octreotide scintiscan (n=2). [n=6 had elevated CA 19.9 levels] Do participants have jaundice? Yes (n=29) Methods: EUS-FNA Performed using linear array echoendoscopes with 7.5 MHz transducer (Pentax FG 34 UX or Olympus GIF-UC 30P) and 22-gauge needle (GIP or Wilson Cook) with patient in the left lateral position under i.v. sedation with diazepam and propofol (individually titrated doses). Doppler US used to characterise vascular structures. All patients monitored by experienced medical staff during sedation and for 2 h after the procedure. No prophylactic antibiotics given, except in two patients who had undergone aortic valve replacements. All patients discharged ~2 h after procedure. Status reviewed after	Malignant vs benign lesions Whole sample (normal pancreas + chronic pancreatitis groups; n=200) Sens=0.85 Sp=1.0 PPV=1.0 NPV=0.83 Normal pancreas group (n=130) Sens=0.893 (95%CI, 0.817-0.946) Sp=1.0 (95%CI, 0.872-1.0) PPV=0.915 (95%CI, 0.961-1.0) NPV=0.711 (95%CI, 0.569-0.866) Chronic pancreatitis group (n=70)	Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of applicability See ROB/applicability section below for full details.

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
Country/ies where the study was carried out Germany Study type: Retrospective cohort Aim of the study: To analyse the diagnostic yield and influence of EUS-FNA on the clinical management of patients with pancreatic lesions, in the presence or absence of chronic pancreatitis. Study dates: 04/1998-07/2000 Source of funding: None reported	With or without known focal lesion Informed consent Exclusion criteria: Pure or predominantly cystic lesion Pseudocyst Less than one-year FU Oesophageal stenosis Coagulation dysfunction Taking acetylsalicyclic acid or other anti-coagulating agents within 6 days before presentation Final diagnosis Whole sample Malignant, n=116 Benign, n=84 Normal pancreas group Malignant, n=91 Borderline=12 Benign=27 CP group Malignant, n=13 (Adenocarcinoma=13)		4–6 days by phone, when the cytology report received by physician in charge. May-Grunwald-Giemsa staining and light microscopy performed blindly by two experienced and independent cytopathologists. Participants divided immediately after EUS-FNA (but before receiving cytology results or data analysis) into normal pancreas (n=130) (i.e. no evidence of CP) and CP (n=70) groups. Cytology: Type of lesion (malignant, borderline and benign) classified using modified Papanicolaou classification): Pap I-III=benign; Pap IV or V=malignant	Sens=0.535 (95%CI, 0.251-0.808) Sp=1.0 (95%CI, 0.937-1.0) PPV=0.914 (95%CI, 0.59-1.0) NPV=0.905 (95%CI,0.804-0.964) Adverse Events: No complications were observed.	

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
	Benign, n=59 (Chronic inflammation, n=57, other=2)				
Full Citation Harewood, G. C., & Wiersema, M. J. (2002). Endosonography-guided fine needle aspiration biopsy in the evaluation of pancreatic masses. The American journal of gastroenterology, 97(6), 1386-1391. Country/ies where the study was carried out: USA Study type: Multi-centre tertiary prospective cohort (2 hospitals) Aim of the study: To determine performance of EUS FNA biopsy in pancreatic malignancy when prior biopsies	Sample size N=185 consecutive patients with suspected or known solid pancreatic mass 1 patient was excluded due to no detection of lesion on EUS (subsequently developed PC on clinical FU) Characteristics: Mean age (years)=65.2 (range 24-90) Gender (M/F)=122/63 Lesion location: 140 head, 29 body, 17 tail Lesion size: mean (cm)=3.2 (SD=1.3)/median=3 (range 0.8-14) Inclusion criteria Presence or clinical suspicion of solid pancreatic mass Biopsy requested by referring physician	Index test=EUS-FNA Reference test=Composite gold standard of surgical pathology, cytology, and clinical course + sequential radiological imaging Surgical pathology (n=42), or Malignant cytology on tissue sampling with EUS-FNA, CT-FNA or ERCP with compatible clinical course (n=130), or Clinical course (>12 months) and sequential radiological imaging consistent with benign disease (n=13).	Type of imaging used to identify abnormality: Abdominal CT scan Did participants have jaundice? No Methods: EUS-FNA Evaluation of lesion performing using radial scanning echoendoscope (Olympus GF-UM20 or GF-UM30). EUS-FNA performed using curved linear array echoendoscope (Olympus GF-UM 30P or Pentax FG-32 UA). Needle advanced into lesion under direct US visualisation and Doppler US used to characterise vascular structures. Stylet removed (10-ml syringe with extension tubing attached to needle hub), and needle moved back and forth with suction (3-5 cc) applied. Aspirated material sprayed onto glass slides and fixed in ethanol or spray fixed, with remainder dried to allow assessment of sample adequacy (before end of procedure). If no adequate sample after 5th pass, procedure continued only if a previous pass demonstrated atypical or suspicious material. Patient observed for minimum 1 hour to ensure recovery. All FNA samples subsequently interpreted by experienced cytopathologist.	Malignant vs benign lesions Whole group (n=185) Sens=0.94 (95%CI, 0.9-0.97) Sp= 0.71 (95%CI, 0.48-0.89) PPV= 0.96 NPV= 0.6 Patients who had negative CT-guided FNA (n=58) Sens=0.9 (95%CI, 0.78-0.97) Sp=0.5 (95%CI, 0.16-0.84) Patients who had negative ERCP tissue sampling (n=36) Sens=0.94 (95%CI, 0.8-0.99) Sp=0.67 (95%CI, 0.09-0.99) Adverse Events One patient developed mild	Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of applicability See ROB/applicability section below for full details.

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
performed by CT guidance or ERCP were negative. Study dates: 1994-1997, 1998-1999 Source of funding: None reported	Informed consent Exclusion criteria Inadequate FU data Final diagnosis: Malignant, n=164 [surgical pathology=34; malignant cytology=130] (Adenocarcinoma=155 ; other=9) Benign, n=21 [surgical pathology=8; clinical course + radiological imaging=13], (Chronic pancreatitis=20; other=1)		Patients whose CT-guided FNA (n=3) or ERCP (n=5) suggested malignancy had EUS-FNA (i) within 1 day of these procedures (n=2) or (ii) to sample suspicious lymph nodes (n=6). CT-guided FNA Performed using coaxial technique using 18- or 20-gauge needle to enter lesion, and 22-gauge or smaller needle to aspirate. Aspirates prepared in same way as for EUS-FNA. Tissue cores fixed in formalin and separately processed. Sample adequacy assessed by site cytopathologist. All FNA samples subsequently interpreted by experienced cytopathologist at tertiary referral centre. ERCP Tissue sampling exclusively at bile duct, with or without guide wire. No on-site cytopathology assessment performed. Biopsies obtained using malleable or paediatric biopsy forceps.	procedure-related pancreatitis requiring 48-hr hospitalisation. Complication rate=0.5% (95%CI, 0-3). No complications observed for either CT-guided FNA or ERCP tissue sampling.	
Full Citation Hikichi, T., Irisawa, A., Bhutani, M. S., Takagi, T., Shibukawa, G., Yamamoto, G., ... & Sato, M. (2009). Endoscopic ultrasound-guided fine-needle aspiration of solid	Sample size N=73 consecutive patients with solid pancreatic mass Group 1: Endosonographer ROSE (n=38) Group 2: Cytopathologist ROSE (n=35)	Index test=EUS-FNA Reference test=Surgery, autopsy, or >12 months clinical follow up	Type of imaging used to identify abnormality: US, CT, and/or ERCP Do participants have jaundice? No Methods: EUS-FNA Performed with convex or linear array echoendoscope (Olympus GF-UCT 240-AL5/GF-UC240P-AL5 or Pentax FG-36 UX, in conjunction with Hitachi EUB-6000) using 22-gauge manually operated	Malignant vs benign lesions Group 1 Sens=0.929 Sp=1.0 PPV=1.0 NPV=0.833 Group 2 Sens=0.931	Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of applicability See ROB/applicability section

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
pancreatic masses with rapid on-site cytological evaluation by endosonographers without attendance of cytopathologists. Journal of gastroenterology, 44(4), 322-328. Country/ies where the study was carried out Japan Study type Single-centre retrospective cohort Aim of the study To evaluate the diagnostic accuracy of EUS-FNA with rapid on-site evaluation (ROSE) by endosono-graphers compared to ROSE by cytopathologists in patients with solid	Characteristics Group 1 Mean age: (years)=60.6 (11.4) (range 36-81) Gender (M/F)=28/10 Lesion location=14 head, 24 body or tail Lesion size (cm)=3.2 (1.2) (range 1.2-8.5) Characteristics Group 2 Mean age: (years)=63.6 (10.5) (range 41-88) Gender (M/F)=21/14 Lesion location=20 head, 15 body or tail Lesion size (cm)=3.6 (1.5) (range 2-9) Inclusion criteria: Patients with unresectable solid mass requiring pathological diagnosis before chemotherapy or radiation therapy or both Difficulty differentiating between localised pancreatitis and pancreatic carcinoma		needle (Olympus NA-10J-1/NA-200H-8022) or automated spring-loaded powershot needle device (Olympus NA-11J-KB). Moderate i.v. sedation used. Two expert endosonographers performed all procedures in Group 1, whilst additional 8 trainees performed all procedures in Group 2. After EUS guidance into lesion with realtime needle visualisation, needle moved back and forth 10-20 times, while suction applied using 10-20ml syringe. Sample adequacy assessed with Diff-Quik or Cyto-Quik technique. Procedure stopped when endosonographer or cytopathologist indicated adequacy. Aspirate materials sprayed onto glass slides by air using syringe, with half fixed in ethanol or spray fixed, and half air-dried to enable ROSE. Samples later stained by Papinicolaou and MaGiemsa technique. All patients observed for post-procedure complications. Blood samples to measure serum amylase levels and C-reactive protein taken 24h before and after EUS-FNA. Pancreatitis diagnosed if (i) abdominal pain reported and (ii) there was 3-fold serum amylase elevation within 24h of procedure. Cytopathological diagnosis by cytopathologists based on Pap/Giemsa stained samples. If lymphoma suspected, immune stain was added. Cytological criteria based on Papanicolaou	Sp=1.0 PPV=1.0 NPV=0.75 Adverse Events No major complications observed	below for full details.

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
pancreatic masses. Study dates 09/2001-09/2003 (Group 1), 10/2003-10/2005 (Group 2) Source of funding None reported	using US, CT and/or ERCP No definite diagnosis using sampling techniques during ERCP Informed consent before EUS-FNA Exclusion criteria: None reported Final diagnosis in Group 1 Malignant, n=28 (Ductal adenocarcinoma=24; other=4) Benign, n=10 (CP=8; other=2) Final diagnosis in Group 2 Malignant, n=29 (Ductal adenocarcinoma=26; metastases=1; other=2) Benign, n=6 (CP=2, other=6)		categories (Class I-II=benign, Class III=atypical/indeterminate, Class IV/V=malignant). Mean # needle passes in group 1=4 (1.6) (range 1-7) Mean # needle passes in group 2=3.4 (1.5) (range 1-7) Reference tests: No details provided.		
Full Citation Iglesias-Garcia, J., Dominguez-Munoz, E., Lozano-Leon, A.,	Sample size N=62 consecutive patients with solid pancreatic mass	Index test=EUS-FNA Reference test=Operated patients: surgical specimen in operated	Type of imaging used to identify abnormality: CT Do participants have jaundice? No Methods	Malignant vs benign lesions Both cytology and histology	Quality of study assessed using QUADAS-2: Overall low risk of bias.

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
Abdulkader, I., Larino-Noia, J., Antunez, J., & Forteza, J. (2007). Impact of endoscopic ultrasound-guided fine needle biopsy for diagnosis of pancreatic masses. World journal of gastroenterology, 13(2), 289. Country/ies where the study was carried out: Spain Study type: Single-centre prospective cohort Aim of the study: To evaluate diagnostic accuracy of histological evaluation of pancreatic tissue samples obtained by modified method for recovering and processing EUS-	Characteristics: Mean age (years)=57 (range 20-83) Gender (M/F)=35/27 Lesion location=45 head, 15 body, 2 tail. Lesion size=not reported Inclusion criteria: Solid pancreatic mass Informed consent Exclusion criteria: Uncorrectable coagulation profile (prothrombin time <60%) considered contraindication Final diagnosis Malignant, n=38 (Adenocarcinoma=33, other=5) Benign, n=24 (Inflammatory mass=24)	patients; Non-operated patients: clinical, morphological (EUS+CT scan) and biochemical evaluation (inc. CA 19.9) over at least 6 months) Criteria for benign course was subjective well-being, absence of weight loss, no disease progression on imaging studies, no elevation in serum tumour markers.	EUS-FNA performed using convex array echoendoscope (Pentax FG-38UX) connected to ultrasound (Hitachi E6000) using 22-gauge needle (Sonotop II). Lesion endosono-graphically visualised and Doppler used to scan for vessels. EUS guidance used to place stylet then removed. Suction applied using 5-ml syringe as needle moved back and forth. Sample from first and second punctures air expelled onto slides and fixed in 96% ethanol using Papincolaou staining. Samples after third puncture recovered into tube containing 10% formol solution by injecting 2-ml saline solution through needle, then embedded in paraffin. Sample adequate if coherent core tissue specimen obtained. No pathologist in room during procedure. Samples initially processed by endoscopists trained by pathologists. Two experienced pathologists subsequently examined both cytological and histological samples. Twenty-seven patients underwent surgery (inc. 20 adenocarcinomas). Remaining 35 patients were followed up for median 10-mo (range 6-20 months).	Sens=0.84241 (95%CI, 0.696-0.926) Sp=1.0 (95%CI, 0.862-1.0) PPV=1.0 NPV=0.8 Cytology Sens=0.765 (95%CI, 0.6-0.876) Sp=1.0 (95%CI, 0.816-1.0) PPV=1.0 (95%CI, 0.871-1.0) NPV=0.68 (95%CI, 0.484-0.828) Histology Sens=0.9285 (95%CI, 0.773-0.98) Sp=1.0 (95%CI, 0.862-1.0) PPV=1.0 (95%CI, 0.871-1.0) NPV=0.923 (95%CI, 0.759-0.979) Adverse events Complication rate=1.6% One case mild acute pancreatitis observed and	Overall low risk of applicability See ROB/applicability section below for full details.

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
FNA material in the differential diagnosis of pancreatic solid masses. Study dates: Not reported, conducted over 2-year period Source of funding: None reported				resolved within 3 days of conservative treatment. No patients died due to procedure.	
Full Citation Kliment, M., Urban, O., Cegan, M., Fojtik, P., Falt, P., Dvorackova, J., Lovecek, M., Straka, M. & Jaluvka, F. (2010). Endoscopic ultrasound-guided fine needle aspiration of pancreatic masses: the utility and impact on management of patients. Scandinavian journal of gastroenterology, 45(11), 1372-1379.	Sample size N=207 consecutive patients with suspected PC Characteristics: Mean age (years)=62.2 (10.9) (range 33-89) Gender (M/F)=121/86 Lesion location=75% head, 13% body, 9% uncinate process, 3% tail. Lesion size (cm)=3.15 (0.97) (range 1.2-7) Inclusion criteria: Solid mass diagnosed as suspected PC using CT, MRI, US or double duct sign on ERCP	Index test=EUS-FNA Reference test= Patients undergoing surgery: gold standard was histology from resection; Not undergoing surgery, gold standard was clinical evaluation methods and repeated imaging studies and final diagnosis after at least 6 months of follow-up.	Type of imaging used to identify abnormality: CT (93.2%), MRI (1%), US (1.5%), or double duct sign on ERCP (4.3%) Do participants have jaundice? Some (n=111; 53.6%) Methods EUS-FNA performed using a curvilinear-array echo-endoscope (Olympus GF UCT 140 AL) and a 22-Gauge FNA needle (EZShot NA-200H-8022) by one of two experienced echoendoscopists. Depending on the echoendoscopist's decision, when clinically relevant, EUS-FNA of ascitic fluid, suspicious lymph node, liver mass or other site was performed before sampling pancreatic mass. Patients were under conscious i.v. sedation using 2–10 mg of Midazolam and 1–2 ml of Fentanyl during the procedure. Quick staining during	Malignant vs benign lesions Sens=0.926 (95%CI, 0.872-0.9596) Sp=0.886 (95%CI, 0.7464-0.9564) PPV=0.9679 (95%CI, 0.9229-0.9881) NPV=0.7647 (95%CI, 0.6218-0.8675) Adverse events Five minor complications (2.4%), no major complications.	Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of applicability See ROB/applicability section below for full details.

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
Country/ies where the study was carried out: Czech Republic Study type: Single-centre tertiary care prospective cohort Aim of the study: To assess diagnostic yield, safety and impact of EUS-FNA on management of patients with solid pancreatic mass. Study dates: 01/2007-08/2007 Source of funding: None reported	Informed consent Exclusion criteria: Aged <18 years No pancreatic mass on EUS High bleeding risk after EUS-FNA (due to coagulation disorder with INR >1.5, thrombocytopenia <50,000/mm3, or large diameter vessel interposed between needle tip and pancreatic mass) Final diagnosis Malignant, n=163 (adenocarcinoma=155, other=8) Benign, n=44		endoscopic procedure performed depending on cytopathologist availability (77% of cases). Resampling until adequate patients with unresectable disease and pancreatic type pain EUS-guided celiac plexus neurolysis (EUS-CPN) - with 20ml of alcohol solution between take-off of celiac artery and aorta, or 10 ml each side of celiac artery - performed during EUS-FNA.. Final cytological diagnosis established by agreement after evaluation of smears in 2 laboratories by 2 independent cytopathologists. Cytological confirmation of atypical cells, cells suspicious for malignancy, malignant cells or neuroendocrine tumor (NET) cells regarded as positive for malignancy. When only normal or reactively changed ductal or acinar and inflammatory cells were present benign cytological diagnosis was established. Smears with inadequate cellularity to establish any cytological diagnosis after final evaluation in the laboratory were classified as inconclusive. In such cases, repeated EUS-FNA was recommended, but final decision was left to the referring physician. If repeated EUS-FNA followed previous one with inconclusive cytology result, both attempts were included in the final		

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
			analysis as two separate patients without exclusion of any case. All patients stayed in the hospital for at least 24 h after EUS-FNA in order to diagnose and treat potential early complications. Information about late complications up to 28 days after EUS-FNA was obtained by phone contact with the patient. Major complication was defined as any change in patients' health requiring immediate therapy, prolongation in hospitalization or death, whereas minor did not. Bleeding was defined as either a drop in hemoglobin level of ‡20 g/l, or clinical signs of upper gastrointestinal bleeding (hematemesis, melena) during 48 h after the procedure. Each patient without surgery and benign initial cytology underwent either repeated CT scan, abdominal or endoscopic ultrasound within 3–6 months after initial EUS-FNA. Patients receiving palliative chemoradiotherapy underwent repeated CT scanning after the treatment period. The subsequent treatment, clinical course and results of repeated imaging after EUS-FNA were regularly checked by contact with the patient or referring physician.		

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
Full Citation Krishna, N. B., LaBundy, J. L., Saripalli, S., Safdar, R., & Agarwal, B. (2009). Diagnostic value of EUS-FNA in patients suspected of having pancreatic cancer with a focal lesion on CT scan/MRI but without obstructive jaundice. Pancreas , 38(6), 625-630. Country/ies where the study was carried out USA Study type: Single-centre prospective cohort Aim of the study: To investigate the performance characteristics of EUS-FNA in patients with suspected pancreatic cancer	Sample size N=213 patients with suspected PC due to solid mass (includes 40 patients not found to have focal pancreatic lesion, and 33 patients found to have cystic lesions, on EUS-FNA) Characteristics Mean age (years)=62.8 (13.7) Gender (M/F)=105/108 Lesion location=144 head and uncinate process, 40 body, 29 tail. Lesion size=3.4 (1.65) Inclusion criteria Focal lesion ≥10 mm detected using CT or MRI Exclusion criteria Cystic lesion using CT or MRI Jaundice (serum bilirubin level ≤ 1 mg/dL Final diagnosis	Index test 1=EUS Index test 2=EUS-FNA Reference test=Definitive cytology, surgical pathology, and >12 months follow up.	Type of imaging used to identify abnormality: CT/MRI Do participants have jaundice? No Methods EUS initially performed using radial echoendoscope (Olympus EUM-130). Whenever the focal lesion noted by CT scan/MRI was identified by EUS (n = 173), FNA of the lesion was then performed using a linear echoendoscopes (Pentax FG-32A). Multiple (1-7) passes using Echo-tip FNA needle until adequate samples secured; stained using Diff-Quik and Papanicolaou methods, and immediately assessed by cytologist. EUS-FNA samples also submitted to make cell blocks for immunostaining if needed. Reference test Cytologic diagnosis suspicious for malignancy counted as negative for malignancy. Adverse events History of abdominal pain in 110 patients. Significant weight loss (≥10 lb)=57 patients; Weight loss <10lbs=6 patients. Recent (before EUS-FNA) acute pancreatitis=40 patients	Malignant vs benign lesions EUS Sens=1.0 Sp=0.66 (95%CI, 0.569-0.752) PPV=0.759 (95%CI, 0.689-0.823) NPV=1.0 EUS-FNA Sens=0.966 (95%CI, 0.929-0.997) Sp=0.99 (95%CI, 0.971-1.0) PPV=0.991 (95%CI, 0.972-1.2) NPV=0.962 (95%CI, 0.926-0.999) Adverse events Not reported	Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of applicability See ROB/applicability section below for full details.

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
based on the presence of a focal lesion in the pancreas on CT scan or MRI and who did not present with obstructive jaundice Study dates: 03/2002-12/2005 Source of funding: None reported	Malignant, n=110 (Adenocarcinoma=89; other=21) Benign, n=103 (normal pancreas=39, CP=32, benign cysts=32)				
Full Citation Lee, Y. N., Moon, J. H., Kim, H. K., Choi, H. J., Choi, M. H., Kim, D. C., Lee, T.H., Cha, S.W., Cho, Y.D., and & Park, S. H. (2014). Core biopsy needle versus standard aspiration needle for endoscopic ultrasound-guided sampling of solid pancreatic masses: a randomized parallel-group	Sample size N=118 consecutive patients with solid pancreatic lesions (EUS-FNA, n=58; EUS-FNB, n=58) 2 patients excluded due to lack of follow-up data Characteristics of EUS-FNA group (n=58) Mean age (years)=63.1 (10.6) Gender (M/F)=40/18 Lesion location=28 Head/uncinate process, 30 body/tail	Index test 1=EUS-FNA Index test 2=EUS-FNB Reference test= Definite proof of malignancy on a surgical specimen (n=19) (endoscopic biopsy during duodenoscopy or ERCP, or biopsy of a metastatic lesion); Malignant diagnosis on EUS-FNB or EUS-FNA and clinical/imaging follow-up compatible with malignant	Type of imaging used to identify abnormality: CT, MRI or EUS Do participants have jaundice? No Methods Randomisation No details provided EUS-FNA and FNB procedure All procedures performed with standardized protocols by two experienced investigators using a linear-array echoendoscope (GF-UCT240; Olympus) in patients under conscious sedation. EUS-FNB carried out with a 22G or 25G FNB device (Echotip ProCore; Wilson-Cook Medical) that features a hollowed-out reverse bevel at the tip of the needle. EUS-FNA was performed with a standard 22G or 25G FNA device (Echotip; Wilson-Cook	Malignant vs benign lesions EUS-FNA (n=58) Sens=0.946 (95%CI, 0.886-1.0) Sp=1.0 Calculated using available data PPV=1.0 NPV=0.4 EUS-FNB (n=58) Sens=0.982 (95%CI, 0.946-1.0) Sp=1.0 Calculated using available data PPV=1.0	Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of applicability See ROB section below for full details.

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
study. Endoscopy, 46(12), 1056-1062. Country/ies where the study was carried out: South Korea Study type: Prospective single-centre RCT Aim of the study: To evaluate the diagnostic accuracy of the EUS-FNB device compared with conventional EUS-FNA Study dates: 01/2012-05/2013 Source of funding: None reported	Median lesion size (cm)=3.65 (range 1.7-7..4; IQR 2.68-4.2) Characteristics of EUS-FNB group (n=58) Mean age (years)=66.7 (12.7) Gender (M/F)=33/25 Lesion location=24 head/uncinated, 34 body/tail Median lesion size (cm)=3.65 (range 1.5-10; IQR=2.9-4.6) Inclusion criteria Presence of solid pancreatic lesion on CT, MRI and/or EUS Need for pathological data to make diagnosis/guide management decision Aged >18 years-old Informed consent Exclusion criteria Presence of cystic lesion Coagulopathy (INR >1.5 or platelet count <80,000/mm3)	disease (n=42); No proof of malignancy on EUS-FNB or EUS-FNA and on clinical/imaging follow-up of at least 6 months (n=55). Cytological and histological diagnoses were categorized as nondiagnostic, negative, atypical, suspicious, and positive for malignancy. Neuroendocrine tumor cells were considered malignant. Samples that were considered positive or suspicious for malignancy were categorized as positive for malignancy, whereas samples that were considered benign, indeterminate, or atypical were categorized as negative for malignancy.	Medical). FNB and FNA procedures performed from the duodenum with a 25G needle for lesions located in the head of the pancreas and from the stomach with a 22G needle for lesions located in the body/tail of the pancreas. After lesion punctured, stylet removed, and suction applied using 10-mL syringe. The needle was then moved to and fro between 10 and 20 times, and was withdrawn from the lesion after suction had been released. Slides were air dried and stained with the Diff-Quik stain for immediate onsite interpretation. After each pass, the cytopathologist determined whether the sample was adequate for cytological examination and diagnosis of malignancy. Regardless of the result of onsite diagnosis, a portion of each pass of the sample was simultaneously processed for cytological and histological analysis. Slides fixed with alcohol and stained with a Papanicolaou-stain for cytological analysis. The cytological analysis was used to describe cellularity and diagnose malignancy in each specimen. The material for histological analysis fixed in formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin (H&E) and periodic acid–Schiff (PAS). Immunohistochemical studies were performed on all cases that	NPV=0.25 Adverse events EUS-FNA 1% complication rate (n=1, mild pancreatitis) EUS-FNB 5.2% complication rate (n=3) (mild bleeding=1; gastric hematoma=2)	

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
	Final Diagnosis in EUS-FNA group (n=58) Malignant, n=56 Benign, n=2 Final Diagnosis in EUS-FNB group (n=58) Malignant, n=55 Benign, n=3	The diagnosis of malignancy using EUS-FNB or EUS-FNA was established when at least one of the specimen preparation methods (onsite cytology, definite cytology, histology) was positive for malignancy.	had adequate histological specimens for staining. For histological analysis, a cytopathologist evaluated whether the tissue was adequate for histological examination and diagnosis of malignancy. Adverse events Complications defined as any post-procedure event attributable to EUS-FNB or EUS-FNA. After procedure, patients observed in the recovery room for 1–2 hours and all were hospitalized for at least 1 day. Vital signs recorded every 30 minutes in the 2 hours after the procedure and every 6 hours thereafter until discharge. All patients routinely underwent follow-up investigations with laboratory testing and simple abdominal radiography after EUS-FNB or EUS-FNA. Clinically significant bleeding, perforation, and hypotension were documented. Bleeding was defined as a drop in the haemoglobin level of 2g/dL or more compared to the baseline level, together with clinical evidence of bleeding. For patients with abdominal pain, serum amylase and lipase levels initially checked, and an abdominal CT scan performed if the symptoms persisted. Acute pancreatitis defined as abdominal pain associated with nausea or vomiting, coupled with a three-fold elevation in serum amylase or lipase.		

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
Full Citation Mishra, G., Zhao, Y., Sweeney, J., Pineau, B. C., Case, D., Ho, C., Blackstock, A.W., Geisinger, K., Howerton, R., Levine, E., Shen P., and Ibdah, J.(2006). Determination of qualitative telomerase activity as an adjunct to the diagnosis of pancreatic adenocarcinoma by EUS-guided fine-needle aspiration. Gastroi ntestinal endoscopy, 63(4), 648-654. Country/ies where the study was carried out: USA Study type: Prospective tertiary care cohort Aim of the study:	Sample size N=52 consecutive suspected PC patients with solid lesions Characteristics Median age (years)=67 (range 37-93) Gender (M/F)=27/25 Lesion location=37 head, 14 body, 7 uncinate, 4 tail Lesion size=not reported Inclusion criteria Referred due to abnormality on CT, transabdominal US, MRI or ERCP Exclusion criteria Prothrombin INR >1.5 Partial thromboplastin >50 secs Platelet count <50,000 mm3 Acute pancreatitis Presence of pancreatic abscess necrosis Final diagnosis Malignant, n=47 Benign, n=5	Index test=EUS-FNA Reference test=(i) cytology on EUS-FNA sample (n=45) or CT-guided biopsy (n=5) and clinical follow up, or (ii) surgical exploration with intraoperative biopsy (n=2)	Type of imaging used to identify abnormality: CT, transabdominal US, MRI, ERCP Do participants have jaundice? No Methods (solid lesions only) All patients underwent EUS-FNA using a curved linear array echoendoscope (GF-UCT/P 140; Olympus). Indications for the examination, lesion size, location, tumour staging including vascular involvement, and the number of passes made were documented prospectively at the EUS examination. Oral ciprofloxacin, 500 mg twice a day for 3 days, was given after the procedure. A 22-gauge needle (EUS N1 needle; Cook Endoscopy, Winston-Salem, NC) was used to perform the aspiration. Aspirates were interpreted during the procedure by a cytotechnologist in attendance. Solid lesions underwent multiple passes until the cytotechnologist felt adequate cellular material was obtained. One extra pass then was made, and all contents were directly injected into 10 mL of RPMI-1640 tissue culture medium; this extra pass is reflected in the number of passes per lesion recorded. The needle then was inserted into this fluid, and both the syringe and needle were rinsed. This specimen was immediately processed and stored at -80 degrees F. All patients	Malignant vs benign lesions Cytology results Sens=0.85 (95%CI, 0.72-0.94) Sp=1.0 (95%CI, 0.55-1.0) Calculated from above data: PPV=1.0 NPV=0.4149 Adverse events Not reported	Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of applicability See ROB/applicability section below for full details.

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
To determine the sensitivity and specificity of telomerase activity for neoplasia in a series of EUS-FNA biopsies of pancreatic mass lesions. Study dates: 01/2002-06/2003 Source of funding: Grant from American Cancer Society (ACS IRG-93-035-6).			also had telomerase activity assessed using EUS-FNA samples.		
Full Citation Ramesh, J., Bang, J. Y., Hebert-Magee, S., Trevino, J., Eltoum, I., Frost, A., Hasan, M.K., Logue, A., Hawes, R. & Varadarajulu, S. (2015). Randomized trial comparing the flexible 19G and 25G needles for endoscopic ultrasound-guided fine needle	Sample size N=100 consecutive patients with suspected solid pancreatic lesion (19G group, n=50; 25G group, n=50) Characteristics of 19G group Mean age (years)=68.1 (11) Gender (M/F)=31/19 Lesion location=30 head/uncinate process, 12 body, 8 tail	Index test 1=EUS-FNA with 19-gauge needle Index text 2=EUS-FNA with 25-gauge needle Reference test=Histology	Type of imaging used to identify abnormality: CT Do participants have jaundice? No Methods Randomisation Computer-generated randomization assignments were obtained before study enrolment using the block randomization method by the statistician. These were then placed in sequentially numbered sealed opaque envelopes and opened by the endoscopy nurse during the procedure when patients met criteria for study inclusion. Patients were randomized equally to the 2 needle types (1:1 allocation).	Malignant vs benign lesions EUS-FNA 19-gauge Calculated from 41 malignant (TP), 7 benign (TN) and 2 failed onsite diagnosis (=FN) Sens=0.954 Sp=1.0 PPV=1.0 NPV=0.78 EUS-FNA 25-gauge Calculated from 40 malignant (TP), 6	Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of applicability See ROB section below for full details.

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
aspiration of solid pancreatic mass lesions. Pancreas, 44(1), 128-133. Country/ies where the study was carried out: USA Study type: Prospective multicentre RCT Aim of the study: To compare technical performance of 19G and 25G needles for EUS-FNA of solid pancreatic lesions Study dates: 08/2012-01-2013 Source of funding: None reported	Lesion size (cm)=4.02 (1.4) Characteristics of 25G group Mean age (years)=68.8 (11) Gender (M/F)=30/20 Lesion location=31 head/uncinate, 11 body, 8 tail Lesion size (cm)=34.9 (12.9) Inclusion criteria ≥19 years-old Solid lesion identified by CT scan Exclusion criteria Lesion not identified on EUS Mass has cystic component Abnormal coagulation parameters Final diagnosis in 19-G group Malignant, n=43 (adenocarcinoma=40; other=3) Benign, n=7 (CP=5, other=2)		EUS-FNA procedure Performed by 1 of 5 experienced endosono-graphers at 1 of 2 sites. All pancreatic head and uncinate masses were accessed via the duodenum; all pancreatic body and tail masses sampled via the stomach. All procedures performed using a linear array echoendoscope (Olympus UCT140) with patients in left lateral decubitus position under moderate sedation or after administration of propofol. At EUS, during individual FNA passes, after puncturing the pancreatic mass, stylet was removed, and needle moved to-and-fro, 12 to 16 times, at different areas within the lesion using the fanning technique. Suction not applied, and stylet not reintroduced into the needle after the first pass in any patient. Tissue material expressed onto slides by advancing stylet within the needle assembly. After the initial pass, which was collected in cell block (Hank balanced salt solution; Invitrogen, Grand Island, NY), an attending pathologist blinded to type of needle used processed the subsequent specimens onsite. A maximum of 6 passes (excluding the cell block) were performed using the original needle type, and if there was diagnostic or technical failure, patient underwent crossover to the alternate	benign (TN) and 4 failed onsite diagnosis (=FN) Sens=0.909 Sp=1.0 PPV=1.0 NPV=0.6 Adverse events 19-gauge group 2% complication rate (bleeding during procedure=1) 25-gauge group No adverse events occurred	

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
	Final diagnosis in 25-G group Malignant, n=42 (adenocarcinoma=34; other=8) Benign, n=8 (all CP)		needle. However, if a definitive diagnosis was established during the initial attempt, the procedure was terminated, and the number of passes performed was documented. Onsite cytological analysis Air-dried and alcohol-stained smears prepared on-site after individual passes. Air-dried smears stained with Three-Step Stain (and immediately reviewed by cytopathologist blinded to needle type, to establish the on-site diagnosis and bloodiness of the specimen. Alcohol-stained smears were prepared offsite in the pathology laboratory using the Papanicolaou stain. Histological analysis In the laboratory, a 10-mL vial of Hank balanced salt solution containing collected specimen was placed into the centrifuge, counter-balanced, and spun for 5 minutes. If the specimen quantity was sufficient, the supernatant was removed, and 3 drops of plasma and thrombin were added to the sediment. Upon formation of a clot, the cell button was removed intact, enclosed in a Tissue-Loc HistoScreen cassette and fixed in formalin. The cassette was processed, embedded in paraffin, and then prepared in hematoxylin and eosin to be evaluated for the presence of a histological core. Core tissue was		

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
			quantified using cellSens. When required, immunohistochemical or special staining was performed for the differentiation of morphologically challenging lesions.		
Full Citation Seicean, A., Gheorghiu, M., Zaharia, T., Calinici, T., Samarghitan, A., Marcus, B., Cainap, S. & Seicean, R. (2016). Performance of the Standard 22G Needle for Endoscopic Ultrasound-guided Tissue Core Biopsy in Pancreatic Cancer. J Gastrointestin Liver Dis, 25(2), 213-218. Country/ies where the study was carried out: Romania	N=118 patients with suspected PC due to solid pancreatic mass Characteristics Mean age (years)=63.25 (9.77 (range 40-83) Gender (M/F)=59/59 Lesion location=77 head+uncinated process, 33 body, 8 tail Lesion size (cm)=3.56 (1.14) Inclusion criteria Solid pancreatic mass on CT Solid component >80% total lesion volume Informed consent Exclusion criteria Prior surgical treatment or chemoradiotherapy for pancreas disease	Index test=EUS-FNA Reference test=EUS, EUS-FNA, hepatic biopsy, or quarterly follow up Gold standard was the EUS-FNA (core biopsy) pathology result (n=96); a second EUS-FNA was proposed if results were non-conclusive with a high susceptibility of malignancy (n=8), or by hepatic biopsy of their metastasis (n=3) or they were followed up to 6 months by clinical examination and abdominal ultrasound at 3-month intervals, with repeated spiral CT / EUS if needed (n=11).	Type of imaging used to identify abnormality: CT Do participants have jaundice? No Methods All patients first examined using linear echoendoscope (Olympus GF-UCT140 AL5) in conjunction with Aloka Alpha 5 or 7 ultrasound unit with patient under light i.v. midazolam sedation under continuous real-time US guidance using 22-gauge needle. Stylet left inside needle with slow pull during puncture, without suction, and fanning technique performed wherever possible. Between 1 and 3 passes made until macroscopic length of visible core superior to 0.5 cm. Core expelled by reintroduction of stylet and placed in 10% buffered formalin. After FNA, patients observed for immediate adverse events for at least 2 hours. Contact maintained for 24 hours post-procedure to monitor for moderate or severe events. After fixation, issue processed as standard then processed by paraffin embedding with haematoxylin-eosin	Malignant vs benign lesions After first EUS-FNA (n=111; 7 patients excluded due to inadequate sample or without histological core but with atypia) Sens=0.89 (95%CI, 0.911-0.939) Sp=1.0 (95%CI, 0.735-1.0) PPV=1.0 (95%CI, 0.97-1.0) NPV=0.5 (95%CI, 0.435-0.632) (If 7 excluded patients treated as FN then Sens=0.832 Sp=1.0 PPV=1.0 NPV=0.379)	Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of applicability See ROB/applicability section below for full details.

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
Study type: Tertiary single-centre prospective cohort Aim of the study: To establish diagnostic yield of the length of the visible core biopsy samples in pancreatic cancer by using the same type of 22G needle, and the factors which can influence the results. Study dates: 09/2014-04/2015 Source of funding: None reported	Cystic pancreatic tumour or duodenal stenosis Lost to follow up Coagulopathy (INR>1.5) Trombocytopenia (<60,000/mm3) Final diagnosis Malignant, n=107 (Adenocarcinoma=103 ; other=4) Benign, n=11 (CP=11)		staining. Samples blindly examined by one pathologist. Positive specimens were those categorized as unequivocally positive for malignancy. Only core biopsy was taken into consideration and a specimen was deemed adequate for histological examination when it contained coherent tissue sample from the target organ, which measured more than half of a field with a lengthwise magnification of 40x. Specimens that contained inadequate material or atypia were not excluded from our analysis, but were considered negative.	After second EUS-FNA (8 patients from the 11 false negative cases accepted to have EUS-FNA repeated) Sens=0.93 (95%CI, 0.911-0.939) Sp=1.0 (95%CI, 0.735-1.0) PPV=1.0 (95%CI, 0.97-1.0) NPV=0.63 (95%CI, 0.894-0.944). Adverse events No EUS-FNA-related events reported.	
Full Citation Strand, D. S., Jeffus, S. K., Sauer, B. G., Wang, A. Y., Stelow, E. B., & Shami, V. M. (2014). EUS-guided 22-gauge fine-needle aspiration versus	N=32 patients with suspected PC due to solid mass Characteristics Mean age (years)=67.8 (13.3) Gender (M/F)=13/19 Lesion location=23 head, 6 body, 3 tail	Index test 1=EUS-FNB Reference test=EUS-FNA cytology	Type of imaging used to identify abnormality: Cross-sectional, type not stated Do participants have jaundice? 12 patients had jaundice (38%). Methods All patients received both EUS-FNA and EUS-FNB using high definition endoscope (Olympus GIF-H180/GIF-H180J) and linear echo-endoscope	Malignant vs benign lesions EUS-FNB (reference test=EUS-FNA) Sens=0.25 (95%CI, 0.1-0.47) Sp=0.88 (95%CI, 0.47-1.0)	Quality of study assessed using QUADAS-2: Overall unclear risk of bias. Overall low risk of applicability See ROB section below for full details.

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
core biopsy needle in the evaluation of solid pancreatic neoplasms. Diagnostic cytopathology, 42(9), 751-758. Country/ies where the study was carried out: USA Study type: Prospective cohort study Aim of the study: To examine ability of 22G EUS-FNB to obtain core biopsy specimens and compare it to cytology from 22G EUS-FNA. Study dates: 11/2011-09/2012 Source of funding: None reported	ECOG score=0.781 (0.75) Presenting symptoms: pain =14; jaundice=12; weight loss=23 Inclusion criteria Aged 18-90 years-old Patient at subspecialty clinic or university hospital-based endoscopy unit from Nov 2011 Evidence of solid pancreatic mass lesion (>60%) by cross sectional imaging Patients who had previously received percutaneous or EUS-guided tissue acquisition were eligible Exclusion criteria No mass identified on EUS Predominantly cystic lesion (>40%) Known uncorrectable coagulopathy No pancreatic tissue sampling during study procedure		(Olympus GF-UCT140/GF-UC140P) performed by 1 of 3 experienced endoscopists. Procedural sedation determined at discretion of endoscopist/anaesthesiologist. Following identification of solid lesion, tissue sampling performed using 22G FNA and 22G FNB. Order of sampling alternated sequentially with patient enrolment. Immediate complications noted. EUS-FNA Mass identified and overlying vasculature excluded using colour Doppler. FNA device advanced into lesion, and stylet then removed and needle moved back and forth within lesion. Tissue material evacuated onto slide. Maximum of 5 passes (alternating FNA/FNB) allowed if on-site analysis equivocal or negative for diagnosis. EUS-FNB Mass punctured as above; stylet removed and 10-mL suction syringe attached in closed position. Syringe opened to provide suction for 30s and needle moved to-and-fro within lesion. Suction removed and needle withdrawn. Contents evacuated onto slide as above. Maximum of r2 core biopsy passes performed (alternating with FNA) until adequate sample collected. Onsite evaluation of all FNA material performed by cytopathologist. Air dried	PPV=0.86 (95%CI, 0.46-0.98) NPV=0.28 (95%CI, 0.22-0.36) Note: calculated from TP=6, FP=1, FN=18 and TP=7; data from available diagnosis by FNA and FNB, treating technical failures (n=5), tissue attrition during processing (n=8), and remaining disagreement with FNA diagnosis (n=5) diagnosis as false negatives; there was one case which both FNA and FBB diagnosed as PNET (assumed by technical team to be malignant); PPV and NPV and related 95%CIs was also calculated by technical team. Adverse events There were no procedure-related complications. Four	

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
	Final diagnosis (EUS-FNA cytology) Malignant, n=24 PAC=20; other=4 Benign/atypical, n=8		Diff Quick stained smears used for ROSE. Alcohol fixed stains prepared with Pap stain. FNB was formalin fixed, processed, paraffin embedded and stained with haematoxylin and eosin. Cytology and core biopsy specimens subsequently reviewed by one cytopathologist.	patients developed abdominal pain or pancreatitis within 30 days of EUS procedures but this was deemed to be due to ERCP, biliary sphincterotomy, and trans-papillary stent placement for relief of obstructive jaundice.	
Full Citation Tamm, E. P., Loyer, E. M., Faria, S. C., Evans, D. B., Wolff, R. A., & Charnsangavej, C. (2007). Retrospective analysis of dual-phase MDCT and follow-up EUS/EUS-FNA in the diagnosis of pancreatic cancer. Abdominal imaging, 32(5), 660-667. Country/ies where the study was carried out:	N=117 patients with suspected PC due to solid mass Characteristics Mean age (years)=69 (range 48-89) Gender (M/F)=63/54 Lesion location=not reported Lesion size (cm)=2.9 (1.39); #<2 cm=27 Inclusion criteria Had MDCT and follow-up EUS Definite or questionable tumours identified on CT Exclusion criteria Cystic mass	Index test 1=Multidetector CT Index test 2=EUS Index test 3=EUS-FNA Reference test= Histopathologic findings in either biopsy or surgical specimens. In cases in which the biopsy findings were negative, chart reviewed to determine the follow-up and stability of the patient's condition over a period of at least 9 months. Patients with	Type of imaging used to identify abnormality: MDCT Do participants have jaundice? No Methods All patients had CT then EUS. Multidetector CT (MDCT) Scans obtained with four-detector-row CT scanner (Lightspeed Plus; General Electric Medical Systems, Milwaukee, WI, USA) using dual-phase pancreatic protocol. Each phase obtained from the level of the diaphragm to below the horizontal portion of the duodenum. First phase obtained at a 2.5-mm slice thickness at a table speed of 7.5 mm/s, reconstructed to 1.25-mm contiguous images. Second phase was obtained at a 5-mm slice thickness at a table speed of 15 mm/s, reconstructed to 2.5-mm	Malignant vs benign lesions MDCT Sens=0.97 (95%CI, 0.91-0.99) Sp=0.72 (95%CI,0.46-0.89) PPV=0.95 (95%CI, 0.88-0.98) NPV=0.81 (95%CI, 0.54-0.95) EUS Sens=0.99 (95%CI, 0.94-0.99) Sp=0.5 (95%CI, 0.27-0.73) PPV=0.92 (95%CI, 0.84-0.95)	Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of applicability See ROB/applicability section below for full details.

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
USA Study type: Single centre retrospective cohort Aim of the study To compare the sensitivity, specificity, and accuracy of dual-phase MDCT and follow-up EUS, with or without FNA, in the detection of pancreatic cancers regardless of tumor size and in the detection of small tumors (<2 cm). Study dates: Not reported Source of funding: None reported	Hypervascular mass suggestive of neuroendocrine tumour Final diagnosis Malignant, n=99 (Adenocarcinoma=95; other=4) Benign, n=18 (CP=10; other=8)	indeterminate histopathologic proof or insufficient follow-up in the event of negative CT or EUS findings were excluded from this analysis.	contiguous images. After insertion of an 18- or 20-gauge catheter into an antecubital vein, 150 ml of ioversol at a concentration of 350 mg I/ml (Optiray) injected at a rate of 5 ml/s. First phase obtained beginning at 25 s and the second phase at 55 s after the start of contrast injection. This protocol allowed for the pancreas to be imaged approximately 35–45 s after the start of contrast injection during the first phase. The images were transferred to a Picture Archiving and Communications System, or PACS (iSite; Stentor, Brisbane, CA, USA). All images (the 5-, 2.5-, and 1.25-mm-thick sections) were available for soft copy review by the three radiologists participating in this study. MDCT images reviewed on PACS reading station independently by 3 radiologists in abdominal imaging section. Baseline CT images reviewed without knowledge of the clinical, pathologic, or surgical data. Each radiologist indicated whether tumour was present or absent on a 5-point scale of confidence, with one representing definite presence of tumour and five representing definite absence of tumour. This score was based on a combined assessment for a hypodense mass, deformity of the pancreatic contour, pancreatic duct dilatation and/or cutoff, secondary vascular involvement, and liver metastases	NPV=0.9 (95%CI, 0.54-0.99) EUS-FNA Sens=0.82 (95%CI, 0.74-0.89) Sp=0.94 (95%CI, 0.17-1.0) PPV= 0.99 (95%CI, 0.93-1.0) NPV= 0.5 (95%CI, 0.33-0.67) Adverse events None reported	

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
			EUS Performed using radial and linear endoscopic sonography Olympus EUM-30 (Olympus), and Pentax FG-32A. EUS performed with knowledge of the MDCT findings. Any mass identified by EUS was biopsied at the time of the endoscopic examination. A statement indicating that a ‘‘mass’’ or ‘‘tumour’’ had been identified, or words to that effect, was interpreted as a positive reading for tumour. In those cases where the MDCT study was read as negative for tumour by one or more of the three radiologists, and the EUS was reported as positive, the hardcopy printed images from the EUS study in the patients paper chart were reviewed to confirm the presence of a mass. The FNA results from only the initial EUS examination at our institution (if more than one had been done) were used for calculating the sensitivity, specificity, and accuracy of EUS.		
Full Citation Touchefeu, Y., Le Rhun, M., Coron, E., Alamdari, A., Heymann, M. F., Mosnier, J. F., Matysiak, T. & Galmiche, J. P. (2009). Endoscopic	N=90 consecutive patients with suspected PC due to solid mass Characteristics Mean age (years)=66 (range 24-90) Gender (M/F)=not reported	Index test=EUS-FNA Reference test= Gold standard for patients undergoing surgery was histological analysis (n=20); in patients who did not have surgery, gold standard was	Type of imaging used to identify abnormality: Abdominal CT Do participants have jaundice? No Methods EUS-FNA performed by one of two authors. No antibiotic prophylaxis given before procedures. Radial echoendoscope EUS examination with Pentax EG3630 RT, then EUS-FNA with linear Pentax EG3830 UT using 22-gauge	Malignant vs benign lesions Cytology and histology Sens=0.78 Sp=0.75 (Calculated from available data PPV=0.96	Quality of study assessed using QUADAS-2: Overall high risk of bias (reference standard/flow and timing) Overall low risk of applicability

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
ultrasound-guided fine-needle aspiration for the diagnosis of solid pancreatic masses: the impact on patient-management strategy. Alimentary pharmacology & therapeutics, 30(10), 1070-1077. Country/ies where the study was carried out: France Study type: Single-centre prospective cohort Aim of the study: To investigate the diagnostic yield and the therapeutic impact of EUS-FNA in the management of solid pancreatic masses Study dates: 01/2005-01-2009 Source of funding:	Lesion location=63 head, 14 body, 8 isthmus, 3 tail, 4 uncinate Lesion size (cm)=3.57 (0.8-7) Inclusion criteria Consecutive referrals Preliminary CT scan of abdomen No prior biopsy Solid pancreatic mass Suspicion of malignancy Clinically-relevant doubt of management decision Exclusion criteria None reported Final diagnosis Malignant, n=80 (Pancreatic adenocarcinoma=71; other=9) Premalignant., n=5 Benign, n=5 (CP=4)	additional investigations (e.g. a second EUS-FNA [n=4], CT biopsy [n=4], surgical biopsy [n=1]). Final diagnosis also established by follow up (e.g. in case of death or disease progression; or cases whether clinical/imaging reassessment shows stability or regression after minimum of 6 months [n=61])	needles. Colour Doppler used to exclude interposing vascular structures. Needle introduced under EUS guidance, approx. 10 passes while maintaining needle aspiration. Needle then removed. Procedure repeated twice in different areas of mass. Aspirates placed into glass slides for cytological examination, with larger fragments fixed in formaldehyde for histological examination. No onsite cytopathological examination. Slides stained with Giemsa, microbiopsies with Haematoxylin-eosin0safran. Immunohistochemistry performed if useful. Patients observed for 12 hours before leaving hospital.	NPV=0.30) Cytology only Sens=0.72 Sp=0.75 Histology only Sens=0.43 Sp=1.0 Adverse events One case of fever and one case of abdominal pain. No major complications.	See ROB/applicability section below for full details.

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
None reported					
Full Citation Wakatsuki, T., Irisawa, A., Bhutani, M. S., Hikichi, T., Shibukawa, G., Takagi, T., Yamamoto, G., Takahashi, Y., Yamada, Y., Obara, K., Suzuki, T. & Sato, Y. (2005). Comparative study of diagnostic value of cytologic sampling by endoscopic ultrasonography-guided fine-needle aspiration and that by endoscopic retrograde pancreatography for the management of pancreatic mass without biliary stricture. Journal of gastroenterology and	N=83 patients with suspected solid pancreatic mass (includes EUS-FNA, n=53; ERCP, n=30) Characteristics for EUS-FNA group Mean age (years)=60 (12) Gender (M/F)=40/13 Lesion location=23 head, 24 body, 6 tail. Lesion size (cm)=3.42 (1.37) Inclusion criteria Suspected pancreatic mass without biliary stricture on US and/or CT Enrolled from 10/1997 to 12/2003 Exclusion criteria Cystic mass Final diagnosis in EUS-FNA group Malignant, n=43 (Adenocarcinoma=38; other=5) Benign, n=10 (CP=7; Other=3)	Index test=EUS-FNA Reference test=gold standard was composite including surgery, autopsy and long-term FU (>6 months).	Type of imaging used to identify abnormality: Transabdominal US and/or CT Do participants have jaundice? No Methods ERCP performed from 10/1997 to 12/2000 in all patients; although ERP was performed as initial test, in some patients, however, EUS-FNA was performed as the first endoscopic procedure. EUS-FNA performed for cases in which cytology on ERP was negative or cell samples were not collected. In addition, EUS-FNA was performed first for cases in which histological evidence of malignancy was needed before chemotherapy. The EUS-FNA and ERP examinations were performed by six experienced endoscopists and endosonographers, each with more than 5 years of experience of endoscopy. EUS-FNA Performed using linear array echoendoscope (Pentax 36-UX or Olympus GF-UCT240 AL-5) using 22-gauge automated spring-loaded powershot needle device. Colour Doppler used to identify vascular anatomy. Needle moved back and forth while suction applied using 10 ml syringe. Cytopathologist present in endoscopy room during procedure to assess	Malignant vs benign lesions EUS-FNA group only (all patients, n=53) Sens=0.929 Sp=1.0 PPV=1.0 NPV=0.786 EUS-FNA group only (n=47, patients with adenocarcinoma and ductal abnormalities) Sens=0.921 Sp=1.0 PPV=1.0 NPV=0.75 Adverse events No major or minor complications reported. Serum amylase level 24h before EUS-FNA=201.1 (229.1) IU/L Serum amylase level 24h after EUS-	Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of applicability See ROB/applicability section below for full details.

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
hepatology, 20(11), 1707-1711. Country/ies where the study was carried out: Japan Study type: Single-centre retrospective cohort Aim of the study: To compare value of cytology obtained by EUSFNA with that by endoscopic retrograde pancreatography (ERP), and to assess the complications associated with these procedures Study dates: 10/1997-12/2003 Source of funding: None reported			adequacy; samples stained using Diff-Quik on glass slides. Procedure halted when samples adequate. All patients given prophylactic antibiotics by drip infusion and/or by opening for 3 days. Adverse events All patients observed prospectively for post-endoscopic procedure complications. Clinical symptoms after the procedures carefully evaluated. Blood sample was obtained to measure the serum amylase level, an inflammatory maker (C-reactive protein [CRP]) and hematologic profiles before and 24 h after EUS-FNA or ERP. Pancreatitis as a post-procedure complication was diagnosed when abdominal pain and a fourfold elevation of serum amylase 24 h after the procedures were observed.	FNA=216.3 (216.8) IU/L No pancreatitis in EUS-FNA group.	
Full Citation Wittmann, J., Kocjan, G.,	N=83 consecutive patients with	Index test 1= EUS-FNA	Type of imaging used to identify abnormality: Percutaneous biopsy under transabdominal US or CT-guidance.	Malignant vs benign lesions	Quality of study assessed using QUADAS-2:

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
Sgouros, S. N., Deheragoda, M., & Pereira, S. P. (2006). Endoscopic ultrasound-guided tissue sampling by combined fine needle aspiration and trucut needle biopsy: a prospective study. Cytopathology, 17(1), 27-33. Country/ies where the study was carried out: UK Study type: Single-centre prospective cohort Aim of the study: To evaluate the safety and the relative merits of EUS-FNA and EUS-TNB, with particular reference to the advantage of EUS-FNA/TNB for lesions within or in close proximity to	suspected malignant solid pancreatic lesion Characteristics of pancreatic lesion group (n=83) Mean age (years)=61 (13) Gender (M/F)=46/37 Lesion location=not reported Lesion size (cm)=3 (2.1; range 0.4-8) Inclusion criteria Had EUS-tissue sampling from 05/2002 to 04/2005 Exclusion criteria for EUS-FNB using trucut needle lesion size <2 cm in diameter Lesions approachable from second part of duodenum only Cystic lesions without associated mass component Uncorrected coagulopathy Failure to obtain consent	Index test 2=EUS-TNB Index test 3=EUS-FNA+TNB Reference test=Patients with malignancy gold standard was cytology (EUS-FNA), histology (EUS-TNB), or surgical resection; benign patients, confirmed by clinical FU.	Do participants have jaundice? No Methods First-line investigation was percutaneous biopsy under transabdominal US or CT-guidance. EUS-guided sampling reserved for patients with (1) inconclusive diagnosis with percutaneous biopsy, (2) easier/safer access to lesion using EUS, or (3) lesion too small for percuteous biopsy. EUS performed under midazolam and fentanyl sedation by experienced endoscopist using standard protocol of up to max 4 FNAs and 3 TNBs of lesion. EUS-FNA Lesions <2 cm EUS-FNA maximum 4 passes; lesions ≥2 cm, additional 19-gauge TNB performed with max. 3 passes. 22-gauge needle in conjunction with linear array echoendoscope with 2.8mm accessory channel (Olympus GIF UC 30P; Pentax 38UX). Sampling performed using real time EUS guidance and Doppler examination. Needle visualised throughout procedure. Needle moved back and forth up to 40 times during each pass, whilst applying suction using 10 ml syringe. Aspirated material thinly smeared and alcohol fixed. EUS-FNB	Pancreatic lesion group EUS-FNA (n=83) Sens=0.6 Sp=1.0 PPV=1.0 NPV=0.65 EUS-FNB only (n=36) Sens=0.41 Sp=1.0 PPV=1.0 NPV=0.36 EUS-FNA + FNB only (n=36) Sens=0.76 Sp=1.0 PPV=1.0 NPV=0.65 Adverse events Complications (n=159)=0.6% Complications in pancreatic lesion group (n=83)=0.6% One patient in EUS-FNA+Core group, who did not require analgesia, reported one day of	Overall low risk of bias. Overall low risk of applicability See ROB/applicability section below for full details.

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
the gastrointestinal tract, and to determine whether histology conferred additional clinical benefit to cytological assessment alone. Study dates: 05/200204/2005 Source of funding: None reported	Final diagnosis (pancreatic lesion group only) Malignant, n=43 Benign, n=40		Performed using 19-gauge outer cutting needle, which has 20mm tissue tray. Tissue core placed into specimen container containing formalin (4% formaldehyde). Patients monitored for at least 2 hours in endoscopy recovery bay, discharged when fully awake and pain free. Follow up 24 hours and 7 days after procedure. Cytopathological preparations from EUS-FNA spray fixed in 95% alcohol or air-dried in even proportions. FNA needle flushed using sterile saline after each biopsy pass.	moderate self-limiting abdominal pain after biopsy of a pancreatic tail lesion.	
Full Citation Yang, R. Y., Ng, D., Jaskolka, J. D., Rogalla, P., & Sreeharsha, B. (2015). Evaluation of percutaneous ultrasound-guided biopsies of solid mass lesions of the pancreas: a center's 10-year experience. Clinical imaging, 39(1), 62-65. Country/ies where the study was carried out:	N=88 consecutive patients with suspected PC due to solid mass Characteristics Mean age (years)=66 (range 29-87) Gender (M/F)=43/45 Lesion location=64 head/neck, 21 body/tail, 3 unclear Lesion size=not reported Inclusion criteria Consecutive patients who underwent percutaneous US-guided biopsy due to	Index test 1 = Percutaneous US-guided Core Index test 2= Percutaneous US-guided- FNA Index test 3= Percutaneous US-guided Core+FNA Reference test=Surgical pathology (n=12), Follow up imaging and clinical course (n=76) A biopsy result was considered true	Type of imaging used to identify abnormality: CT, MRI, US, or combination of these Do participants have jaundice? No Methods All biopsies performed by 1 of 14 trained radiologists with at least 7 years US-guided experience. Percutaneous US-guided biopsies performed with transducers ranging from 2.5 to 5.0 MHz. Before sampling, lesion routinely studied with grayscale and Doppler US and relation to adjacent blood vessels assessed prior to choosing suitable route. Coaxial (17-gauge introducer needle and matching 18-gauge core biopsy needles) or non-coaxial technique (18-gauge needle) used to perform core biopsy; FNA, tissue sampling used 22-gauge	Malignant vs benign lesions All (n=88) Sens=0.925 (95%CI, 0.87-0.98) Sp=1.0 PPV=1.0 NPV=0.571 (95%CI, 0.312-0.831). Core (n=60)* Sens=0.926 (95%CI, 0.82-0.98) Sp=1.0 (0.54-1.0) PPV=1.0 NPV=0.6 (95%CI, 0.37-0.79)	Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of applicability See ROB/applicability section below for full details.

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
Canada Study type: Multicentre tertiary retrospective cohort Aim of the study: To assess the effectiveness of percutaneous US-guided pancreatic mass biopsy and to determine whether the type of biopsy (core vs. FNA vs. combined core and FNA) or the location of the mass in the pancreas affects the diagnostic yield Study dates: 01/2001-11/2011 Source of funding: None reported	discovery of mass on imaging Exclusion criteria Biopsy of transplanted pancreas CT-guided biopsy Final diagnosis Malignant, n=74 Non-malignant, n=14	negative if pathology was negative for malignancy without subsequent evidence (such as follow-up imaging or repeat pathology) suggestive of malignancy. A biopsy result was considered false negative if pathology was negative for malignancy but additional evidence suggested malignancy. Finally, a biopsy result was considered false positive if pathology was positive for or strongly suggestive of malignancy but further evidence resulted in an alternative diagnosis if pathology was positive for or strongly suggestive of malignancy but further evidence resulted in an alternative diagnosis.	needle either directly or with coaxial technique through 17-gauge introduced needle. Number of cores obtained and aspirations performed determined by radiologist. When FNA performed, sample adequacy assessed by onsite cytologist whenever possible. Biopsies generally performed using anterior approach with patient in supine position. Procedures performed under local anaesthesia and conscious fentanyl and midazolam i.v. sedation. Patients monitored for 4h prior to discharge.	*reported CIs do not match provided data, recalculated using reported sens/NPV FNA (n=13)* Sens=0.923 (95%CI, 0.778-1.0) Sp=not calculable (no false positive nor true negatives) PPV=1.0 NPV=0 (detected no true negative sample, and 1 non-diagnostic sample) *Not included in review Core + FNA (n=15)* Sens=0.923 (95%CI, 0.0.64-1.0) Sp=1.0 PPV=1.0 NPV=0.667 (95%CI, 0.16-1.0) *reported CIs do not match provided data, recalculated using reported sens/NPV Adverse events	

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
				Procedure was uneventful in ~97% of cases. In one patient who underwent core biopsy only, a small hematoma developed around the portal vein immediately after the biopsy was taken. Follow-up evaluation showed no adverse consequences. Two Patients experienced pain without clinically significant findings immediately after the biopsy. One of them underwent core biopsy only, the other had core+FNA biopsies. No major complication was found in any patient. No patients were lost to follow-up. Also, there were no differences in complication rates relating to type of	

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
				biopsy or location of biopsy.	
Full Citation Yusuf, T. E., Ho, S., Pavey, D. A., Michael, H., & Gress, F. G. (2009). Retrospective analysis of the utility of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) in pancreatic masses, using a 22-gauge or 25-gauge needle system: a multicenter experience. Endoscopy, 41(05), 445-448. Country/ies where the study was carried out: USA Study type: Multisite tertiary retrospective cohort	22-gauge group=540 consecutive patients with suspected PC due to solid mass 25-gauge group=302 consecutive patients with suspected PC due to solid mass Characteristics 22-gauge group Mean age (years)=65 (range 18-91) Gender (M/F)=300/240 Lesion location=410 head, 100 body, 23 tail, unspecified=7 Lesion size=not reported Characteristics 25-gauge group Mean age (years)=69 (range 18-91) Gender (M/F)=172/130 Lesion location=not reported Lesion size=not reported Inclusion criteria	Index test 1=EUS-FNA with 22-gauge needle Index test 2=EUS-FNA with 25-gauge needle Reference test=Surgical histopahology or long-term FU 22-gauge Surgical histopathology (n=159); long-term FU (n=380) [mean FU=6.5 months] 25-gauge Surgical histopathology (n=82); long-term FU (n=220)	Type of imaging used to identify abnormality: EUS for 22-gauge group; CT and/or MRI. Confirmed by EUS, for 25-gauge group Do participants have jaundice? No Methods EUS performed using radial echoendoscope (Olympus GF-UM20) or linear-array echoendoscope (Pentax FG36UX/FG38UX or Olympus GFUCT140) using standard techniques. EUS-FNA with GIP FNA 22-gauge or 25-gauge needle system. Cytopathologist available in room for immediate specimen evaluation in 90% cases in both 22- and 25-gauge groups. All patients monitored for intra- and post-procedural complications as standard protocol; called 24 hours after procedure to check for complications.	Malignant vs benign lesions 22-gauge group (n=540) Sens=0.84 Sp=1.0 PPV=1.0 NPV=0.73 Ref +ive / Ref -ive +ive 314 / 0 -ive 60 / 166 25-gauge group (n=302) Sens=0.92 Sp=0.97 PPV=0.98 NPV=0.87 Ref +ive / Ref -ive +ive 180 / 3 -ive 16 / 103 Adverse events Complication rate=2% (11 of 540 patients had mild post-procedural	Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of applicability See ROB/applicability section below for full details.

Study details	Participants	Index and reference tests	Description	Outcomes	Overall Risk of bias/Applicability (Low/High/Unclear)
Aim of the study: To evaluate performance of the 22-gauge and 25-gauge needles in obtaining cytologic diagnosis of solid pancreatic masses. Study dates: 02/2001-06/2007 Source of funding: None reported	Patients referred for EUS-FNA between 02/2001 and 06/2007 Exclusion criteria None reported Final diagnosis 22-gauge Malignant, n=374 Benign, n=166 25-gauge Malignant, n=196 Benign, n=106			pancreatitis that resolved with supportive therapy. No intra- nor post-procedural complications reported in 25-gauge group)	

F.31 Pancreatic Cysts

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
Full citation Ardengh JC, Lopes CV, de Lima LF, de Oliveira JR, Venco F, et al. Diagnosis of pancreatic tumours by endoscopic ultrasound-guided fine-needle aspiration. World J Gastroenterol. 2007 Jun 14;13(22):3112-6. Ref Id 523148	Sample size n=197 Characteristics M/F (n): n.r./n.r. Median age (range): n.r.	Index test 1 (n= 196): EUS-FNA cytology Final diagnosis: Benign (n): 44 Malign (n): 152 Reference standard: The final diagnosis was based on surgical findings or by a mean clinical follow-up of 11.8 months (356 and 255 respectively, numbers refer to the overall cohort of patients - n==611)	EUS-FNA cytology T + | F - | F + | T - 30 | 14 | 8 | 144 Diagnostic accuracy Sensitivity Specificity NPV PPV Adverse events/complications* (Five patients developed FNA-related minor complications -fever in 2 after puncturing of cystic lesions,	Limitations QUADAS 2 checklist Patient selection Risk of bias: Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? yes Could the selection of participants have introduced bias? Low risk Applicability:

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
Country/ies where the study was carried out: Brazil Study type: Retrospective observational study Aim of the study To evaluate the diagnostic accuracy of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) for pancreatic solid tumours larger or smaller than 3 cm, and cystic lesions. Study dates Data collection: 1997-2006 Study publication: 2007 Source of funding: n.r.			acute pancreatitis in 2 and haemorrhage in 1)	Is there concern that the included participants do not match the review question? Low concern Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Unclear (no details given in the report) If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Unclear risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low concern Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear (no information given about blinding) Could the reference standard, its conduct or interpretation have introduced bias? Unclear risk Applicability: Is there concern that the target condition as defined by the reference

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests and methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>standard does not match the review question? Low concern
Flow and timing
Risk of bias:
Was there an appropriate interval between index tests and reference standard? Unclear (no details given in the report)
Did participants receive the same reference standard? Not
Were all patients included in the analysis? Yes
Could the participant flow have introduced bias? High risk
Overall risk of bias: Serious risk of bias</td></tr>
<tr><td>Full citation
Brugge WR, Lewandrowski K, Lee-Lewandrowski E, Centeno BA, Szydlo T, et al. Diagnosis of pancreatic cystic neoplasms: a report of the cooperative pancreatic cyst study. Gastroenterology. 2004 May;126(5):1330-6.
Country/ies where the study was carried out: USA
Study type: Prospective observational study (multicentre)
Aim of the study:</td><td>Sample size
n=112
Characteristics
M/F (n): 41/71
Mean age (yr): 60.1</td><td>Index test 1 (n=111): Cyst fluid CEA -192 ng/ml
Final diagnosis:
Mucinous(n): 56
Non-mucinous(n):55
Index test 2 (n=111): EUS
Final diagnosis:
Mucinous(n): 56
Non-mucinous(n): 55
Index test 3 (n=110): EUS-FNA cytology
Final diagnosis:
Mucinous(n): 56
Non-mucinous(n): 54</td><td>1) Cyst fluid CEA
<table><tr><td>T +</td><td>F -</td><td>F +</td><td>T -</td></tr><tr><td>42</td><td>14</td><td>9</td><td>46</td></tr></table>Diagnostic accuracy
Sensitivity
Specificity
NPV
PPV
2) EUS
<table><tr><td>T +</td><td>F -</td><td>F +</td><td>T -</td></tr><tr><td>31</td><td>25</td><td>30</td><td>25</td></tr></table>Diagnostic accuracy
Sensitivity
Specificity
NPV
PPV</td><td>Limitations
QUADAS 2 checklist
Patient selection
Risk of bias:
Was a consecutive or random sample of patients enrolled? Yes
Was a case-control design avoided? Yes
Did the study avoid inappropriate exclusions? yes
Could the selection of participants have introduced bias? Low risk
Applicability:
Is there concern that the included participants do not match the review question? Low concern
Index tests</td></tr>
</table>

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
To determine the most accurate test for differentiating mucinous from nonmucinous cystic lesions Study dates: Data collection: 1999-n.r. Study publication: 2004 Source of funding: n.r.		Reference standard: The final diagnosis was based on surgical histopathology (n=111)	Adverse events/complications** 3) EUS-FNA cytology T + | F - | F + | T - 19 | 36 | 9 | 45 Diagnostic accuracy Sensitivity Specificity NPV PPV Adverse events/complications**	Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Yes If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Low risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low concern Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Yes Could the reference standard, its conduct or interpretation have introduced bias? Low risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low concern Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Yes

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests and methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Did all participants receive a reference standard? Yes
Did participants receive the same reference standard? Yes
Were all patients included in the analysis? Yes
Could the participant flow have introduced bias? Low risk
Overall risk of bias: Serious risk of bias</td></tr>
<tr><td>Full citation
Cao S, Hu Y, Gao X et al. (2016) Serum Carbohydrate Antigen 19-9 in Differential Diagnosis of Benign and Malignant Pancreatic Cystic Neoplasms: A Meta-Analysis. PLoS One 11(11): e0166406
Ref Id
608475
Country/ies where the study was carried out: Canada (n=1); China(n=1); Germany(n=1); Italy(n=1); Japan(n=4); Korea (n=2); USA(n=3)
Study type: Systematic review -SR
Aim of the study:
To evaluate the diagnostic value of serum CA 19-9 in</td><td>Sample size
SR
n=16 studies (n=1437)
Included studies
Where possible data was extracted from the SR. The full copy of the study was checked for accuracy and completeness.
Goh et al. 2008
Included (n): (n=176)
Analysed (n): (n=137)
Xu et al. 2011
Included (n): (n=86)
Analysed (n): (n=86)
Fritz et al. 2011
Included (n): (n=142)</td><td>SR
Cyst fluid CA 19-9 – 37 ng/ml (n=1437)
Final diagnosis:
Benign (n): 489
Malign (n): 648
Included studies
Where possible data was extracted from the SR. The full copy of the study was checked for accuracy and completeness.
Goh et al. 2008
Cyst fluid CA 19-9 – 37 ng/ml (n=137)
Final diagnosis:
Benign (n): 79
Malign (n): 58
Xu et al. 2011
Cyst fluid CA 19-9 – 45 ng/ml (n=86)
Final diagnosis:</td><td><table><tr><th>Included studies</th><th>T+</th><th>F-</th><th>F+</th><th>T-</th></tr><tr><td>Fritz et al. 2011</td><td>37</td><td>13</td><td>13</td><td>79</td></tr><tr><td>Goh et al. 2008</td><td>29</td><td>6</td><td>50</td><td>52</td></tr><tr><td>Grobmyer et al. 2009</td><td>5</td><td>5</td><td>3</td><td>27</td></tr><tr><td>Hirono et al. 2012</td><td>27</td><td>6</td><td>51</td><td>50</td></tr><tr><td>Hwang et al. 2011</td><td>11</td><td>20</td><td>28</td><td>178</td></tr><tr><td>Ingkakul et al. 2010</td><td>10</td><td>17</td><td>12</td><td>107</td></tr><tr><td>Jones et al. 2009</td><td>14</td><td>8</td><td>11</td><td>29</td></tr><tr><td>Kitagawa et al. 2003</td><td>17</td><td>3</td><td>4</td><td>18</td></tr><tr><td>Ohtsuka et al. 2012</td><td>3</td><td>7</td><td>19</td><td>70</td></tr><tr><td>Sadakari et al. 2010</td><td>1</td><td>2</td><td>5</td><td>45</td></tr></table></td><td>Limitations
Included studies - QUADAS 2 checklist
Where possible data was extracted from the SR. The full copy of the study was checked for accuracy and completeness.
Fritz et al. 2011
Patient selection
Risk of bias:
High risk
Applicability:
Low concern
Index tests
Risk of bias:
Low risk
Applicability:
Low concern
Reference standard
Risk of bias:
Low risk
Applicability:
Low concern</td></tr>
</table>

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
predicting malignant pancreatic cystic lesions. Study dates: Data collection: The literature search was up to March 2016. The included paper ranged from 2007 to 2011 Study publication: 2016 Source of funding: None	Analysed (n): (n=142) Sperti et al. 2007 Included (n): (n=64) Analysed (n): (n=64) Hirono et al. 2012 Included (n): (n=134) Analysed (n): (n=134) Ingkakul et al. 2010 Included (n): (n=200) Analysed (n): (n=146) Ohtsuka et al. 2012 Included (n): (n=138) Analysed (n): (n=99) Sadakari et al. 2010 Included (n): (n=73) Analysed (n): (n=53) Hwang et al. 2011 Included (n): (n=237) Analysed (n): (n=237) Shin et al. 2010 Included (n): (n=204) Analysed (n): (n=195) Grobmyer et al. 2009	Benign (n): 64 Malign (n): 22 Fritz et al. 2011 Cyst fluid CA 19-9 – 37 ng/ml (n=142) Final diagnosis: Benign (n): 50 Malign (n): 92 Sperti et al. 2007 Cyst fluid CA 19-9 – 37 ng/ml (n=64) Final diagnosis: Benign (n): 26 Malign (n): 38 Hirono et al. 2012 Cyst fluid CA 19-9 – n.r. ng/ml (n=134) Final diagnosis: Benign (n): 78 Malign (n): 56 Ingkakul et al. 2010 Cyst fluid CA 19-9 – 37 ng/ml (n=146) Final diagnosis: Benign (n): 22 Malign (n): 124 Ohtsuka et al. 2012 Cyst fluid CA 19-9 – 37 ng/ml (n=99) Final diagnosis: Benign (n): 22 Malign (n): 77 Sadakari et al. 2010	<table><tr><td>Shin et al. 2010</td><td>21</td><td>12</td><td>28</td><td>134</td></tr><tr><td>Sperti et al. 2007</td><td>11</td><td>5</td><td>15</td><td>33</td></tr><tr><td>Xu et al. 2011</td><td>45</td><td>3</td><td>19</td><td>19</td></tr></table> Diagnostic accuracy Sensitivity Specificity NPV PPV	Flow and timing Risk of bias: Low risk Overall risk of bias: Serious risk of bias Goh et al. 2008 Patient selection Risk of bias: High risk Applicability: Low concern Index tests Risk of bias: Low risk Applicability: Low concern Reference standard Risk of bias: Low risk Applicability: Low concern Flow and timing Risk of bias: Low risk Overall risk of bias: Serious risk of bias Grobmyer et al. 2009 Patient selection Risk of bias: Low risk Applicability: Low concern Index tests

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
	Included (n): (n=78) Analysed (n): (n=40) Jones et al. 2009 Included (n): (n=114) Analysed (n): (n=62) Kitagawa et al. 2003 Included (n): (n=63) Analysed (n): (n=42)	Cyst fluid CA 19-9 – 37 ng/ml (n=53) Final diagnosis: Benign (n): 6 Malign (n): 47 Hwang et al. 2011 Cyst fluid CA 19-9 – 37 ng/ml (n=237) Final diagnosis: Benign (n): 39 Malign (n): 198 Shin et al. 2010 Cyst fluid CA 19-9 – 37 ng/ml (n=195) Final diagnosis: Benign (n): 49 Malign (n): 146 Grobmyer et al. 2009 Cyst fluid CA 19-9 – 37 ng/ml (n=40) Final diagnosis: Benign (n): 8 Malign (n): 32 Jones et al. 2009 Cyst fluid CA 19-9 – 35 ng/ml (n=62) Final diagnosis: Benign (n): 25 Malign (n): 37 Kitagawa et al. 2003 Cyst fluid CA 19-9 – n.r. ng/ml (n=42) Final diagnosis:		Risk of bias: Low risk Applicability: Low concern Reference standard Risk of bias: Low risk Applicability: Low concern Flow and timing Risk of bias: Low risk Overall risk of bias: No serious risk of bias Hirono et al. 2012 Patient selection Risk of bias: Unclear risk Applicability: Low concern Index tests Risk of bias: Low risk Applicability: Low concern Reference standard Risk of bias: Low risk Applicability: Low concern Flow and timing Risk of bias:

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
		Benign (n): 21 Malign (n): 21 Reference standard: The final diagnosis was based on histopathology		Low risk Overall risk of bias: No serious risk of bias Hwang et al. 2011 Patient selection Risk of bias: Unclear risk Applicability: Low concern Index tests Risk of bias: Low risk Applicability: Low concern Reference standard Risk of bias: Low risk Applicability: Low concern Flow and timing Risk of bias: Low risk Overall risk of bias: No serious risk of bias Ingkakul et al. 2010 Patient selection Risk of bias: Low risk Applicability: Low concern Index tests Risk of bias: Low risk

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
				Applicability: Low concern Reference standard Risk of bias: High risk Applicability: Low concern Flow and timing Risk of bias: High risk Overall risk of bias: Very serious risk of bias Jones et al. 2009 Patient selection Risk of bias: High risk Applicability: Low concern Index tests Risk of bias: Low risk Applicability: Low concern Reference standard Risk of bias: Low risk Applicability: Low concern Flow and timing Risk of bias: Low risk Overall risk of bias: Serious risk of bias

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
				Kitagawa et al. 2003 Patient selection Risk of bias: Unclear risk Applicability: Low concern Index tests Risk of bias: Low risk Applicability: Low concern Reference standard Risk of bias: Low risk Applicability: Low concern Flow and timing Risk of bias: Low risk Overall risk of bias: No serious risk of bias Ohtsuka et al. 2012 Patient selection Risk of bias: High risk Applicability: Low concern Index tests Risk of bias: Low risk Applicability: Low concern

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
				Reference standard Risk of bias: Low risk Applicability: Low concern Flow and timing Risk of bias: Low risk Overall risk of bias: Serious risk of bias Sadakari et al. 2010 Patient selection Risk of bias: Low risk Applicability: Low concern Index tests Risk of bias: Low risk Applicability: Low concern Reference standard Risk of bias: Low risk Applicability: Low concern Flow and timing Risk of bias: Low risk Overall risk of bias: No serious risk of bias Shin et al. 2010 Patient selection

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
				Risk of bias: Low risk Applicability: Low concern Index tests Risk of bias: Low risk Applicability: Low concern Reference standard Risk of bias: Low risk Applicability: Low concern Flow and timing Risk of bias: Low risk Overall risk of bias: No serious risk of bias Sperti et al. 2007 Patient selection Risk of bias: Low risk Applicability: Low concern Index tests Risk of bias: Low risk Applicability: Low concern Reference standard Risk of bias:

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
				High risk Applicability: Low concern Flow and timing Risk of bias: High risk Overall risk of bias: Very serious risk of bias Xu et al. 2011 Patient selection Risk of bias: Low risk Applicability: Low concern Index tests Risk of bias: Low risk Applicability: Low concern Reference standard Risk of bias: Low risk Applicability: Low concern Flow and timing Risk of bias: Low risk Overall risk of bias: No serious risk of bias
Full citation Cizginer S, Turner BG, Bilge AR, Karaca C,	Sample size n=198	Index test 1 (n=154): Cyst fluid CEA - 109,9 ng/ml	1) Cyst fluid CEA T + | F - | F + | T -	Limitations QUADAS 2 checklist

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
Pitman MB, et al. Cyst fluid carcinoembryonic antigen is an accurate diagnostic marker of pancreatic mucinous cysts. Pancreas. 2011 Oct;40(7):1024-8. Ref Id 525450 Country/ies where the study was carried out: USA Study type: Prospective observational study Aim of the study: To determine the most accurate test for differentiating mucinous from nonmucinous cysts. Study dates: Data collection: n.r. Study publication: 2011 Source of funding: none	Characteristics M/F (n): 77/121 Mean age (yr): 60.6	Final diagnosis: Mucinous(n):110 Non-mucinous(n):44 Index test 2 (n=194): EUS Final diagnosis: Mucinous(n):141 Non-mucinous(n):53 Index test 3 (n=194): EUS -FNA cytology Final diagnosis: Mucinous(n):141 Non-mucinous(n):53 Reference standard: The final diagnosis was based on histology (n=194) or malignant cytology (n=4) -number provided for the total study cohort, n=198	89 | 21 | 1 | 43 Diagnostic accuracy Sensitivity Specificity NPV PPV 2) EUS T + | F - | F + | T - 50 | 91 | 10 | 43 Diagnostic accuracy Sensitivity Specificity NPV PPV 3) EUS-FNA cytology T + | F - | F + | T - 61 | 80 | 2 | 51 Diagnostic accuracy Sensitivity Specificity NPV PPV	Patient selection Risk of bias: Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? not Could the selection of participants have introduced bias? unclear risk Applicability: Is there concern that the included participants do not match the review question? Low concern Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Yes If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Low risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low concern Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests and methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Were the reference standard results interpreted without knowledge of the results of the index test? Yes
Could the reference standard, its conduct or interpretation have introduced bias? Low risk
Applicability:
Is there concern that the target condition as defined by the reference standard does not match the review question? Low concern
Flow and timing
Risk of bias:
Was there an appropriate interval between index tests and reference standard? Yes
Did all participants receive a reference standard? Yes
Did participants receive the same reference standard? No
Were all patients included in the analysis? Yes
Could the participant flow have introduced bias? Unclear risk
Overall risk of bias: Serious risk of bias</td></tr>
<tr><td>Full citation
Frossard JL, Amouyal P, Amouyal G, Palazzo L, Amaris J, et al. Performance of endosonography-guided fine needle aspiration and biopsy in the</td><td>Sample size
n=127
Characteristics
M/F (n): 49/78
Median age (range): 59.3 (15)</td><td>Index test 1 (n=67): EUS
Index test 2 (n=67): EUS -FNA cytology
Final diagnosis:
Mucinous(n):40
Non-mucinous(n): 27
Reference standard: The final diagnosis was</td><td>1) EUS<table><tr><td>T +</td><td>F -</td><td>F +</td><td>T -</td></tr><tr><td>33</td><td>7</td><td>12</td><td>15</td></tr></table>Diagnostic accuracy
Sensitivity
Specificity
NPV</td><td>Limitations
QUADAS 2 checklist
Patient selection
Risk of bias:
Was a consecutive or random sample of patients enrolled? Unclear
Was a case-control design avoided? Yes</td></tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests and methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>diagnosis of pancreatic cystic lesions. Am J Gastroenterol. 2003 Jul;98(7):1516-24.
Ref ID
523641
Country/ies where the study was carried out: France
Study type: Prospective observational study
Aim of the study:
To assess the performance of EUSand EUS-guided FNA in the diagnosis of pancreatic cystic lesions.
Study dates:
Data collection: 1997-2001
Study publication: 2003
Source of funding:
Association for Cancer Research (ARC 35 5106XA9921F) to M.F. and the Fonds de Pe´re´quation des Hoˆpitaux Universitaires de Gene`ve to J.L.F.</td>
<td></td>
<td>based on surgery (n=59) or post-mortem (n=8)</td>
<td>PPV
Adverse events/complications**
2) EUS-FNA cytology
<table>
<tr><td>T +</td><td>F -</td><td>F +</td><td>T -</td></tr>
<tr><td>38</td><td>1</td><td>2</td><td>26</td></tr>
</table>
Diagnostic accuracy
Sensitivity
Specificity
NPV
PPV
Adverse events/complications**</td>
<td>Did the study avoid inappropriate exclusions? yes
Could the selection of participants have introduced bias? Unclear risk
Applicability:
Is there concern that the included participants do not match the review question? Low concern
Index tests
Risk of bias:
Were the index tests interpreted without knowledge of the reference standard? Unclear (no details given in the report)
If a threshold was used, was it pre-specified? N/A
Could the conduct or interpretation of the index test have introduced bias? Unclear risk
Applicability:
Is there concern that the index test, its conduct or interpretation differ from the review question? Low concern
Reference standard
Risk of bias:
Is the reference standard likely to correctly classify the target condition? Yes
Were the reference standard results interpreted without knowledge of the results of the index test? Unclear (no information given about blinding)</td>
</tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests and methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Could the reference standard, its conduct or interpretation have introduced bias? Unclear risk
Applicability:
Is there concern that the target condition as defined by the reference standard does not match the review question? Low concern
Flow and timing
Risk of bias:
Was there an appropriate interval between index tests and reference standard? Yes
Did all participants receive a reference standard? No
Did participants receive the same reference standard? Yes
Were all patients included in the analysis? Yes
Could the participant flow have introduced bias? Low risk
Overall risk of bias: Serious risk of bias</td></tr>
<tr><td>Full citation
Gaddam S, Ge PS, Keach JW, Mullady D, Fukami N, et al. Suboptimal accuracy of carcinoembryonic antigen in differentiation of mucinous and nonmucinous pancreatic cysts: results of a large multicenter study.</td><td>Sample size
n=226
Characteristics
M/F (n): 88/138
Mean age (SD): 60.9 (13.1)</td><td>Index test 1 (n=226): Cyst fluid CEA -5, 105,192, 800 ng/ml
Final diagnosis:
Mucinous(n): 150
Non-mucinous(n): 76
Reference standard: The final diagnosis was based on surgical histopathology (n=226)</td><td>1) Cyst fluid CEA
<table><tr><th></th><th>T +</th><th>F -</th><th>F +</th></tr><tr><td>5</td><td>141</td><td>9</td><td>44</td></tr><tr><td>105</td><td>105</td><td>45</td><td>28</td></tr><tr><td>192</td><td>92</td><td>58</td><td>17</td></tr><tr><td>800</td><td>50</td><td>100</td><td>11</td></tr></table>Diagnostic accuracy
Sensitivity
Specificity</td><td>Limitations
QUADAS 2 checklist
Patient selection
Risk of bias:
Was a consecutive or random sample of patients enrolled? Yes
Was a case-control design avoided? Yes
Did the study avoid inappropriate exclusions? yes</td></tr>
</table>

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
Gastrointest Endosc. 2015 Dec;82(6):1060-9. Ref Id 525477 Country/ies where the study was carried out: USA Study type: Retrospective observational study Aim of the study: To evaluate the diagnostic accuracy of cyst fluid CEA levels for differentiating between MCNs and NMCNs. METHODS: Consecutive patients who underwent EUS with FNA at 3 tertiary care centers were identified Study dates: Data collection: 2006-2011 Study publication: 2015 Source of funding: none			NPV PPV	Could the selection of participants have introduced bias? Low risk Applicability: Is there concern that the included participants do not match the review question? Low concern Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Unclear (no details given in the report) If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Unclear risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low concern Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear (no information given about blinding) Could the reference standard, its conduct or interpretation have introduced bias? Unclear risk Applicability:

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests and methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Is there concern that the target condition as defined by the reference standard does not match the review question? Low concern
Flow and timing
Risk of bias:
Was there an appropriate interval between index tests and reference standard? Unclear (no details given in the report)
Did participants receive the same reference standard? No
Were all patients included in the analysis? Yes
Could the participant flow have introduced bias? High risk
Overall risk of bias: Serious risk of bias</td></tr>
<tr><td>Full citation
Gerke H, Jaffe TA, Mitchell RM, Byrne MF, Stiffler HL, et al. Endoscopic ultrasound and computer tomography are inaccurate methods of classifying cystic pancreatic lesions. Dig Liver Dis. 2006 Jan;38(1):39-44.
Country/ies where the study was carried out: USA</td><td>Sample size
n=66
Characteristics
M/F (n): 28/38
Median age (range): 59 (27-82)</td><td>Index test 1 (n=41): CT
Final diagnosis:
Benign (n): 20
Malign (n): 21
Index test 2 (n=66): EUS
Final diagnosis:
Benign (n): 35
Malign (n): 31
Reference standard: The final diagnosis was based on surgical pathology (n = 43), diagnostic fine needle aspiration (n = 13) or follow-up imaging (n = 10)</td><td>1) CT
<table><tr><td>T +</td><td>F -</td><td>F +</td><td>T -</td></tr><tr><td>13</td><td>8</td><td>4</td><td>16</td></tr></table>Diagnostic accuracy
Sensitivity
Specificity
NPV
PPV
2) EUS
<table><tr><td>T +</td><td>F -</td><td>F +</td><td>T -</td></tr><tr><td>22</td><td>9</td><td>13</td><td>22</td></tr></table>Diagnostic accuracy
Sensitivity
Specificity</td><td>Limitations
QUADAS 2 checklist
Patient selection
Risk of bias:
Was a consecutive or random sample of patients enrolled? Yes
Was a case-control design avoided? Yes
Did the study avoid inappropriate exclusions? Yes
Could the selection of participants have introduced bias? Low risk
Applicability:
Is there concern that the included participants do not match the review question? Low concern</td></tr>
</table>

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
Study type: Retrospective observational study Aim of the study: To assess the accuracy of endoscopic ultrasound and computer tomography to preoperatively distinguish benign from potentially malignant and malignant pancreatic cystic lesions Study dates: Data collection: 1998-2003 Study publication: 2006 Source of funding: none			NPV PPV	Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Yes If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Low risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low concern Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Yes Could the reference standard, its conduct or interpretation have introduced bias? Low risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low concern Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests and methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>standard? Unclear (no details given in the report)
Did participants receive the same reference standard? No
Were all patients included in the analysis? Yes
Could the participant flow have introduced bias? High risk
Overall risk of bias: Serious risk of bias.</td></tr>
<tr><td>Full Citation
Ghaneh P, Hanson R, Titman A, Lancaster G, Plumpton C, Lloyd-Williams H, et al. (2018) PET-PANC:
multicentre prospective diagnostic accuracy and health economic analysis study of the impact of
combined modality ^{18}fluorine-2-fluoro-2-deoxy-d-glucose positron emission tomography with
computed tomography scanning in the diagnosis and management of pancreatic cancer.
Health Technology Assessment 22(7)
Country/ies where the study was carried out:</td><td>Participants
N=393 patients with suspected PC

Inclusion criteria
Written informed consent
Able to have MDCT scan and attend PET/CT scan
Able to attend 12-mo FU
Patients with suspected pancreatic malignancy, defined as: (1) Focal lesion in pancreas/bulky pancreas/dilated pancreatic duct (with or without metastases) detected by MDCT (without or without MRI/EUS/ultrasound</td><td>Index test 1= MDCT
Index 2= PET/CT
Reference test=Histology (biopsy or resection) or 12-mo clinical FU

TNM staging classification used: UICC 2009 (7th edition)

Procedure
Study comprised 18 major pancreatic centres. All participants received standard diagnosis and staging with MDCT. Patients then underwent PET/CT with reference standard diagnosis within 2 weeks following informed consent. Follow up was 12 months. For 18-F-FDG PET/CT, patients</td><td>Study flow
910 patients screened, 619 registered, 589 underwent PET/CT scan (ITT, n=583; per protocol, n=550)

Identification of malignant cystic neoplasms
MDCT (per protocol analysis, n=550)

<table><tr><td>T +</td><td>F -</td><td>F +</td><td>T -</td></tr><tr><td>6</td><td>2</td><td>39</td><td>503</td></tr></table>Sensitivity= 75.0% (95% CI 45.0% to 99.9%)
Specificity= 92.8% (95% CI, 90.6% to 95.0%)
PPV=13.3% (95% CI 3.4% to 23.3%)
NPV=99.6% (95% CI 99.1 to 99.9)

PET/CT (per protocol analysis, n=550)</td><td>Limitations
QUADAS 2 checklist
Patient selection
Risk of bias:
Was a consecutive or random sample of patients enrolled? Yes
Was a case-control design avoided? Yes
Did the study avoid inappropriate exclusions? Yes
Could the selection of participants have introduced bias? Low
Applicability:
Is there concern that the included participants do not match the review question? Low
Index tests
Risk of bias:
Were the index tests interpreted without knowledge of the reference standard? Yes
If a threshold was used, was it pre-specified? N/A</td></tr>
</table>

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
UK Study type: Multicentre prospective cohort study Aim of the study: To determine incremental diagnostic accuracy and impact of PET/CT on standard diagnostic work-up in patients with suspected pancreatic cancer. Study dates: 01/2011-05/2014 Source of funding: Funded by HTA project # 08/29/02; DC funded by NIHR Biomedical Research Centre at Royal Marsden and Institute of Cancer Research.	), or (2) Jaundice due to distal obstruction of common bile duct or ampulla (not due to calculi) [defined as serum bilirubin > 35 µmol/l] or (3) Serum CA 19-9>37 kU/l Exclusion criteria Patients <18 years Pregnant Poorly controlled diabetes Characteristics (ITT population, n=583) Median age (years)=66, range 21-87) Male/female=328/255 Eligibility criteria: Focal lesion=538; jaundice=159 CA 19-9 >37=127	fasted for 6 hours before scan; accurate SUV measurements obtained using calibrated class III device with blood glucose recorded using calibrated Boehringer Mannheim glucometer. Patients hydrated before scan; scan started 90 minutes after FDG injection. All PET/CT scans transferred to central reporting centre and reviewed by independent expert. Scans also additionally reviewed by 4 other centres.	<table><tr><td>T +</td><td>F -</td><td>F +</td><td>T -</td></tr><tr><td>6</td><td>2</td><td>21</td><td>521</td></tr></table>Sensitivity= 75.0% (95% CI 45.0% to 99.9%) Specificity= 96.1% (95% CI 94.5% to 97.8%) PPV=22.2% (95% CI 6.5 to 37.9%) NPV=99.6% (99.1% to 99.9%) Adverse events No events related to study procedure. One case of lymphangitis carcinomatosis, related to patient's original condition.	Could the conduct or interpretation of the index test have introduced bias? Low Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Yes Could the reference standard, its conduct or interpretation have introduced bias? Low Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Yes Did participants receive the same reference standard? No Were all patients included in the analysis? No Could the participant flow have introduced bias? High (69 patients not included in analysis)

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests and methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Overall risk of bias: No serious risk of bias</td></tr>
<tr><td>Full citation
Hirono S, Tani M, Kawai M, Okada K, Miyazawa M, et al. The carcinoembryonic antigen level in pancreatic juice and mural nodule size are predictors of malignancy for branch duct type intraductal papillary mucinous neoplasms of the pancreas. Ann Surg. 2012 Mar;255(3):517-22.
Ref Id
522886
Country/ies where the study was carried out:
Japan
Study type:
Retrospective observational study
Aim of the study:
To identify the predictors of malignancy for branch duct type IPMNS
Study dates:
Data collection: 1999-2011
Study publication: 2012
Source of funding:
n.r.</td><td>Sample size
n=134
Characteristics
M/F (n): 74/60
Mean age (SD): 68.9 (9.7)</td><td>Index test 1 (n=134):
Cyst fluid CEA 30 ng/ml
Final diagnosis:
Benign (n): 78
Malign (n): 56
Reference standard: The final diagnosis was based on histopathology (n=134)</td><td>1) Cyst fluid CEA
<table><tr><td>T +</td><td>F -</td><td>F +</td><td>T -</td></tr><tr><td>53</td><td>3</td><td>12</td><td>66</td></tr></table>Diagnostic accuracy
Sensitivity
Specificity
NPV
PPV</td><td>Limitations
QUADAS 2 checklist
Patient selection
Risk of bias:
Was a consecutive or random sample of patients enrolled? Yes
Was a case-control design avoided? Yes
Did the study avoid inappropriate exclusions? Yes
Could the selection of participants have introduced bias? Low risk
Applicability:
Is there concern that the included participants do not match the review question? Low concern
Index tests
Risk of bias:
Were the index tests interpreted without knowledge of the reference standard? Unclear (no details given in the report)
If a threshold was used, was it pre-specified? Yes
Could the conduct or interpretation of the index test have introduced bias? Unclear risk
Applicability:
Is there concern that the index test, its conduct or interpretation differ from the review question? Low concern
Reference standard</td></tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests and methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Risk of bias:
Is the reference standard likely to correctly classify the target condition? Yes
Were the reference standard results interpreted without knowledge of the results of the index test? Unclear (no information given about blinding)
Could the reference standard, its conduct or interpretation have introduced bias? Unclear risk
Applicability:
Is there concern that the target condition as defined by the reference standard does not match the review question? Low concern
Flow and timing
Risk of bias:
Was there an appropriate interval between index tests and reference standard? Unclear (no details given in the report)
Did participants receive the same reference standard? No
Were all patients included in the analysis? Yes
Could the participant flow have introduced bias? High risk
Overall risk of bias: Serious risk of bias</td></tr>
<tr><td>Full citation
Jang KM, Kim SH, Min JH et al. (2014) Value of diffusion-weighted MRI</td><td>Sample size
n=65
Characteristics
M/F (n): 38/27</td><td>Index test 1 (n=65): MRI
Final diagnosis:
Benign (n): 19
Malign (n): 42</td><td><table><tr><td>T +</td><td>F -</td><td>F +</td><td>T -</td></tr><tr><td>15</td><td>7</td><td>4</td><td>35</td></tr></table>Diagnostic accuracy</td><td>Limitations
QUADAS 2 checklist
Patient selection
Risk of bias:</td></tr>
</table>

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
for differentiating malignant from benign intraductal papillary mucinous neoplasms of the pancreas. American Journal of Roentgenology 203(5): 992-1000 Ref Id 610835 Country/ies where the study was carried out: Korea Study type: Retrospective observational study Aim of the study: To evaluate whether the use of diffusion-weighted MRI (DWI) increases diagnostic accuracy in the differentiation of malignant from benign IPMNs of the pancreas over the accuracy of contrast-enhanced MRI with MRCP Study dates: Data collection: 2008-2013 Study publication: 2014 Source of funding: n.r.	Median age (yr): 61.5 (range: 35-83)	Reference standard: The final diagnosis was based on surgical histopathology (n=65)		Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? No Could the selection of participants have introduced bias? Unclear risk Applicability: Is there concern that the included participants do not match the review question? Low concern Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Yes If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Low risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low concern Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Yes

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests and methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Could the reference standard, its conduct or interpretation have introduced bias? Low risk
Applicability:
Is there concern that the target condition as defined by the reference standard does not match the review question? Low concern
Flow and timing
Risk of bias:
Was there an appropriate interval between index tests and reference standard? Yes
Did all participants receive a reference standard? Yes
Did participants receive the same reference standard? No
Were all patients included in the analysis? Yes
Could the participant flow have introduced bias? Unclear risk
Overall risk of bias: Serious risk of bias</td></tr>
<tr><td>Full citation
Jin DX, Small AJ, Vollmer CM, Jhala N, Furth EE, Ginsberg GG, Kochman ML, Ahmad NA, Chandrasekhara V. A lower cyst fluid CEA cut-off increases diagnostic accuracy in identifying mucinous</td><td>Sample size
n=86
Characteristics
M/F (n): 32/54
Mean age (SD): 65.0 (13.0)</td><td>Index test 1 (n=86): Cyst fluid CEA – 30.7, 192, 300, 800 ng/ml
Final diagnosis:
Mucinous(n): 77
Non-mucinous(n): 9
Reference standard: The final diagnosis was based on surgical histology (n=86)</td><td>1) Cyst fluid CEA
<table><tr><th></th><th>T +</th><th>F -</th><th>F +</th></tr><tr><td>30.7</td><td>68</td><td>9</td><td>2</td></tr><tr><td>192</td><td>40</td><td>37</td><td>1</td></tr><tr><td>300</td><td>33</td><td>44</td><td>1</td></tr><tr><td>800</td><td>21</td><td>56</td><td>1</td></tr></table>Diagnostic accuracy
Sensitivity
Specificity</td><td>Limitations
QUADAS 2 checklist
Patient selection
Risk of bias:
Was a consecutive or random sample of patients enrolled? Yes
Was a case-control design avoided? Yes
Did the study avoid inappropriate exclusions? Yes</td></tr>
</table>

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
pancreatic cystic lesions. JOP 2015; 16(3):271-7 Ref Id 524011 Country/ies where the study was carried out: USA Study type: Retrospective observational study Aim of the study: To determine the most accurate cyst carcinoembryonic antigen cut-off value for distinguishing mucinous cysts from non-mucinous cysts with a focus on discriminating intraductal papillary mucinous neoplasms. Study dates: Data collection: 2000-2012 Study publication: 2015 Source of funding: n.r.			NPV PPV	Could the selection of participants have introduced bias? Low risk Applicability: Is there concern that the included participants do not match the review question? Low concern Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Unclear (no details given in the report) If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Unclear risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low concern Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear (no information given about blinding) Could the reference standard, its conduct or interpretation have introduced bias? Unclear risk Applicability:

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests and methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Is there concern that the target condition as defined by the reference standard does not match the review question? Low concern
Flow and timing
Risk of bias:
Was there an appropriate interval between index tests and reference standard? Unclear (no information given about blinding)
Did participants receive the same reference standard? Yes
Were all patients included in the analysis? Yes
Could the participant flow have introduced bias? Low risk
Overall risk of bias: Serious risk of bias</td></tr>
<tr><td>Full citation
Kamata K, Kitano M, Omoto S et al. (2016) Contrast-enhanced harmonic endoscopic ultrasonography for differential diagnosis of pancreatic cysts. Endoscopy 48(1): 35–41
Ref Id
525513
Country/ies where the study was carried out: Japan</td><td>Sample size
n=70
Characteristics
M/F (n): 31/39
Mean age (yr): 62</td><td>Index test 1 (n=70): EUS
Final diagnosis:
Benign (n): 30
Malign (n): 40
Reference standard: The final diagnosis was based on surgical histopathology (n=70)</td><td>1) EUS<table><tr><td>T +</td><td>F -</td><td>F +</td><td>T -</td></tr><tr><td>29</td><td>24</td><td>1</td><td>16</td></tr></table>Diagnostic accuracy</td><td>Limitations
QUADAS 2 checklist
Patient selection
Risk of bias:
Was a consecutive or random sample of patients enrolled? No
Was a case-control design avoided? Yes
Did the study avoid inappropriate exclusions? No
Could the selection of participants have introduced bias? High risk
Applicability:
Is there concern that the included participants do not match the review question? High concern</td></tr>
</table>

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
Study type: Retrospective observational study Aim of the study: To compare B-mode EUS and contrast-enhanced harmonic EUS in the differential diagnosis of pancreatic cysts Study dates: Data collection: 2007-2012 Study publication: 2016 Source of funding: Japan Society for the Promotion of Science.				Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Yes If a threshold was used, was it pre-specified? Unclear Could the conduct or interpretation of the index test have introduced bias? Unclear risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low concern Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear Could the reference standard, its conduct or interpretation have introduced bias? Unclear risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low concern Flow and timing Risk of bias:

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests and methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Was there an appropriate interval between index tests and reference standard? Unclear
Did all participants receive a reference standard? Yes
Did participants receive the same reference standard? No
Were all patients included in the analysis? No
Could the participant flow have introduced bias? High risk
Overall risk of bias: Very risk of bias</td></tr>
<tr><td>Full citation
Kim JH, Eun HW, Park HJ, Hong SS, Kim YJ. Diagnostic performance of MRI and EUS in the differentiation of benign from malignant pancreatic cyst and cyst communication with the main duct. Eur J Radiol. 2012 Nov;81(11):2927-35. Ref Id
525526
Country/ies where the study was carried out: Korea
Study type: Retrospective observational study
Aim of the study:
To assess the diagnostic ability of MRI and EUS for differentiating benign</td><td>Sample size
n=51
Characteristics
M/F (n): 23/28
Mean age (years): 43</td><td>Index test 1 (n=51): EUS
Index test 2 (n=51): MRI
Final diagnosis:
Benign (n): 15
Malign (n): 36
Reference standard: The final diagnosis was based on surgical histopathology (n=51)</td><td>1) EUS
<table><tr><td>T +</td><td>F -</td><td>F +</td><td>T -</td></tr><tr><td>35</td><td>1</td><td>4</td><td>11</td></tr></table>Diagnostic accuracy
Sensitivity
Specificity
NPV
PPV
2) MRI
<table><tr><td>T +</td><td>F -</td><td>F +</td><td>T -</td></tr><tr><td>34</td><td>2</td><td>4</td><td>11</td></tr></table>Diagnostic accuracy
Sensitivity
Specificity
NPV
PPV</td><td>Limitations
QUADAS 2 checklist
Patient selection
Risk of bias:
Was a consecutive or random sample of patients enrolled? Yes
Was a case-control design avoided? Yes
Did the study avoid inappropriate exclusions? Yes
Could the selection of participants have introduced bias? Low risk
Applicability:
Is there concern that the included participants do not match the review question? Low concern
Index tests
Risk of bias:
Were the index tests interpreted without knowledge of the reference standard? Yes</td></tr>
</table>

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
from malignant pancreatic cyst focusing on cyst communication with pancreatic duct. Study dates: Data collection: 2006-2099 Study publication: 2012 Source of funding: n.r.				If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Low risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low concern Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Yes Could the reference standard, its conduct or interpretation have introduced bias? Low risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low concern Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Unclear (no information given about blinding) Did participants receive the same reference standard? Yes

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests and methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Were all patients included in the analysis? Yes
Could the participant flow have introduced bias? Low risk
Overall risk of bias: No serious risk of bias</td></tr>
<tr><td>Full citation
Kim SH, Lee JM, Lee ES et al. (2015) Intraductal papillary mucinous neoplasms of the pancreas: Evaluation of malignant potential and surgical resectability by using MR imaging with MR cholangiography. Radiology 274(3): 723–33
Ref ID
526521
Country/ies where the study was carried out: Korea
Study type: Retrospective observational study
Aim of the study:
To evaluate the diagnostic performance of MRI with MRCP in determining the malignant potential and surgical resectability of pancreas IPMNs
Study dates:</td><td>Sample size
n=123
Characteristics
M/F (n): n.r.
Mean age (yr): n.r.</td><td>Index test 1 (n=70): MRI
Final diagnosis:
Benign (n): 45
Malign (n): 51
Reference standard: The final diagnosis was based on surgical histopathology (n=123)</td><td>1) MRI<table><tr><td>T +</td><td>F -</td><td>F +</td><td>T -</td></tr><tr><td>29</td><td>2</td><td>16</td><td>49</td></tr></table>Diagnostic accuracy</td><td>Limitations
QUADAS 2 checklist
Patient selection
Risk of bias:
Was a consecutive or random sample of patients enrolled? No
Was a case-control design avoided? Yes
Did the study avoid inappropriate exclusions? No
Could the selection of participants have introduced bias? High risk
Applicability:
Is there concern that the included participants do not match the review question? High concern
Index tests
Risk of bias:
Were the index tests interpreted without knowledge of the reference standard? Yes
If a threshold was used, was it pre-specified? Yes
Could the conduct or interpretation of the index test have introduced bias? Low risk
Applicability:</td></tr>
</table>

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
Data collection: 2009-2013 Study publication: 2015 Source of funding: n.r.				Is there concern that the index test, its conduct or interpretation differ from the review question? Low concern Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear Could the reference standard, its conduct or interpretation have introduced bias? Unclear risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low concern Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Unclear Did all participants receive a reference standard? Yes Did participants receive the same reference standard? No Were all patients included in the analysis? Yes Could the participant flow have introduced bias? High risk Overall risk of bias: Very serious risk of bias

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests and methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Full citation
Lee, H. J., Kim, M. J., Choi, J. Y., Hong, H. S., Kim, K. A., Relative accuracy of CT and MRI in the differentiation of benign from malignant pancreatic cystic lesions, Clinical Radiology, 66, 315-21, 2011
Ref ID
524254
Country/ies where the study was carried out:
Korea
Study type:
Retrospective observational study
Aim of the study:
To assess the diagnostic accuracies of multidetector CT and MRI for differentiating benign from malignant lesions and suggesting the specific diagnoses for pancreatic cystic lesions
Study dates:
Data collection: 2001-2008
Study publication: 2011
Source of funding:
n.r.</td>
<td>Sample size
n=63
Characteristics
M/F (n): 25/38
Mean age (range): 55.7 (12-79)</td>
<td>Index test 1 (n=63): CT
Index test 2 (n=63): MRI
Final diagnosis:
Benign (n): 37
Malign (n): 26
Reference standard: The final diagnosis was based on surgical histopathology (n=63)</td>
<td>1) CT
<table>
<tr><td>T +</td><td>F -</td><td>F +</td><td>T -</td></tr>
<tr><td>17</td><td>9</td><td>10</td><td>27</td></tr>
</table>
Diagnostic accuracy
Sensitivity
Specificity
NPV
PPV
2) MRI
<table>
<tr><td>T +</td><td>F -</td><td>F +</td><td>T -</td></tr>
<tr><td>18</td><td>8</td><td>10</td><td>27</td></tr>
</table>
Diagnostic accuracy
Sensitivity
Specificity
NPV
PPV</td>
<td>Limitations
QUADAS 2 checklist
Patient selection
Risk of bias:
Was a consecutive or random sample of patients enrolled? Yes
Was a case-control design avoided? Yes
Did the study avoid inappropriate exclusions? Yes
Could the selection of participants have introduced bias? Low risk
Applicability:
Is there concern that the included participants do not match the review question? Low concern
Index tests
Risk of bias:
Were the index tests interpreted without knowledge of the reference standard? Yes
If a threshold was used, was it pre-specified? N/A
Could the conduct or interpretation of the index test have introduced bias? Low risk
Applicability:
Is there concern that the index test, its conduct or interpretation differ from the review question? Low concern
Reference standard
Risk of bias:</td>
</tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests and methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Is the reference standard likely to correctly classify the target condition? Yes
Were the reference standard results interpreted without knowledge of the results of the index test? Yes
Could the reference standard, its conduct or interpretation have introduced bias? Low risk
Applicability:
Is there concern that the target condition as defined by the reference standard does not match the review question? Low concern
Flow and timing
Risk of bias:
Was there an appropriate interval between index tests and reference standard? Unclear (no details given in the report)
Did participants receive the same reference standard? No
Were all patients included in the analysis? Yes
Could the participant flow have introduced bias? High risk
Overall risk of bias: Serious risk of bias</td></tr>
<tr><td>Full citation
Linder JD, Geenen JE, Catalano MF. Cyst fluid analysis obtained by EUS-guided FNA in the evaluation of discrete</td><td>Sample size
n=102
Characteristics
M/F (n): 60/42
Mean age (range): 51 (23-76)</td><td>Index test 1 (n=71): Cyst fluid CEA – 6000 ng/ml
Final diagnosis:
Mucinous(n): 35
Non-mucinous(n): 36</td><td>1) Cyst fluid CEA
<table><tr><td>T +</td><td>F -</td><td>F +</td><td>T -</td></tr><tr><td>30</td><td>5</td><td>0</td><td>36</td></tr></table>Diagnostic accuracy
Sensitivity</td><td>Limitations
QUADAS 2 checklist
Patient selection
Risk of bias:
Was a consecutive or random sample of patients enrolled? Unclear</td></tr>
</table>

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
cystic neoplasms of the pancreas: a prospective single-center experience. Gastrointest Endosc. 2006 Nov;64(5):697-702. Ref ID 524322 Country/ies where the study was carried out: USA Study type: Retrospective observational study Aim of the study: To retrospectively determine cyst fluid characteristics that differentiate cystic neoplasms Study dates: Data collection: 1998-2002 Study publication: 2006 Source of funding: None		Reference standard: The final diagnosis was based on surgical histopathology (n=71)	Specificity NPV PPV	Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of participants have introduced bias? low risk Applicability: Is there concern that the included participants do not match the review question? Low concern Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Unclear (no details given in the report) If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Unclear risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low concern Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear (no information given about blinding)

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests and methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Could the reference standard, its conduct or interpretation have introduced bias? Unclear risk
Applicability:
Is there concern that the target condition as defined by the reference standard does not match the review question? Low concern
Flow and timing
Risk of bias:
Was there an appropriate interval between index tests and reference standard? Unclear (no details given in the report)
Did participants receive the same reference standard? Unclear (no details given in the report
Were all patients included in the analysis? Yes
Could the participant flow have introduced bias? Unclear risk
Overall risk of bias: Serious risk of bias</td></tr>
<tr><td>Full citation
Moris M, Raimondo M, Woodward TA, Skinner V, Arcidiacono PG, et al. Diagnostic Accuracy of Endoscopic Ultrasound-Guided Fine-Needle Aspiration Cytology, Carcinoembryonic Antigen, and Amylase in Intraductal Papillary Mucinous Neoplasm.</td><td>Sample size
n=180
Characteristics
M/F (n): 58/83
Mean age (SD): 68 (9.2)</td><td>Index test 1 (n=180): Cyst fluid CEA – 129 ng/ml
Final diagnosis:
Mucinous(n): 145
Non-mucinous(n): 35
Reference standard: The final diagnosis was based on surgical histopathology (n=180)</td><td>1) Cyst fluid CEA
<table><tr><td>T +</td><td>F -</td><td>F +</td><td>T -</td></tr><tr><td>112</td><td>6</td><td>33</td><td>29</td></tr></table>Diagnostic accuracy</td><td>Limitations
QUADAS 2 checklist
Patient selection
Risk of bias:
Was a consecutive or random sample of patients enrolled? Yes
Was a case-control design avoided? Yes
Did the study avoid inappropriate exclusions? Yes</td></tr>
</table>

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
Pancreas. 2016 Jul;45(6):870-5. Ref ID 608640 Country/ies where the study was carried out: USA Study type: Retrospective observational study Aim of the study: To determine the accuracy of cytology, CEA, and amylase levels in the preoperative diagnosis of IPMNs Study dates: Data collection: 1997-2014 Study publication: 2016 Source of funding: n.r.				Could the selection of participants have introduced bias? Low risk Applicability: Is there concern that the included participants do not match the review question? Low concern Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? No If a threshold was used, was it pre-specified? No Could the conduct or interpretation of the index test have introduced bias? High risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low concern Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? No Could the reference standard, its conduct or interpretation have introduced bias? Unclear risk Applicability: Is there concern that the target condition as defined by the reference

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests and methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>standard does not match the review question? Low concern
Flow and timing
Risk of bias:
Was there an appropriate interval between index tests and reference standard? Yes
Did all participants receive a reference standard? Yes
Did participants receive the same reference standard? Yes
Were all patients included in the analysis? Yes
Could the participant flow have introduced bias? Low risk
Overall risk of bias: Serious risk of bias</td></tr>
<tr><td>Full citation
Nagashio Y, Hijioka S, Mizuno N, Hara K, Imaoka H, et al. Combination of cyst fluid CEA and CA 125 is an accurate diagnostic tool for differentiating mucinous cystic neoplasms from intraductal papillary mucinous neoplasms. Pancreatology. 2014 Nov-Dec;14(6):503-9.
Ref ID
524527</td><td>Sample size
n=78
Characteristics
M/F (n): 26/42
Mean age (range): n.r.</td><td>Index test 1 (n=68): Cyst fluid CA 19-9 –n.r.
Final diagnosis:
Mucinous(n): 39
Non-mucinous(n): 29
Reference standard: The final diagnosis was based on surgical histopathology (n=58) or cytology, imaging or clinical follow-up (n=20)</td><td>1) Cyst fluid CEA<table><tr><td>T +</td><td>F -</td><td>F +</td><td>T -</td></tr><tr><td>37</td><td>2</td><td>2</td><td>27</td></tr></table>Diagnostic accuracy
Sensitivity
Specificity
NPV
PPV</td><td>Limitations
QUADAS 2 checklist
Patient selection
Risk of bias:
Was a consecutive or random sample of patients enrolled? Yes
Was a case-control design avoided? Yes
Did the study avoid inappropriate exclusions? Yes
Could the selection of participants have introduced bias? Low risk
Applicability:
Is there concern that the included participants do not match the review question? Low concern</td></tr>
</table>

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
Country/ies where the study was carried out: Japan Study type: Retrospective observational study Aim of the study: To determine the utility of cyst fluid analysis (CEA, CA 19-9, CA 125, amylase, and cytology) in categorizing pancreatic cystic lesions, and in differentiating malignant from benign cystic lesions Study dates: Data collection: 1997-2013 Study publication: 2014 Source of funding: None				Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? No If a threshold was used, was it pre-specified? No Could the conduct or interpretation of the index test have introduced bias? High risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low concern Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? No Could the reference standard, its conduct or interpretation have introduced bias? High risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low concern Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests and methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>standard? Unclear (no information given about blinding)
Did participants receive the same reference standard? Yes
Were all patients included in the analysis? Yes
Could the participant flow have introduced bias? Low risk
Overall risk of bias: Serious risk of bias</td></tr>
<tr><td>Full citation
Oh HC, Kang H, Brugge WR. Cyst fluid amylase and CEA levels in the differential diagnosis of pancreatic cysts: a single-center experience with histologically proven cysts. Dig Dis Sci. 2014 Dec;59(12):3111-6.
Ref ID
524604
Country/ies where the study was carried out: USA
Study type: Retrospective observational study
Aim of the study:
To evaluate the diagnostic role of cyst fluid amylase and to determine the optimal cutoff values of cyst fluid amylase and CEA for the</td><td>Sample size
n=69
Characteristics
M/F (n): 32/46
Median age (range): 62 (24-84)</td><td>Index test 1 (n=78): Cyst fluid CEA – 50 ng/ml
Final diagnosis:
Mucinous(n):62
Non-mucinous [pseudocysts] (n): 16
Reference standard: The final diagnosis was based on surgical histology (n=78)</td><td>1) Cyst fluid CEA
<table><tr><td>T +</td><td>F -</td><td>F +</td><td>T -</td></tr><tr><td>52</td><td>10</td><td>2</td><td>14</td></tr></table>Diagnostic accuracy
Sensitivity
Specificity
NPV
PPV</td><td>Limitations
QUADAS 2 checklist
Patient selection
Risk of bias:
Was a consecutive or random sample of patients enrolled? Yes
Was a case-control design avoided? Yes
Did the study avoid inappropriate exclusions? yes
Could the selection of participants have introduced bias? Low risk
Applicability:
Is there concern that the included participants do not match the review question? Low concern
Index tests
Risk of bias:
Were the index tests interpreted without knowledge of the reference standard? Unclear (no details given in the report)</td></tr>
</table>

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
differential diagnosis of pancreatic cysts. Study dates: Data collection: 1999-2012 Study publication: 2014 Source of funding: n.r.				If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Unclear risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low concern Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear (no information given about blinding) Could the reference standard, its conduct or interpretation have introduced bias? Unclear risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low concern Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Unclear (no information given about blinding) Did participants receive the same reference standard? Yes

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests and methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Were all patients included in the analysis? Yes
Could the participant flow have introduced bias? Low risk
Overall risk of bias: Serious risk of bias</td></tr>
<tr><td>Full citation
Oppong KW, Dawwas MF, Charnley RM, Wadehra V, Elamin K, et al. EUS and EUS-FNA diagnosis of suspected pancreatic cystic neoplasms: Is the sum of the parts greater than the CEA?. Pancreatology. 2015 Sep-Oct;15(5):531-7.
Ref ID
524610
Country/ies where the study was carried out: UK
Study type: Retrospective observational study
Aim of the study:
To investigate the yield and diagnostic performance of EUS/EUS-FNA on an intention to diagnose basis and to determine the utility of the</td><td>Sample size
n=119
Characteristics
M/F (n): 37/82
Mean age (range): 61.4 (19-84)</td><td>Index test 1 (n=78): Cyst fluid CEA – 7, 30, 110, 192 ng/ml
Final diagnosis:
Mucinous(n): 50
Non-mucinous(n): 28
Index test 2 (n=111): EUS
Final diagnosis:
Mucinous(n):81
Non-mucinous(n): 30
Index test 3 (n=102): EUS-FNA cytology
Final diagnosis:
Mucinous(n): 72
Non-mucinous(n): 30
Index test 4 (n=119): EUS-FNA imaging
Final diagnosis:
Mucinous(n): 79
Non-mucinous(n): 40
Reference standard: The final diagnosis was based on definitive tissue sampling (n=119 - diagnostic malignant cytology, resection</td><td>1) Cyst fluid CEA
<table><tr><th></th><th>T +</th><th>F -</th><th>F +</th></tr><tr><td>7</td><td>47</td><td>3</td><td>7</td></tr><tr><td>30</td><td>39</td><td>11</td><td>6</td></tr><tr><td>110</td><td>31</td><td>19</td><td>2</td></tr><tr><td>192</td><td>24</td><td>26</td><td>1</td></tr></table>Diagnostic accuracy
Sensitivity
Specificity
NPV
PPV
2) EUS
<table><tr><th>T +</th><th>F -</th><th>F +</th><th>T -</th></tr><tr><td>68</td><td>13</td><td>8</td><td>22</td></tr></table>Diagnostic accuracy
Sensitivity
Specificity
NPV
PPV
3) EUS-FNA cytology
<table><tr><th>T +</th><th>F -</th><th>F +</th><th>T -</th></tr><tr><td>52</td><td>20</td><td>4</td><td>26</td></tr></table>Diagnostic accuracy
Sensitivity</td><td>Limitations
QUADAS 2 checklist
Patient selection
Risk of bias:
Was a consecutive or random sample of patients enrolled? Yes
Was a case-control design avoided? Yes
Did the study avoid inappropriate exclusions? Yes
Could the selection of participants have introduced bias? Low risk
Applicability:
Is there concern that the included participants do not match the review question? Low concern
Index tests
Risk of bias:
Were the index tests interpreted without knowledge of the reference standard? No
If a threshold was used, was it pre-specified? Yes
Could the conduct or interpretation of the index test have introduced bias? high risk
Applicability:</td></tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests and methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td>recommended CEA and amylase cut-off values.
Study dates:
Data collection: 2003-2013
Study publication: 2015
Source of funding:
n.r.</td><td></td><td>histology or biopsy histology)</td><td>Specificity
NPV
PPV
4) EUS-FNA imaging
<table><tr><td>T +</td><td>F -</td><td>F +</td><td>T -</td></tr><tr><td>60</td><td>19</td><td>11</td><td>29</td></tr></table>Diagnostic accuracy
Sensitivity
Specificity
NPV
PPV</td><td>Is there concern that the index test, its conduct or interpretation differ from the review question? Low concern
Reference standard
Risk of bias:
Is the reference standard likely to correctly classify the target condition? Yes
Were the reference standard results interpreted without knowledge of the results of the index test? Unclear (no information given about blinding)
Could the reference standard, its conduct or interpretation have introduced bias? Unclear risk
Applicability:
Is there concern that the target condition as defined by the reference standard does not match the review question? Low concern
Flow and timing
Risk of bias:
Was there an appropriate interval between index tests and reference standard? Unclear (no information given about blinding)
Did participants receive the same reference standard? Yes
Were all patients included in the analysis? Yes
Could the participant flow have introduced bias? Low risk
Overall risk of bias: Serious risk of bias</td></tr>
</table>

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
Full citation Othman MO, Patel M, Dabizzi E, et al. Carcino embryonic antigen and long-term follow-up of mucinous pancreatic cysts including intraductal papillary mucinous neoplasm. Digestive and Liver Disease 2012;44:844–8. Country/ies where the study was carried out: USA Study type: Retrospective observational study Aim of the study: To examine the role of CEA in differentiating benign from malignant cysts Study dates: Data collection: 1998-2010 Study publication: 2012 Source of funding: None	Sample size n=63 Characteristics M/F (n): 19/44 Mean age (SD): 68.9 (0.8)	Index test 1 (n=63): Cyst fluid CEA – 6000 ng/ml Final diagnosis: Benign (n): 47 Malign (n): 16 Reference standard: The final diagnosis was based on surgical histopathology (n=63)	1) Cyst fluid CEA T + | F - | F + | T - 5 | 11 | 7 | 40 Diagnostic accuracy Sensitivity Specificity NPV PPV	Limitations QUADAS 2 checklist Patient selection Risk of bias: Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of participants have introduced bias? Low risk Applicability: Is there concern that the included participants do not match the review question? Low concern Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Unclear (no details given in the report) If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Unclear risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low concern Reference standard

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests and methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Risk of bias:
Is the reference standard likely to correctly classify the target condition? Yes
Were the reference standard results interpreted without knowledge of the results of the index test? Unclear (no information given about blinding)
Could the reference standard, its conduct or interpretation have introduced bias? Unclear risk
Applicability:
Is there concern that the target condition as defined by the reference standard does not match the review question? Low concern
Flow and timing
Risk of bias:
Was there an appropriate interval between index tests and reference standard? Unclear (no information given about blinding)
Did participants receive the same reference standard? Yes
Were all patients included in the analysis? Yes
Could the participant flow have introduced bias? Low risk
Overall risk of bias: Serious risk of bias</td></tr>
<tr><td>Full citation
Pais SA, Attasaranya S, Leblanc JK, Sherman S, Schmidt CM, et al. Role</td><td>Sample size
n=74
Characteristics
M/F (n): 38/36</td><td>Index test 1 (n=65): EUS-FNA cytology
Final diagnosis:
Benign (n): 45</td><td>1) EUS-FNA cytology<table><tr><td>T +</td><td>F -</td><td>F +</td><td>T -</td></tr><tr><td>15</td><td>5</td><td>4</td><td>41</td></tr></table></td><td>Limitations
QUADAS 2 checklist
Patient selection
Risk of bias:</td></tr>
</table>

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
of endoscopic ultrasound in the diagnosis of intraductal papillary mucinous neoplasms: correlation with surgical histopathology. Clin Gastroenterol Hepatol. 2007 Apr;5(4):489-95. Ref ID 522963 Country/ies where the study was carried out: USA Study type: Retrospective observational study Aim of the study: To evaluate the role of EUS in differentiating benign and malignant IPMNS Study dates: Data collection: 1996-2005 Study publication: 2007 Source of funding: n.r.	Mean age (range): 65 (41-84)	Malign (n): 20 Reference standard: The final diagnosis was based on histopathology (n=65)	Diagnostic accuracy Sensitivity Specificity NPV PPV Adverse events/complications**	Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? No Could the selection of participants have introduced bias? Unclear risk Applicability: Is there concern that the included participants do not match the review question? Low concern Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Unclear (no details given in the report) If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Unclear risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low concern Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests and methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Were the reference standard results interpreted without knowledge of the results of the index test? Yes
Could the reference standard, its conduct or interpretation have introduced bias? Low risk
Applicability:
Is there concern that the target condition as defined by the reference standard does not match the review question? Low concern
Flow and timing
Risk of bias:
Was there an appropriate interval between index tests and reference standard? Unclear (no information given about blinding)
Did participants receive the same reference standard? Yes
Were all patients included in the analysis? Yes
Could the participant flow have introduced bias? Low risk
Overall risk of bias: Serious risk of bias</td></tr>
<tr><td>Full citation
Park WG, Mascarenhas R, Palaez-Luna M, Smyrk TC, O'Kane D, et al. Diagnostic performance of cyst fluid carcinoembryonic antigen and amylase in histologically confirmed pancreatic cysts.</td><td>Sample size
n=124
Characteristics
M/F (n): n.r./n.r.
Median age (range): n.r.</td><td>Index test 1* (n=124): Cyst fluid CEA – n.r.
Final diagnosis:
Benign (n): 104
Malign (n): 20
Index test 2** (n=124): Cyst fluid CEA – 30, 200, 800 mg
Final diagnosis:</td><td>1) Cyst fluid CEA*
Data not reported
2) Cyst fluid CEA**
<table><tr><th></th><th>T +</th><th>F -</th><th>F +</th></tr><tr><td>30</td><td>74</td><td>7</td><td>11</td></tr><tr><td>200</td><td>49</td><td>32</td><td>3</td></tr><tr><td>800</td><td>31</td><td>50</td><td>2</td></tr></table>Diagnostic accuracy</td><td>Limitations
QUADAS 2 checklist
Patient selection
Risk of bias:
Was a consecutive or random sample of patients enrolled? Yes
Was a case-control design avoided? Yes</td></tr>
</table>

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
Pancreas. 2011 Jan;40(1):42-5. Ref ID 524684 Country/ies where the study was carried out: USA Study type: Retrospective observational study Aim of the study: To evaluate and validate cyst fluid CEA in differentiating (1) nonmucinous from mucinous PCLs, (2) benign mucinous from malignant mucinous PCLs Study dates: Data collection: 1996-2007 Study publication: 2011 Source of funding: NIH training grant 5T32DK007056.		Mucinous(n): 81 Non-mucinous(n): 43 Reference standard: The final diagnosis was based on surgical histopathology (n=104), true-cut histology or cytology (22)	Sensitivity Specificity NPV PPV	Did the study avoid inappropriate exclusions? Yes Could the selection of participants have introduced bias? Low risk Applicability: Is there concern that the included participants do not match the review question? Low concern Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Unclear (no details given in the report) If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Unclear risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low concern Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear (no information given about blinding)

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests and methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Could the reference standard, its conduct or interpretation have introduced bias? Unclear risk
Applicability:
Is there concern that the target condition as defined by the reference standard does not match the review question? Low concern
Flow and timing
Risk of bias:
Was there an appropriate interval between index tests and reference standard? Unclear (no information given about blinding)
Did participants receive the same reference standard? Yes
Were all patients included in the analysis? Yes
Could the participant flow have introduced bias? Low risk
Overall risk of bias: Serious risk of bias</td></tr>
<tr><td>Full citation
Pitman MB, Genevay M, Yaeger K, Chebib I, Turner BG, et al. High-grade atypical epithelial cells in pancreatic mucinous cysts are a more accurate predictor of malignancy than "positive" cytology. Cancer Cytopathol. 2010 Dec 25;118(6):434-40.</td><td>Sample size
n=112
Characteristics
M/F (n): 39/73
Mean age (years): 68</td><td>Index test 1 (n=112): EUS-FNA cytology
Final diagnosis:
Mucinous(n): 39
Non-mucinous(n): 73
Reference standard: The final diagnosis was based on confirmed histology (n=112)</td><td>1) EUS-FNA cytology
<table><tr><td>T +</td><td>F -</td><td>F +</td><td>T -</td></tr><tr><td>11</td><td>28</td><td>0</td><td>73</td></tr></table>Diagnostic accuracy
Sensitivity
Specificity
NPV
PPV</td><td>Limitations
QUADAS 2 checklist
Patient selection
Risk of bias:
Was a consecutive or random sample of patients enrolled? Yes
Was a case-control design avoided? Yes
Did the study avoid inappropriate exclusions? Yes
Could the selection of participants have introduced bias? Low risk</td></tr>
</table>

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
Ref ID 525627 Country/ies where the study was carried out: USA Study type: Retrospective observational study Aim of the study: To calculate the sensitivity, specificity and accuracy of EUS-FNA, the cytology diagnosis was compared with the surgical follow-up. Study dates: Data collection: n.r. Study publication: 2010 Source of funding: None				Applicability: Is there concern that the included participants do not match the review question? Low concern Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Yes If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Low risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low concern Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Yes Could the reference standard, its conduct or interpretation have introduced bias? Low risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low concern

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests and methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Flow and timing
Risk of bias:
Was there an appropriate interval between index tests and reference standard? Unclear (no information given about blinding)
Did participants receive the same reference standard? Yes
Were all patients included in the analysis? Not
Could the participant flow have introduced bias? High risk
Overall risk of bias: Serious risk of bias</td></tr>
<tr><td>Full citation
Pitman MB, Yaeger KA, Brugge WR, Mino-Kenudson M. Prospective analysis of atypical epithelial cells as a high-risk cytologic feature for malignancy in pancreatic cysts. Cancer Cytopathol. 2013 Jan;121(1):29-36.
Ref ID
524729
Country/ies where the study was carried out: USA
Study type: Prospective observational study
Aim of the study:</td><td>Sample size
n=70
Characteristics
M/F (n): 24/46
Mean age (range): 57 (19-60)</td><td>Index test 1 (n=66): EUS-FNA cytology
Final diagnosis:
Benign (n): 24
Malign (n): 42
Reference standard: The final diagnosis was based on confirmed histology (n=66)</td><td>1) EUS-FNA cytology
<table><tr><td>T +</td><td>F -</td><td>F +</td><td>T -</td></tr><tr><td>20</td><td>4</td><td>6</td><td>36</td></tr></table>Diagnostic accuracy
Sensitivity
Specificity
NPV
PPV</td><td>Limitations
QUADAS 2 checklist
Patient selection
Risk of bias:
Was a consecutive or random sample of patients enrolled? Yes
Was a case-control design avoided? Yes
Did the study avoid inappropriate exclusions? not
Could the selection of participants have introduced bias? Unclear risk
Applicability:
Is there concern that the included participants do not match the review question? Low concern
Index tests
Risk of bias:</td></tr>
</table>

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
To assess the accuracy of EUS-FNA cytology (AECs-atypical epithelial cells) in predicting malignancy in pancreatic cysts Study dates: Data collection: 2006-2011 Study publication: 2013 Source of funding: None				Were the index tests interpreted without knowledge of the reference standard? Unclear (no details given in the report) If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Unclear risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low concern Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear (no information given about blinding) Could the reference standard, its conduct or interpretation have introduced bias? Unclear risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low concern Flow and timing Risk of bias:

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests and methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Was there an appropriate interval between index tests and reference standard? Yes
Did all participants receive a reference standard? No
Did participants receive the same reference standard? Yes
Were all patients included in the analysis? Yes
Could the participant flow have introduced bias? Low risk
Overall risk of bias: Serious risk of bias</td></tr>
<tr><td>Full citation
Smith AL, Abdul-Karim FW, Goyal A. Cytologic categorization of pancreatic neoplastic mucinous cysts with an assessment of the risk of malignancy: A retrospective observational study study based on the Papanicolaou Society of Cytopathology guidelines. Cancer Cytopathol. 2016 Apr;124(4):285-93.
Ref ID
525666
Country/ies where the study was carried out: USA</td><td>Sample size
n=127
Characteristics
M/F (n): 38/89
Median age (range): n.r.</td><td>Index test 1 (n=127): EUS-FNA cytology
Final diagnosis:
Benign (n): 29
Malign (n): 98
Reference standard: The final diagnosis was based on confirmed histology (n=127)</td><td>1) EUS-FNA cytology
<table><tr><td>T +</td><td>F -</td><td>F +</td><td>T -</td></tr><tr><td>14</td><td>15</td><td>5</td><td>93</td></tr></table>Diagnostic accuracy
Sensitivity
Specificity
NPV
PPV</td><td>Limitations
QUADAS 2 checklist
Patient selection
Risk of bias:
Was a consecutive or random sample of patients enrolled? Yes
Was a case-control design avoided? Yes
Did the study avoid inappropriate exclusions? Yes
Could the selection of participants have introduced bias? Low risk
Applicability:
Is there concern that the included participants do not match the review question? Low concern
Index tests
Risk of bias:</td></tr>
</table>

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
Study type: Retrospective observational study Aim of the study: To assess the malignancy risk of cytology diagnoses of histologically proven pancreatic neoplastic mucinous cysts Study dates: Data collection: 2000-2014 Study publication: 2016 Source of funding: None				Were the index tests interpreted without knowledge of the reference standard? Yes If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Low risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low concern Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear (no information given about blinding) Could the reference standard, its conduct or interpretation have introduced bias? Unclear risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low concern Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests and methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>standard? Unclear (no information given about blinding)
Did participants receive the same reference standard? Yes
Were all patients included in the analysis? Yes
Could the participant flow have introduced bias? Low risk
Overall risk of bias: Serious risk of bias</td></tr>
<tr><td>Full citation
Song SJ, Lee JM, Kim YJ, Kim SH, Lee JY, et al. Differentiation of intraductal papillary mucinous neoplasms from other pancreatic cystic masses: comparison of multirow-detector CT and MR imaging using ROC analysis. J Magn Reson Imaging. 2007 Jul;26(1):86-93.
Ref ID
525042
Country/ies where the study was carried out: South Korea
Study type: Retrospective observational study
Aim of the study:
To compare the diagnostic performance</td><td>Sample size
n=53
Characteristics
M/F (n): 29/24
Median age (range): 67 (44-87)</td><td>Index test 1 (n=53): CT
Index test 2 (n=53): MRI
Final diagnosis:
Mucinous(n): 31
Non-mucinous(n): 22
Reference standard: The final diagnosis was based on histopathology findings (n=53)</td><td>1) CT
<table><tr><td>T +</td><td>F -</td><td>F +</td><td>T -</td></tr><tr><td>25</td><td>6</td><td>13</td><td>83</td></tr></table>Diagnostic accuracy
Sensitivity
Specificity
NPV
PPV
2) MRI
<table><tr><td>T +</td><td>F -</td><td>F +</td><td>T -</td></tr><tr><td>30</td><td>1</td><td>2</td><td>20</td></tr></table>Diagnostic accuracy
Sensitivity
Specificity
NPV
PPV</td><td>Limitations
QUADAS 2 checklist
Patient selection
Risk of bias:
Was a consecutive or random sample of patients enrolled? Yes
Was a case-control design avoided? Yes
Did the study avoid inappropriate exclusions? Yes
Could the selection of participants have introduced bias? Low risk
Applicability:
Is there concern that the included participants do not match the review question? Low concern
Index tests
Risk of bias:
Were the index tests interpreted without knowledge of the reference standard? Yes
If a threshold was used, was it pre-specified? N/A</td></tr>
</table>

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
of multirow-detector CT and MRI in the differentiation of IPMNS from other pancreatic cystic masses Study dates Data collection: 2002-2006 Study publication: 2007 Source of funding: n.r.				Could the conduct or interpretation of the index test have introduced bias? Low risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low concern Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear (no information given about blinding) Could the reference standard, its conduct or interpretation have introduced bias? Unclear risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low concern Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Unclear (no details given in the report) Did participants receive the same reference standard? No Were all patients included in the analysis? Yes

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests and methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Could the participant flow have introduced bias? High risk
Overall risk of bias: No serious risk of bias</td></tr>
<tr><td>Full citation
Sperti C, Pasquali C, Chierichetti F, Liessi G, Ferlin G, et al. Value of 18-fluorodeoxyglucose positron emission tomography in the management of patients with cystic tumours of the pancreas. Ann Surg. 2001 Nov;234(5):675-80.
Ref ID
525053
Country/ies where the study was carried out: Italy
Study type: Retrospective observational study
Aim of the study:
To assess the reliability of 18-FDG PET in distinguishing benign from malignant cystic lesions of the pancreas
Study dates:
Data collection: 1996-2000
Study publication: 2001
Source of funding:</td><td>Sample size
n=56
Characteristics
M/F (n): 21/35
Mean age (range): 60.1 (31-86)</td><td>Index test 1 (n=56): CT
Index test 2 (n=56): F-18-PET
Final diagnosis:
Benign (n): 39
Malign (n): 17
Reference standard: The final diagnosis was based on definitive pathology: resection (n=36) biopsy (n=19); and follow-up (n=1)</td><td>1) CT
<table><tr><td>T +</td><td>F -</td><td>F +</td><td>T -</td></tr><tr><td>11</td><td>6</td><td>5</td><td>34</td></tr></table>Diagnostic accuracy
Sensitivity
Specificity
NPV
PPV
2) F-18 PET
<table><tr><td>T +</td><td>F -</td><td>F +</td><td>T -</td></tr><tr><td>16</td><td>1</td><td>1</td><td>38</td></tr></table>Diagnostic accuracy
Sensitivity
Specificity
NPV
PPV</td><td>Limitations
QUADAS 2 checklist
Patient selection
Risk of bias:
Was a consecutive or random sample of patients enrolled? Yes
Was a case-control design avoided? Yes
Did the study avoid inappropriate exclusions? Yes
Could the selection of participants have introduced bias? Low risk
Applicability:
Is there concern that the included participants do not match the review question? Low concern
Index tests
Risk of bias:
Were the index tests interpreted without knowledge of the reference standard? Unclear (no details given in the report)
If a threshold was used, was it pre-specified? N/A
Could the conduct or interpretation of the index test have introduced bias? Unclear risk
Applicability:</td></tr>
</table>

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
Italian Ministry for the University, Scientific and Technological Research (MURST), projects #9906218982 and #9906195987.				Is there concern that the index test, its conduct or interpretation differ from the review question? Low concern Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear (no information given about blinding) Could the reference standard, its conduct or interpretation have introduced bias? Unclear risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low concern Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Unclear (no information given about blinding) Did participants receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the participant flow have introduced bias? Low risk Overall risk of bias: Serious risk of bias

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests and methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation
Sperti C, Pasquali C, Decet G, Chierichetti F, Liessi G, et al. F-18-fluorodeoxyglucose positron emission tomography in differentiating malignant from benign pancreatic cysts: a prospective study. J Gastrointest Surg. 2005 Jan;9(1):22-8; discussion 28-9.
Ref ID
525054
Country/ies where the study was carried out: Italy
Study type: Prospective observational study
Aim of the study:
To assess the reliability of 18-FDG PET in distinguishing benign from malignant cystic lesions of the pancreas
Study dates:
Data collection: 2000-2003
Study publication: 2005
Source of funding:
Italian Ministry for the University, Scientific and Technological Research</td><td>Sample size
n=50
Characteristics
M/F (n): 17/33
Mean age (range): 58.1 (14-87)</td><td>Index test 1 (n=50): CT
Index test 2 (n=50): F-18-PET
Final diagnosis:
Benign (n): 33
Malign (n): 17
Reference standard: The final diagnosis was based on pathologic findings of resected specimen, biopsy, or follow-up (numbers are not provided)</td><td>1) CT
<table><tr><td>T +</td><td>F -</td><td>F +</td><td>T -</td></tr><tr><td>11</td><td>6</td><td>4</td><td>29</td></tr></table>Diagnostic accuracy
Sensitivity
Specificity
NPV
PPV
2) F-18 PET
<table><tr><td>T +</td><td>F -</td><td>F +</td><td>T -</td></tr><tr><td>16</td><td>1</td><td>2</td><td>31</td></tr></table>Diagnostic accuracy
Sensitivity
Specificity
NPV
PPV</td><td>Limitations
QUADAS 2 checklist
Patient selection
Risk of bias:
Was a consecutive or random sample of patients enrolled? Yes
Was a case-control design avoided? Yes
Did the study avoid inappropriate exclusions? Yes
Could the selection of participants have introduced bias? Low risk
Applicability:
Is there concern that the included participants do not match the review question? Low concern
Index tests
Risk of bias:
Were the index tests interpreted without knowledge of the reference standard? Unclear (no details given in the report)
If a threshold was used, was it pre-specified? N/A
Could the conduct or interpretation of the index test have introduced bias? Unclear risk
Applicability:
Is there concern that the index test, its conduct or interpretation differ from the review question? Low concern
Reference standard</td></tr>
</table>

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
(MURST), 2001068593-001, Rome, Italy.				Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear (no information given about blinding) Could the reference standard, its conduct or interpretation have introduced bias? Unclear risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low concern Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Yes Did all participants receive a reference standard? Yes Did participants receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the participant flow have introduced bias? Low risk Overall risk of bias: Serious risk of bias
Full citation Takanami K, Hiraide T, Tsuda M, Nakamura Y,	Sample size n=59* Characteristics	Index test 1 (n=16*): F-18-PET Final diagnosis:	1) F-18-PET T + | F - | F + | T -	* Number of patients who were excluded from the analysis: 43 (72.9%)

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
Kaneta T, Takase K, et al. Additional value of FDG PET/CT to contrast-enhanced CT in the differentiation between benign and malignant intraductal papillary mucinous neoplasms of the pancreas with mural nodules. Annals of Nuclear Medicine 2011;25(7):501–10. Ref ID 610834 Country/ies where the study was carried out: Japan Study type: Retrospective observational study Aim of the study: To examine the additional value of FDG PET/CT to contrast-enhanced CT in the differentiation between benign and malignant IPMNs of the pancreas with mural nodules. Study dates: Data collection: 2011 Study publication: 2011 Source of funding: n.r.	M/F (n): 56/3 Mean age (SD): 66 (n.r.)	Benign (n): 7 Malign (n): 9 Reference standard: The final diagnosis was based on surgical histopathology	7 | 0 | 2 | 7 Diagnostic accuracy	Limitations QUADAS 2 checklist Patient selection Risk of bias: Was a consecutive or random sample of patients enrolled? No Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? No Could the selection of participants have introduced bias? High risk Applicability: Is there concern that the included participants do not match the review question? High concern Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Yes If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Low risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low concern Reference standard Risk of bias:

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests and methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Is the reference standard likely to correctly classify the target condition? Yes
Were the reference standard results interpreted without knowledge of the results of the index test? Unclear
Could the reference standard, its conduct or interpretation have introduced bias? Unclear risk
Applicability:
Is there concern that the target condition as defined by the reference standard does not match the review question? Low concern
Flow and timing
Risk of bias:
Was there an appropriate interval between index tests and reference standard? Yes
Did all participants receive a reference standard? Yes
Did participants receive the same reference standard? No
Were all patients included in the analysis? No
Could the participant flow have introduced bias? High risk
Overall risk of bias: Very serious risk of bias</td></tr>
<tr><td>Full citation
Talar-Wojnarowska R, Pazurek M, Durko L, Degowska M, Rydzewska G, et al.</td><td>Sample size
n=52
Characteristics
M/F (n): 28/24</td><td>Index test 1 (n=52): Cyst fluid CEA – 45 ng/ml
Index test 2 (n=52): Cyst fluid CA 19-9 – 37 ng/ml
Final diagnosis:</td><td>1) Cyst fluid CEA<table><tr><td>T +</td><td>F -</td><td>F +</td><td>T -</td></tr><tr><td>15</td><td>1</td><td>13</td><td>23</td></tr></table>Diagnostic accuracy</td><td>Limitations
QUADAS 2 checklist
Patient selection
Risk of bias:</td></tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests and methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Pancreatic cyst fluid analysis for differential diagnosis between benign and malignant lesions. Oncol Lett. 2013 Feb;5(2):613-616.
Ref ID
525107
Country/ies where the study was carried out: Poland
Study type: Retrospective observational study
Aim of the study:
To assess the diagnostic utility and clinical value of CEA and CA 19-9 in pancreatic cyst fluid.
Study dates:
Data collection: n.r.
Study publication: 2013
Source of funding:
Medical University of Lodz and the Polish Sociaty for the Digestive Tract Neoplasms Prevention.</td>
<td>Mean age (SD): 55 (3.2)</td>
<td>Benign (n): 36
Malign (n): 16
Reference standard: The final diagnosis was based on surgical histopathology, cytology results and/or imaging follow-up (>18 months)</td>
<td>Sensitivity
Specificity
NPV
PPV
2) Cyst fluid CA 19-9
<table>
<tr><td>T +</td><td>F -</td><td>F +</td><td>T -</td></tr>
<tr><td>13</td><td>3</td><td>11</td><td>25</td></tr>
</table>
Diagnostic accuracy
Sensitivity
Specificity
NPV
PPV</td>
<td>Was a consecutive or random sample of patients enrolled? Yes
Was a case-control design avoided? Yes
Did the study avoid inappropriate exclusions? yes
Could the selection of participants have introduced bias? Low risk
Applicability:
Is there concern that the included participants do not match the review question? Low concern
Index tests
Risk of bias:
Were the index tests interpreted without knowledge of the reference standard? Unclear (no details given in the report)
If a threshold was used, was it pre-specified? Yes
Could the conduct or interpretation of the index test have introduced bias? Unclear risk
Applicability:
Is there concern that the index test, its conduct or interpretation differ from the review question? Low concern
Reference standard
Risk of bias:
Is the reference standard likely to correctly classify the target condition? Yes
Were the reference standard results interpreted without knowledge of the</td>
</tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests and methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>results of the index test? Unclear (no information given about blinding)
Could the reference standard, its conduct or interpretation have introduced bias? Unclear risk
Applicability:
Is there concern that the target condition as defined by the reference standard does not match the review question? Low concern
Flow and timing
Risk of bias:
Was there an appropriate interval between index tests and reference standard? Unclear (no information given about blinding)
Did participants receive the same reference standard? Yes
Were all patients included in the analysis? Yes
Could the participant flow have introduced bias? Low risk
Overall risk of bias: Serious risk of bias</td></tr>
<tr><td>Full citation
Wu H, Yan LN, Cheng NS, Zhang YG, Ker CG. Role of cystic fluid in diagnosis of the pancreatic cystadenoma and cystadenocarcinoma. Hepatogastroenterology. 2007 Oct-Nov;54(79):1915-8.</td><td>Sample size
n=85
Characteristics
M/F (n): 26/69
Median age (range): n.r.</td><td>Index test 1 (n=85): Cyst fluid CEA – n.r.
Index test 2 (n=85): Cyst fluid CA 19-9 – n.r.
Index test 3 (n=85): Serum fluid CEA – n.r.
Index test 4 (n=85): Serum fluid CA 19-9 – n.r.
Final diagnosis:</td><td>1) Cyst fluid / serum CEA
<table><tr><th></th><th>T +</th><th>F -</th><th>F +</th><th>T -</th></tr><tr><td>Cyst fluid</td><td>30</td><td>18</td><td>5</td><td>32</td></tr><tr><td>Serum</td><td>17</td><td>31</td><td>6</td><td>31</td></tr></table>Diagnostic accuracy
Sensitivity
Specificity
NPV
PPV</td><td>Limitations
QUADAS 2 checklist
Patient selection
Risk of bias:
Was a consecutive or random sample of patients enrolled? Yes
Was a case-control design avoided? Yes
Did the study avoid inappropriate exclusions? yes</td></tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests and methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Ref ID
525699
Country/ies where the study was carried out:
Taiwan
Study type:
Retrospective observational study
Aim of the study:
To compare EUS-guided fine needle aspiration biopsy combined with measurement of the cyst fluid and serum levels of CEA, and CA19-9 for the preoperative diagnosis of pancreatic cystadenoma or cystadenocarcinoma
Study dates:
Data collection: 1998-2005
Study publication: 2007
Source of funding:
n.r.</td>
<td></td>
<td>Benign (n): 37
Malign (n): 48
Reference standard: The final diagnosis was based on surgical histopathology (n=85)</td>
<td>2) Cyst fluid/ serum CA 19-9
<table>
<tr><th></th><th>T +</th><th>F -</th><th>F +</th><th>T -</th></tr>
<tr><td>Cyst fluid</td><td>41</td><td>7</td><td>2</td><td>35</td></tr>
<tr><td>Serum</td><td>28</td><td>20</td><td>5</td><td>32</td></tr>
</table>
Diagnostic accuracy
Sensitivity
Specificity
NPV
PPV</td>
<td>Could the selection of participants have introduced bias? Low risk
Applicability:
Is there concern that the included participants do not match the review question? Low concern
Index tests
Risk of bias:
Were the index tests interpreted without knowledge of the reference standard? Unclear (no details given in the report)
If a threshold was used, was it pre-specified? No
Could the conduct or interpretation of the index test have introduced bias? High risk
Applicability:
Is there concern that the index test, its conduct or interpretation differ from the review question? Low concern
Reference standard
Risk of bias:
Is the reference standard likely to correctly classify the target condition? Yes
Were the reference standard results interpreted without knowledge of the results of the index test? Unclear (no information given about blinding)
Could the reference standard, its conduct or interpretation have introduced bias? Unclear risk
Applicability:</td>
</tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests and methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Is there concern that the target condition as defined by the reference standard does not match the review question? Low concern
Flow and timing
Risk of bias:
Was there an appropriate interval between index tests and reference standard? Unclear (no information given about blinding)
Did participants receive the same reference standard? Yes
Were all patients included in the analysis? Yes
Could the participant flow have introduced bias? Low risk
Overall risk of bias: Serious risk of bias</td></tr>
<tr><td>Full citation
Zhang S, Defrias DV, Alasadi R, Nayar R. Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA): experience of an academic centre in the USA. Cytopathology. 2010 Feb;21(1):35-43.
Ref ID
525380
Country/ies where the study was carried out: USA</td><td>Sample size
n=140
Characteristics
M/F (n): n.r./n.r.
Median age (range): n.r.</td><td>Index test 1 (n=54): EUS-FNA cytology
Final diagnosis:
Mucinous(n): 25
Non-mucinous(n): 29
Reference standard: The final diagnosis was based on surgical histopathology (n=54)</td><td>1) EUS-FNA cytology
<table><tr><td>T +</td><td>F -</td><td>F +</td><td>T -</td></tr><tr><td>7</td><td>18</td><td>3</td><td>26</td></tr></table>Diagnostic accuracy
Sensitivity
Specificity
NPV
PPV</td><td>Limitations
QUADAS 2 checklist
Patient selection
Risk of bias:
Was a consecutive or random sample of patients enrolled? Yes
Was a case-control design avoided? Yes
Did the study avoid inappropriate exclusions? Yes
Could the selection of participants have introduced bias? Low risk
Applicability:
Is there concern that the included participants do not match the review question? Low concern</td></tr>
</table>

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
Study type: Retrospective observational study Aim of the study: To calculate the sensitivity, specificity and accuracy of EUS-FNA, the cytology diagnosis was compared with the surgical follow-up. Study dates: Data collection: 2001-2006 Study publication: 2010 Source of funding: n.r.				Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Yes If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Low risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low concern Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Yes Could the reference standard, its conduct or interpretation have introduced bias? Low risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low concern Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
				standard? Unclear (no information given about blinding) Did participants receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the participant flow have introduced bias? Low risk Overall risk of bias: Serious risk of bias
Full citation Zhu H, Jiang F, Zhu J, Du Y, Jin Z, et al. Assessment of morbidity and mortality associated with EUS-guided FNA for pancreatic cystic lesions: A System Review and Meta-Analysis. Dig Endosc. 2017. Ref ID 608483 Country/ies where the study was carried out: Canada; Brazil; China; Germany; Italy, France, UK; Japan; Korea; USA Study type: Systematic review Aim of the study: To systematically evaluate morbidity and mortality associated with	Sample size SR n=40 studies with 5124 patients Inclusion criteria Studies including 10 or more patients: Who had undergone EUS-FNA for PCLs For whom adverse events after EUS-FNA had been reported Exclusion criteria Conference abstracts and letters; Reviews and guidelines; Case reports; Studies reporting insufficient data; Therapeutic EUS-FNA.	Description of the intervention, methods, outcome measures. Intervention Diagnostic EUS-guided FNA for pancreatic cystic lesions Methods Search strategy: Data collection: The literature search was up to September 2015. The included paper ranged from 1997 to 2015 PubMed and EMBASE databases were searched for all relevant clinical trials published in English language Data synthesis: Data on puncture devices, type of trial, type of study, number of needle passes, and use of antibiotics were also	Results Overall morbidity= 2.66% (95% CI: 1.84%-3.62%) Pancreatitis = 0.92% (95% CI: 0.63%-1.28%) Hemorrhage 0.69% (95% CI: 0.42%-1.02%) Pain 0.49% (95% CI: 0.27%-0.79%) Infection 0.44% (95% CI: 0.27%-0.66%) Desaturation 0.23% (95% CI: 0.12%-0.38%) Perforation 0.21% (95% CI: 0.11%-0.36%)	Limitations AMSTAR score= 11/11: low risk of bias

Bibliographic details	Participants	Tests and methods	Outcomes and results	Comments
EUS-FNA for the diagnosis of PCLs Study dates: Study publication: 2017 Source of funding: Not reported		included in the analysis. Random-effects model was used to obtain pooled estimates, and DerSimonian-Laird method was used to calculate the weighted rate of adverse events. For the meta-analysis, I2 was calculated for quantification of heterogeneity; Cochran's Q test was used to secondary assess heterogeneity amongst the included studies Outcome Post-EUS-FNA adverse events and mortality. Post-procedure events (pancreatitis, haemorrhage, infection, perforation and pain) and related fatalities were deemed to be due to EUS-FNA.		

F.41 Inherited high risk

Study details	Participants, index and reference tests	Description	Outcomes Overall risk of bias/applicability (low/high/unclear)
Full Citation Al-Sukhni, W., Borgida, A., Rothenmund, H., Holter, S., Semotiuk, K., Grant,	N=262 HRIs from 158 HR families (FPC family=159; predisposing mutation p16, BRCA2 or BRCA1=84; PJS=7;	Definition of FPC: family with ≥2 members in same lineage with PC. Methods	Study flow 36 participants dropped out (6 did not undergo MRI; 30 withdrew after MRI).

Study details	Participants, index and reference tests	Description	Outcomes Overall risk of bias/applicability (low/high/unclear)
R., Wilson, S., Moore, M., Narrod, S., Jhaveri, K., Haider, M. A. & Gallinger, S. (2012). Screening for pancreatic cancer in a high-risk cohort: an eight-year experience. Journal of gastrointestinal surgery, 16(4), 771-783. Country/ies where the study was carried out: Canada Study type: Single tertiary care centre case series Aim of the study: To report on 8-year experience of screening program for PC in HRI Study dates: 2003-2011 Source of funding: Pancreas Cancer Canada; NIH-PACGENE (Grant # 5R01CA097975-08); Princess Margaret Hospital Foundation Invest-in-Research Fund	HP=2; FDR with multiple primary cancers=10) Index test=MRI; if abnormal, MRI with contrast, multiphase contrast-enhanced CT scan, EUS, and/or ERCP Reference test=Surgical pathology, radiological findings, clinical follow up Inclusion criteria Resident in Ontario, Canada Enrolled in PC screening study between 2003-2011 Asymptomatic individuals aged 50+ years-old or 10 years younger than youngest PC diagnosis in family (whichever was youngest) and FDR or SDR of PC patient in FPC family, or Carriers of known predisposition genetic mutations p16, STK11, BRCA2, or BRCA1 with family history of PC, or FDR of people with PC and other primary cancers (double primary cancer). Asymptomatic individuals aged 25+ years old with clinical diagnosis of PJS Asymptomatic individuals aged 35+ years old with clinical diagnosis of HP	Recruitment FPC kindreds identified through clinic-based Familial Gastrointestinal Cancer Registry (FGICR) or the population-based Ontario Pancreas Cancer Study (OPCS) at Mount Sinai Hospital in Toronto. Carriers of mutations in p16, BRCA2, and BRCA1 identified through Familial Breast Cancer Research Unit at Princess Margaret Hospital and the Familial Breast Cancer Clinics at Mount Sinai Hospital and Sunnybrook Regional Cancer Centre. People with PJS identified through the polyposis database in the FGICR. Finally, some participants self-referred or referred by their physicians or local genetics centres. All eligible individuals contacted by mail with an invitation letter and reply form for participation in the screening study. Screening 2003-2009: Consisted of non-contrast MRI (1.5-T axial and coronal single shot T2-weighted Rapid acquisition with relaxation enhancement [RARE]). 2009-2011: MRI (3-T axial and coronal single shot T2-weighted RARE). If possible, pancreatic cancer diagnoses in the families of participants were confirmed by pathology reports, medical records, and/or death certificates. Molecular test reports were obtained. Baseline psychosocial and personal history questionnaire completed before first appointment. If abnormal findings, participants underwent MRI with contrast, multiphase contrast-enhanced CT scans, EUS, and/or ERCP within 3-6 months. Findings considered abnormal if: Pancreatic mass, Main duct dilation suggesting MD-IPMN or mass causing duct obstruction,	Diagnostic yield Total=19/262 (1.1%) (includes at baseline and follow up) Solid pancreatic neoplasm Diagnosed via biopsy with: PDAC=3 (FPC=2; BRCA2=1); Pancreatic NET=1 Cystic pancreatic lesions Radiologically diagnosed with BD-IPMN=15 (FPC=9; BRCA2=4; HP=1; double primary cancer=1) 9/15 remained stable over median 5.1 years (range 1-7.7) MRI Normal=176 Abnormal=86 In addition to solid and cystic lesions above, also 65 simple pancreatic cysts, 2 PanIN1-2, and 7 extrapancreatic cysts were detected. Adverse events Not reported Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of applicability

Study details	Participants, index and reference tests	Description	Outcomes Overall risk of bias/applicability (low/high/unclear)
	Informed consent Exclusion criteria None reported Participant characteristics Male/Female: 89/173 White/Causcasian non-Jewish=168 Ashkenazi Jewish=54 Other=40 Mean age at enrolment (years)=54 (range 22-89) Mean # completed appointments=4.5 (range 1-9) Mean length follow up=4.2 (range 0-8) years Former/current smoker, n=89/29 Alcohol consumption: Never or <1/month=64 ; <1/week=59; 1-6/week=76; ≥1/day=44	Branch duct dilation with communication to main duct suggesting BD-IPMN, or Extra-pancreatic mass or lesion Subsequent screening appointments included meeting with the genetic counsellor, radiological imaging, and provision of a blood sample for banking. Follow up Participants were asked to return annually, unless abnormalities noted requiring more frequent follow-up. Abnormal findings reviewed by hepatobiliary surgeon and a radiologist sub-specialized in abdominal imaging, and surgery was recommended if malignancy or dysplasia was suspected. Patients undergoing surgery followed as part of the annual screening protocol if they did not have invasive cancer.	See ROB section below for full details
Full Citation Bartsch, D. K., Slater, E. P., Carrato, A., Ibrahim, I. S., Guillen-Ponce, C., Vasen, H. F. A., Steinkamp, M. et al. (2016). Refinement of screening for familial pancreatic cancer. Gut, 65(8), 1314-1321. Country/ies where the study was carried out:	N=253 IARs (High-risk=96; Moderate risk=140; BRCA1=3; BRCA2=8; PALB2=6) High-risk=≥3 FDRs with PC; moderate risk=2 FDRs with PC. Index test=MRI/MRCP and EUS Reference test=Surgical pathology, clinical follow up Inclusion criteria Informed consent	Definition of FPC: family with ≥2 members in same lineage with PC. Recruitment Participants from 1 of 3 screening/surveillance programs run from: (1) Philipps University of Marburg (FaPaCa), (2) Ramon y Cajal University Hospital Madrid (PanGen-Fam), and (3) Leiden University Medical Centre. Screening EUS: radial, linear or curvilinear echoendoscopes with US processor under conscious i.v. sedation. MRI/MRCP: 1.5T or 3.0T clinical MR scanner. MRCP images acquired prior and after stimulation with secretin at	Study flow All participants received MRI/MRCP and EUS. Diagnostic yield Total=15/253 (5.9%) (surgical pathology only, baseline+follow up) (PDAC=2, pancreatic NET=1; Multifocal PanIN2 and Pan IN3=3; BD-IPMN with high-grade dysplasia=1; Multifocal PanIN2+BD-IPMN with low-/moderate-grade

Study details	Participants, index and reference tests	Description	Outcomes Overall risk of bias/applicability (low/high/unclear)
Netherlands, Germany and Spain Study type: Multicentre case series Aim of the study: To identify most effective screening protocol in non-CDKN2a positive individuals at risk of PC due to FPC Study dates: 07/2002-06/2015 Source of funding: Deutsche Krebshilfe (grant no. 111092) to the Marburg group. Red Temática de Investigación Cooperativa en Cáncer (grant no. RD12/0036/0034 and RD12/0036/0073); Institute of Health Carlos III (grant no. PI09/02221 and PI12/01635); European Cooperation in Science and Technology (COST) action (BM1204) to the Madrid group.	40 years-old or 10 years younger than youngest affected relative with PC* FDRs of individuals with PC that are members of FPC families, or BRCA1/2 or PALB2 germline mutation carriers with ≥1 relative with PC Exclusion criteria History of PC Patient characteristics Total sample, n=253 Median age (years)=48 (range 25-81) Male/female=115/138 All participants were Caucasian. High risk group, n=96 Median age (years)=48 (range 28-71) Male/female=43/53 Moderate risk group, n=140 Median age (years)=48 (range 26-81) Male/female=68/72 BRCA1/BRCA2/PALB2 group, n=17 Median age (years)=46 (range 25-70) Male/female=4/13	same session. All MRIs independently reviewed by experienced radiologist. FaPaCa: From 2002-2010, annual screening with MRI/MRCP and EUS (protocol 1); from 2011, annual MRI with MRCP and EUS every 3rd year or when suspicious MRI (protocol 2). If suspicious lesion detected, imaging repeated with or without EUS-FNA after 4 weeks. Multidisciplinary team decides whether to follow up or undergo surgery. PanGen-Fam: annual EUS and MRI for individuals at risk of PC. Suspicious or malignant lesions discussed by multidisciplinary team, who then decided between intensive follow up via imaging or surgery. Leiden: annual MRI with MRCP for FPC individuals at risk of PC. From 2011, EUS offered as option additional to MRI/MRCP. Individuals with suspicious lesions imaged with EUS and CT within 2-3 weeks. Suspicious cases discussed by multidisciplinary team and offered surgery if appropriate. Follow up If normal at baseline, follow-up examination recommended after 12 months. Abnormal result in MRI/MRCP or EUS were reviewed by multidisciplinary team to determine whether intensive follow up or surgery required. Suspicious cases who did not undergo surgery followed up every 3 months with EUS, MRI and MRCP for 12 months. Further screening dependent on imaging results. Criteria for surgery: Solid lesions Cystic lesions >3cm or <3cm with solid component Indeterminate lesions with irregular boundaries Positive or highly suspicious cytology on EUS-FNA Significant change in size and morphology during follow up	dysplasia with and without atypical flat lesion=6; Multifocal PanIN2=2) Total=7/253 (lesions detected at baseline) Total=8/253 (lesions detected at follow up) MRI and EUS Normal=164 Abnormal=89 Adverse events No MRI-related nor EUS-related complications were reported. Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of applicability See ROB section below for full details

Study details	Participants, index and reference tests	Description	Outcomes Overall risk of bias/applicability (low/high/unclear)
		Patient preference	
Full Citation Canto, M. I., Goggins, M., Yeo, C. J., Griffin, C., Axilbund, J. E., Brune, K., Piantadosi, S. et al. (2004). Screening for pancreatic neoplasia in high-risk individuals: an EUS-based approach. Clinical Gastroenterology and Hepatology, 2(7), 606-621. Country/ies where the study was carried out: USA Study type: Single case series Aim of the study: To evaluate feasibility of screening for pancreatic neoplasia in HRI Study dates: 1998-2001 Source of funding: None reported	N=38 IARs (FPC=37; PJS=1) Index test=EUS; if abnormal EUS-FNA, CT, and/or ERCP Reference test=Surgical pathology, clinical follow up Inclusion criteria General FPC Informed consent NFPTR participants FPC≥3 blood relatives with PC ≥40 years-old or within 10 years of age of youngest affected relative FDR of at least one family member with PC JHCTR participants Pathologically confirmed hamartomatous gastrointestinal polyps Family history of PJS and/or characteristic mucotaneous pigmentation Exclusion criteria None reported Patient characteristics Mean age (years)=56.5 Male/female=15/23 Ashkenazi Jewish descent=5	Definition of FPC: family with ≥2 members in same lineage with PC. Methods Recruitment Participants from (i) National Familial Pancreas Tumor Registry (NFPTR); (ii) asymptomatic HRI self-referred or referred by other physicians from 1998-2001 for clinical screening due to family history of PC; (iii) John Hopkins Colorectal Tumour Registry (JHCTR). Screening Participants completed comprehensive questionnaire and underwent baseline outpatient evaluation, consisting of complete history, physical examination and the screening EUS procedure. Participants also were offered genetic counselling during the initial visit, usually performed before any endoscopic procedures. Findings considered abnormal if: Focal lesion (e.g. mass, nodule or cyst) At least 3 of 9 EUS features indicative of chronic pancreatitis If abnormal EUS, participants also had EUS-FNA during same procedure. High-risk participants also had MDCT and were offered ERCP. Participants contacted within 7 days of EUS/ERCP to assess post-procedure complications. Follow up Participants suspected of having PC due to imaging or severe dysplasia on EUS-FNA referred to pancreatic surgeon and also given option of close follow up evaluation with repeat imaging and cytological sampling.	Study flow All 38 HRIs received EUS. Diagnostic yield Total=4/38 (surgery) PDAC=1 (FPC=1); IPMN=1 (PJS=1), PanIN≥2=2 EUS, n=38 Normal=9 Abnormal=29 EUS-FNA following EUS, n=21 No abnormalities detected Spiral CT following EUS, n=21 Four masses detected, all interpreted as neoplasia and possibly malignant. Two hyperechoic masses visualised by EUS not visualised by CT. ERCP following EUS, n=24 Pancreatograms were abnormal in all patients. Surgery 7 patients had exploratory surgery (partial pancreatectomy for mass [n=6] or abnormal cytology on EUS-FNA [n=1]) due to

Study details	Participants, index and reference tests	Description	Outcomes Overall risk of bias/applicability (low/high/unclear)
	Former/current smoker, n=17/5	Surgery if chosen was partial pancreatectomy (pylorus-sparing Whipple procedure or distal pancreatectomy with or without splenectomy). HRI with abnormal EUS who did not have surgery offered follow up EUS-FNA and CT scans within 3-6 months to assess stability of abnormality. All patients offered repeat EUS within 1 year from baseline evaluation. End of study in December 2002.	inability to exclude malignancy Adverse events No post-EUS-FNA complications Mild post-ERCP pancreatitis=2/24 (8.3%) Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of applicability See ROB section below for full details
Full Citation Canto, M. I., Goggins, M., Hruban, R. H., Petersen, G. M., Giardiello, F. M., Yeo, C., Ali, S. et al. (2006). Screening for early pancreatic neoplasia in high-risk individuals: a prospective controlled study. Clinical gastroenterology and hepatology, 4(6), 766-781. Country/ies where the study was carried out: USA Study type:	N=78 HRIs (FPC=72; PJS=6) Control group=161 Index test=CT and EUS; if abnormal then EUS-FNA and/or ERCP Reference test=Surgical pathology, clinical follow up Inclusion criteria General FPC or PJS Informed consent FPC patients ≥40 years old or 10 years younger than age of youngest relative with PC from kindred with 3 or more affected family members (one of	Definition of FPC: family with ≥2 members in same lineage with PC. Recruitment HRIs referred by physician/genetic counsellor or by letter via (i) National Familial Pancreas Tumor Registry (NFPTR) and (ii) John Hopkins Colorectal Tumour Registry (JHCTR). Control group recruited from John Hopkins Hospital endoscopy unit. Screening All HRIs had baseline OP evaluation (inc. visit with gastroenterologist and genetic counsellor) and at least one FU clinical and radiologic (EUS and CT) evaluation. Comprehensive family history/personal medical history questionnaire administered. Detailed clinical history and physical examination performed. An intravenous line was inserted into patient, and blood drawn for specimen bank. Findings considered abnormal if: Focal lesion (e.g. mass, nodule or cyst)	Data for HRIs only Study flow All 78 HRIs received EUS. Diagnostic yield Total=8/78 (10.3%) (includes at baseline and follow up) IPMN/≥PanIN-2=7 (FPC=6; PJS=1); PanIN1-2=1 (FPC=1) EUS, n=78 Normal=61 Abnormal=17 (includes at baseline and follow up) Abnormal findings were: 1 small mass, 11 cystic lesions/focally dilated

Study details	Participants, index and reference tests	Description	Outcomes Overall risk of bias/applicability (low/high/unclear)
Single-centre tertiary care prospective controlled cohort Aim of the study: To report results of early screening for pancreatic neoplasia in HRI and compare findings to control group. Study dates: 2001-2004 Source of funding: None reported	whom must have been a first-degree relative to participant) PJS patients ≥30 years old At least 2 of following: characteristic intestinal hamartomatous polyps, mucocutaneous melanin deposition, family history of PJS Control group Undergoing EUS and/or ERCP for non-pancreatic indications ≥30 years-old No personal or family history of PC No clinical or radiological suspicion of pancreatic disease No symptoms referable to pancreas Exclusion criteria for HRI and control groups Medical comorbidities or coagulopathy that contraindicated endoscopy Karnofsky performance status<60 Suspicion or diagnosis of PC, acute or CP, or pancreatic lesion by prior imaging studies Partial or complete resection of pancreas	At least 3 of 9 EUS features indicative of chronic pancreatitis If EUS abnormal, participants had: (i) EUS-FNA at same EUS procedure; and (ii) dual-phase multidetector spiral CT of abdomen and pelvis. ERCP also offered to those with abnormal EUS. EUS performed without knowledge of CT results; CT performed without knowledge of EUS and ERCP results. All patients contacted by telephone within 7 days of EUS and ERCP to assess for post-procedural complications. Follow up Participants suspected of having abnormality due to imaging or severe dysplasia in EUS-FNA were referred to pancreatic surgeon and also given option of close follow up evaluation with repeat imaging and cytological sampling. Surgery if chosen was partial pancreatectomy (pylorus-sparing Whipple procedure or distal pancreatectomy with or without splenectomy). HRI with abnormal EUS who did not receive surgery offered follow-up EUS/EUS-FNA and CT scan within 3-6 months to assess stability of abnormality. All participants offered repeat EUS within 1 year of baseline evaluation.	pancreatic ducts, and 5 nodules. EUS correctly diagnosed 7 of 8 pancreatic neoplasms. CT, n=78 Correctly diagnosed 5 of 8 pancreatic neoplasms. ERCP, n=65 Correctly diagnosed 2 of 8 pancreatic neoplasms. Surgery 8 of abnormal EUS had surgery; of remaining 9 abnormal EUS, 1 declined surgery and 7 had normal CT scans. Adverse events No severe complications related to EUS/EUS-FNA. Mild post-procedure abdominal pain=22 Mild adverse events (prolonged sedation, muscle ache, nausea, vomiting) during endoscopic procedures=2 Post-ERCP pancreatitis=5 (4 required hospitalisation for mean 8.25 days [range 2-12 days]) No significant post-operative complications.

Study details	Participants, index and reference tests	Description	Outcomes Overall risk of bias/applicability (low/high/unclear)
	Gastrectomy with Billroth or Roux-en-Y anastomosis Stricture or obstruction in upper gastrointestinal tract that did not allow passage of the echo-endoscope HRI group characteristics Mean age (years)=52 (range 32-77) Male/female=34/44 White=73 (94%) Ashkenazi Jewish=39%* Ever smoked=45% Current smoker=19% Mean FU (months)=22.4 (range 11.3-50.5) Significant difference in number of Ashkenazi Jewish participants in HRI group. No other significant differences between groups.		Quality of study assessed using QUADAS-2: Overall low risk of bias Overall low risk of applicability See ROB section below for full details
Full Citation Canto, M. I., Hruban, R. H., Fishman, E. K., Kamel, I. R., Schulick, R., Zhang, Z., Klein, A. P., et al. (2012). Frequent detection of pancreatic lesions in asymptomatic high-risk individuals. Gastroenterology, 142(4), 796-804.	N=216 HRIs (FPC=195; BRCA2 + relative with PC=19; PJS=2) Index test=MRI/MRCP, CT and EUS±FNA Reference test=Clinical follow up, repeat abdominal imaging, EUS-FNA, + surgical pathology. Inclusion criteria Informed consent Aged 40-80 years-old and ≥1 FDR or SDR with PC, or	American Cancer of the Pancreas Screening (CAPS) study Recruitment Participants recruited at one of 5 tertiary care medical centres or one of 3 websites. Screening All participants received gadolinium and secretin-enhanced MRCP, CT, and radial and linear EUS in this order. EUS-FNA performed as appropriate; specimens from aspirated cysts also had CEA test of volume of cyst fluid adequate. ERCP performed at discretion of clinical team to investigate ductal abnormalities. Radiologists and	Study flow Of 225 enrolled participants, 9 were excluded due to meeting exclusion criteria or withdrawal from study. Diagnostic yield Total=85/216 (39.4%) (IPMNs=82; Pancreatic NET=3) (baseline + follow up)

Study details	Participants, index and reference tests	Description	Outcomes Overall risk of bias/applicability (low/high/unclear)
Country/ies where the study was carried out: USA Study type: Multicentre case series Aim of the study: To evaluate multicentre screening and surveillance program Study dates: 12/2006-12/2009 Source of funding: Supported by the National Cancer Institute Specialized Program in Research Excellence Clinical Intervention Supplement 2 P50 CA62924, the Lustgarten Foundation for Pancreatic Cancer Research, the Michael Rolfe Foundation, Olympus Corporation, Cook Medical, Karp Family H.H. & M. Metals, Inc, Fund for Cancer Research, and ChiRhoClin.	Relatives of patients with FPC and ≥1 PC-affected FDR, OR Aged ≥30 years-old and Have PJS Exclusion criteria Inability to provide informed consent Prior pancreas screening or surgery Karnofsky performance score < 60 Suspicion of pancreatic disease Severe medical illness Bleeding diathesis or thrombocytopaenia Renal insufficiency Allergic reaction to radiographic contrast material Morbid Obesity Severe claustrophobia Upper gastrointestinal tract obstruction Patient characteristics, n=216 Age (years) <50 =62; 50-59=80; 60-69=55; ≥70=19. Male/female=100/116 Non-Hispanic White=212; Hispanic White=1; Black=2; Native American=1; Jewish ancestry=28	gastroenterologist performed tests without knowledge of results from other tests. Abnormality was abnormal result for any one modality and consisted of: Mass or dilated main pancreatic duct Surgical treatment recommended for suspected prevalent neoplasms (solid masses, suspected main duct or mixed IPMNs, branch-duct IPMNs ≥2 cm or with worrisome features for malignancy, and/or abnormal cytology. If no surgery, repeat imaging within 3 months. Surveillance with MRI/EUS recommended for small cysts (suspected BD-IPMNs) and other pancreatic lesions without worrisome features at 6-12 months. Surgery also offered for suspected extrapancreatic neoplasms if detected. Final diagnosis for all patients determined by each site's gastroenterologist based on consensus agreement between baseline imaging tests, repeat imaging, ERCP, cytology and pathology, clinical FU for minimum of 1 year from baseline. Follow up Participants called within 1 week of screening and seen by primary physician/gastroenterologist as part of routine care. If normal test or only non-specific chronic pancreatitis abnormalities, then follow up clinical visit and abdominal imaging recommended from 1 to 3 years after screening (depending on age, medical status). Patients with lesions managed according to consensus of clinical team.	Confirmed or suspected BD-IPMN=82; combined IPMN=2; pancreatic endocrine tumour=3; isolated main pancreatic duct dilation=4; indeterminate benign cyst=1, No lesion, n=124 (Non-specific chronic pancreatitis-like abnormalities =32; normal pancreas=92). Total=5/216 (surgical pathology only) [all had main duct or branch duct IPMN with multifocal PanIN≥2] Percentage agreement between EUS and MRI for detection of any lesion=91% (per patient analysis) …EUS vs CT=73% EUS EUS-FNA performed in 12 patients. # of detected lesions CT / MRI / EUS Lesion detected (n=216): 24 / 72 / 92 Solid mass: 3 / 1 / 3

Study details	Participants, index and reference tests	Description	Outcomes Overall risk of bias/applicability (low/high/unclear)
	History of smoking=18 Regular/heavy alcohol use=120 Mean FU=28.8 mo (range 14-47.2)		(any size) 24 72 79 Cystic mass (any size) 8/24 38/72 21/79 Cyst communication with MPD 1/24 1/72 3/79 Mural nodule 5 5 21 MD_pancreatic dilation (n=216) 10 29 37 BD dilation (n=216) Adverse events No surgery-related events Quality of study assessed using QUADAS-2: Overall unclear risk of bias. Overall low risk of applicability See ROB section below for full details

Study details	Participants, index and reference tests	Description	Outcomes Overall risk of bias/applicability (low/high/unclear)
Full Citation Chang, M. C., Wu, C. H., Yang, S. H., Liang, P. C., Chen, B. B., Jan, I. S., Chang, Y.T. & Jeng, Y. M. (2017). Pancreatic cancer screening in different risk individuals with family history of pancreatic cancer-a prospective cohort study in Taiwan. American Journal of Cancer Research, 7(2), 357. Country/ies where the study was carried out: Taiwan Study type: Tertiary care prospective cohort Aim of the study: To evaluate PC screening program in Taiwan Study dates: 2003-2015 Source of funding: Ministry of Health and Welfare (MOHW): MO-HW103-TD-B-111-04, MOHW104-TDU-B-211-124-002 and MOHW105-TDU-B-211-134005; Ministry of Science and	N=303 IARs (HP=31 [PSRSS1=24; SPINK1=7]; BRCA1/2=1) (High risk=119, moderate risk=32, low risk=152) Index test=MRI/MRCP and/or EUS±FNA Reference test=surgical and other (CT) pathology or clinical follow up Inclusion criteria FPC Informed consent Enrolled from 2003-2015 Exclusion criteria None reported Patient characteristics Mean age (years)=51.1 (13.9) Male/female=116/187 History of smoking=62 (21%) Mean FU (years)=6.5 (range 1-12) Ethnicity of all participants was Han Chinese. ≥2 FDR with PC=47; ≥2 FDR, SDR, or 3rd degree relative with PC=68	FPC defined as ≥2 FDRs with PC and no identified genetic abnormality. 'High-risk'=risk of PC>10 times that of normal population (e.g. FPC, BRCA2, hereditary pancreatitis (PRSS1 or SPINK1 mutations), ≥3 relatives of any degree with PC) 'Moderate risk'=risk of PC between 5 and 10 times that of normal population (>2 relatives of any degree with PC; 1 FDR with PC <55 years-old) 'Low risk'=risk of PC<5 times that of normal population (1 relative with PC >55 years-old). Recruitment All individuals with family history of PC and who were interested in risk of disease were enrolled in screening program at largest tertiary care referral centre in Taiwan (National Taiwan University Hospital). Screening Program included detailed history and physical examination, family history, personal and family health history, results of all imaging and blood tests, storage of frozen serum and any surgically resected tissue if relevant. On initial visit, participants assessed for level of risk and classified into high, moderate and low risk categories. Low risk individuals not normally recommended screening. All screened participants received MRI/MRCP and/or curvilinear EUS± (linear) FNA, CA-19-9 and lipase examination. All participants also received genetic counselling and genetic testing for relevant mutations. If abnormality detected then annual MRI arranged. If no abnormality detected on initial screening, follow up MRI/MRCP conducted every 2-3 years. MRI/MRCP images reviewed by radiologists blinded to risk status. Follow up	Study flow All participants received MRI/MRCP. Diagnostic yield (includes all groups) Total=15/303 (pathology only, baseline + follow up) (PDAC=7; IPMN=3; PNET=1; solid+papillary epithelial neoplasm=1; mucinous cystic neoplasm=3) [High risk=5; moderate risk=1; low risk=9] High-and moderate-risk groups only Total=6/151 (High risk: PDAC=2, IPMN=3; moderate risk=PDAC=1) MRI/MRCP, n=303 Normal=175 Abnormal=128 (Any focal lesion=97 [solid=47; cystic=54 (IMPN=47; other=6)]; chronic pancreatitis=68) EUS, n=18 18 participants received EUS due to abnormal or uncertain MRI or MRI/MRCP findings indicating surgery.

Study details	Participants, index and reference tests	Description	Outcomes Overall risk of bias/applicability (low/high/unclear)
Technology (MOST): MOST 102-2321-B-002-083-, MOST 103-2321-B-002-048-, and MOST 104-2321-B-002 -009-; Taiwan Pancreas Foundation.		Participants evaluated as clinically indicated. Surgery considered for those found to have resectable solid mass lesions, high suspicion of MD-IPMN or abnormal EUS cytology. At risk participants who did not have surgery entered surveillance. HRIs who had surgery followed up with MRI and/or EUS. Moderate risk participants had annual imaging. Low risk individuals had annual tests and further testing if developed or had new onset diabetes mellitus.	EUS-FNA, n=11 6 participants received EUS-FNA for solid lesions, and 6 for cystic lesions. 3 cases showed cellular atypia and received surgery: 1 had stage 1 PAC and 2 had CP with pseudotumour formation. Pathological diagnosis, n=18 17 participants had surgery whilst one had CT-guided biopsy. Adverse events There were no procedure-related complications. Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of applicability See ROB section below for full details
Full Citation Del Chiaro, M., Verbeke, C. S., Kartalis, N., Mucelli, R. P., Gustafsson, P., Hansson, J., Löhr, J. M. et al. (2015). Short-term Results of a Magnetic Resonance Imaging–Based Swedish Screening Program for Individuals at	N=40 IARs (FPC=38; 1 FDR with PC and BRCA2 syndrome=2) Index test=MRI/MRCP; if abnormal, EUS (±FNA) and/or CT scan Reference test=Surgical pathology, clinical follow up Inclusion criteria	Recruitment Participants were (i) relatives of patients treated for PC at Karolinska University Hospital that had positive family history of PC of positive history of associated genetic syndrome; (ii) referred from other Swedish Centres or GPs and at genetically increased risk. Screening Full personal and family medical history (including pedigree) obtained and clinical evaluation performed. All	Study flow All 40 patients received MRI/MRCP. Diagnostic yield Total=5/40 (includes baseline [n=4] and follow up [n=1]) IPMN=2; PDAC=2; Mixed IPMN+PDAC=1

Study details	Participants, index and reference tests	Description	Outcomes Overall risk of bias/applicability (low/high/unclear)
Risk for Pancreatic Cancer. JAMA surgery, 150(6), 512-518. Country/ies where the study was carried out: Sweden Study type: Single-centre case series Aim of the study: To report short-term results of PC screening program using non-invasive MRI Study dates: 01/2010-01/2013 Source of funding: Not reported	Written informed consent ≥45 years-old or 10 years younger than youngest affected relative 2 relatives (≥1 FDR) with PC in same lineage, or ≥3 FDR, SDR or third-degree relative with PC in same lineage, or Mutation carrier for BRCA1, BRCA2 or p16 with ≥1 FDR or SDR with PC, or Germline carrier of PJS kindred Exclusion criteria None reported Patient characteristics Mean age (years)=49.9 (range 23-76) Male/female=16/24 Current smoker=4 Mean FU (months)=12.9 (range 0-36 months) Mutations: p16=4; BRCA1=1; BRCA2=3.	patients had MRI/MRCP with secretin and also had genetic testing for BRCA1, BRCA2 and p16. If abnormal MRI/MRCP then patients had EUS (±FNA) and/or CT scan. Abnormal findings consisted of: Solid nodules IPMN lesions All abnormal findings discussed at pancreatic multidisciplinary conference. Patients with suspected PC treated with radical surgical procedure; suspected pre-malignant IPMN lesion had radical or parenchyma-sparing surgical resection. Follow up If normal results, rescreening with MRI/MRCP after 1 year recommended. If unspecific findings or IPMN without indication for surgery, 6-month MRI follow up recommended.	All 5 of these patients were from FPC group and had no detected genetic mutations. MRI/MRCP, n=40 Normal=24 Abnormal=16 (includes at baseline [n=12] and follow up n=4]) BD-IPMN=9; mixed-type IPMN=2; MD-IPMN=2; PDAC=1; PDAC + mixed-type IPMN=1 Surgery 5 of 16 abnormal MRI/MRCP patients underwent surgery (total pancreatectomy=2; distal pancreatectomy=1; pancreato-duodenectomy=1; mutiple enucleations=1). Remaining 11 screened with MRI at 6-mo intervals (7 stable, 4 non-significant progression). Adverse events Not reported Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of applicability See ROB section below for full details

Study details	Participants, index and reference tests	Description	Outcomes Overall risk of bias/applicability (low/high/unclear)
Full Citation 1. Harinck, F., Konings, I. C. A. W., Kluijt, I., Poley, J. W., van Hooft, J. E., van Dullemen, H. M., Wagner, A. et al. (2016). A multicentre comparative prospective blinded analysis of EUS and MRI for screening of pancreatic cancer in high-risk individuals. Gut, 65(9), 1505-1513. 2. Konings, I. C., Sidharta, G. N., Harinck, F., Aalfs, C. M., Poley, J. W., Kieffer, J. M., Rens, A. et al. (2016). Repeated participation in pancreatic cancer surveillance by high-risk individuals imposes low psychological burden. Psycho-Oncology, 25, 971-978. Country/ies where the study was carried out: Netherlands Study type: Multicentre case series Aim of the study: To compare efficacy of EUS and MRI to detect clinically-relevant lesions	(Harinck 2016) N=166 HRIs (FPC=68; CDKN2A=38; BRCA1=3; BRCA2=20; PJS=7; Li-Fraumeni syndrome/p53=3) (Konings 2016) N=152 HRIs (FPC=75; CDKN2A=43; BRCA1=4; BRCA2=20; PJS/LKB1 or STK11=7; p53=3) Index test=MRI and EUS Reference test=Surgical pathology, clinical follow up Inclusion criteria Informed consent ≥45 years-old or 10 years younger than youngest relative with PC CDKN2A carrier (familial cutaneous malignant melanoma), regardless of family history of PC, or PJS (LKB1) and ≥30 years-old or 10 years younger than youngest relative with PC, or BRCA1 or BRCA2 (hereditary ovarian and breast cancer), Li-Fraumeni syndrome (p53) or Mismatch Repair Gene syndrome (Lynch Syndrome) with family history of PDAC ≥2 family members, or FDR of patients with FPC Exclusion criteria History of PAC	FPC defined as families affected by PDAC with at least (i) two FDRs, (ii) three relatives in which the affected cases are FDR or SDR of each other or (iii) two SDRs of whom at least one relative was aged <50 years at the time of diagnosis. Recruitment Participants from Familial Pancreatic Cancer Surveillance Study. Screening Participants have detailed evaluation to confirm eligibility (includes personal and family medical history evaluation, verification of reported clinical diagnoses by review of medical/pathological records and revision of histological slides if available, genetic testing for relevant mutations). All patients received (radial or curvilinear) EUS and MRI. Gastreoenterologists and radiologists blinded to baseline results of either EUS or MRI as appropriate. Abnormal findings consist of: Solid lesions suspicious for malignancy Lesions satisfying revised Sendai criteria for surgery or close FU (MD-IPMN, cysts≥10mm) If solid lesion morphologically suspicious for a malignancy, cystic lesion >30 mm, cystic lesions with malignant features (thickened/ enhancing cyst walls and/or mural nodules) or main branch IPMN with main pancreatic duct ≥10 mm, then patient underwent surgical resection. Follow up Policy agreed by expert panel (endosonographists, surgeons, radiologists and pathologists) consisted of: annually if normal EUS and/or MRI; 3-month follow up if lesion of unknown clinical significance detected on EUS and/or MRI; 6-month follow up if cyst or side branch IPMN	Date for Harinck 2016 Study flow 27 excluded (pancreatic screening prior to inclusion=22; did not receive EUS or MRI=5) Diagnostic yield Total=9/139 (all detected at baseline) Solid lesions=2 PDAC=1 (HMMM/CDKN2A=1) Multifocal PanIN-2=1 (FPC=1) Cysts FPC=6; PJS/LKB1=1; HMMM/CDKN2A=1 EUS and MRI, n=139 Normal=130 Abnormal=9 There were 11 abnormal lesions detected (2 patients had 2 cystic abnormalities each); 6 of them detected by both EUS and MRI, 8 by EUS only and 9 by MRI only; MRI did not detect the 2 solid lesions. Agreement at baseline per participant (n=9)/per lesion (n=11)=56%/55%

Study details	Participants, index and reference tests	Description	Outcomes Overall risk of bias/applicability (low/high/unclear)
in HRI (Harinck 2016); to evaluate psychological burden of annual screening (Konings 2015) Study dates: Data until 09/2013 (Harinck 2016) 2008-? Source of funding: ZonNW grant number 10520016	Aged <18 years-old Upper CI tract obstruction Severe medical illness (American Society of Anaesthesiologists' score ≥3) Inability to provide informed consent Language barrier Patient characteristics Mean age (years)=51 (sd=9.7; range 20-73) Male/female=63/76 Current smoker=16	with a diameter >10 mm and <30 mm without malignant features detected on EUS and/or MRI. Questionnaire details (Konings 2016) Participants receive their questionnaires 1–4 weeks after counselling/intake or surveillance results. Time 0 (T0): Participants receive a first questionnaire on background data after having undergone counselling by the clinical geneticist. Time 1 (T1): second questionnaire received after explanation of study procedures by the gastroentero-logist (T1). Time 2+ (T2/T3 etc.): subsequent questionnaires received annually after surveillance results from T1 received. Questionnaire study added after the first inclusion period of original clinical study protocol. Therefore some participants had already had their first investigations and therefore started their questionnaires at T2. Measurements included: Sociodemographic and clinical data Motivations for participation in PC surveillance Attitudes towards and experiences with participation in PC surveillance Perceived risk of PC Cancer Worry Scale Anxiety and depression (HADS-A, HADS-D) Topics of concern and need for additional psychosocial support	Agreement at 12-mo FU per participant (n=8)/per lesion (n=12)=50%/67% Adverse events No procedure-related complications occurred. Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of applicability See ROB section below for full details Data for Konings 2016 140 of 152 HRIs returned at least one questionnaire. No significant differences on patient characteristics between those that did and did not return questionnaire. 477 questionnaires received and analysed: 36 of 38 at T0; 69 of 74 at T1; 127 of 136 at T2; 109 of 116 at T3; 85 of 93 at T4; 51 of 54 at T5. Mean # questionnaires returned per respondent=3.4 (range 1-6), Cancer Worry Scale (scale 8-32) Mean CWS score=13 (sd 3.6)

Study details	Participants, index and reference tests	Description	Outcomes Overall risk of bias/applicability (low/high/unclear)
			Mean score at T0=14.4 (sd 4.3); T1=14; T2=13.3; T3=12.4; T4=12.5; T5=12.1. Significant intra-individual decrease over time relative to T0 (0.5 point each year) – β=-0.53, SE=0.09, 99% CI (-0.78 to -0.28). P<0.001 (proportional analysis; non-proportional analysis p<0.01; Note that α=0.01 due to multiple testing) Anxiety (HADS-A, scale 0-21) T0=5.3; T1=4.6; T2=4.3; T3=4.3; T4=4.4; T5=4.5. Mean HADS-A=4.5 (sd=3.7) Depression (HADS-D, scale 0-21) T0=2.5; T1=2.4; T2=2.6; T3=2.9; T4=3.2; T5=2.8. Mean HADS-D=2.8 (sd=3.2) No significant intra-individual changes over time on either HADS measure. Severe anxiety experienced by 7% and depression experienced by 5% of participants.
Full Citation Kimmey, M. B., Bronner, M. P., Byrd, D. R., & Brentnall, T. A. (2002).	N=46 HRIs (FPC with >2 FDR or SDR with PC) Index test=EUS; if abnormal, ERCP	Recruitment University of Washington screening program for FPC. Screening	Study flow All 46 HRIs received EUS Diagnostic yield

Study details	Participants, index and reference tests	Description	Outcomes Overall risk of bias/applicability (low/high/unclear)
Screening and surveillance for hereditary pancreatic cancer. Gastrointestinal endoscopy, 56(4), S82-S86. Country/ies where the study was carried out: USA Study type: Single-centre case series Aim of the study: To report on results of PC screening program Study dates: 1997-2002 Source of funding: Not reported	Reference test=Surgical pathology, clinical follow up Inclusion criteria FPC with >2 FDR or SDR with PC Exclusion criteria None reported Patient characteristics No patient characteristics reported.	Detailed personal, medical and family history of PC and other cancers taken. Patients with abnormal EUS offered ERCP if no alcohol consumption in past 6 months; if alcohol consumption within 6 months, patients asked to abstain for 6 months before repeat EUS. Surgery offered to patients with abnormal ERCP findings: total pancreatectomy advised for symptomatic patients, laparaoscopic distal pancreatectomy for asymptomatic patients, and completion pancreatectomy for those with high grade dysplasia. Note: no definition of 'abnormal' findings provided. Follow up If abnormal EUS but normal ERCP, then follow up EUS occurs. Repeat ERCP performed if EUS findings indicate progression.	Total=12/46 (26.0%) (baseline + follow up, pathology only) Small- and medium-sized ducts with dysplasia=12 EUS, n=46 Normal=22 Abnormal=24 ERCP, n=28 Normal=15 Abnormal=13 Surgery, n=12 Normal=0 Abnormal=12 Adverse events No post-ERCP complications occurred. Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of applicability See ROB section below for full details
Full Citation Ludwig, E., Olson, S. H., Bayuga, S., Simon, J., Schattner, M. A., Gerdes, H., Allen, P.J., Jarnagin, W.R. & Kurtz, R. C.	N=109 IARs (FPC=102; BRCA1 or BRCA2 and FPC=7) Index test=MRCP or CT; if abnormal, EUS±FNA Reference test=Surgical pathology, clinical follow up	Recruitment Participants from Familial Pancreatic Tumor Registry (FPTR) at Memorial-Sloan Kettering Cancer Center. Screening All participants had detailed evaluation of family history and related epidemiology. Genetic counselling also	Study flow 11 participants received initial CT rather than MRCP. Diagnostic yield Total=9/109 (8.3%) (baseline and follow up)

Study details	Participants, index and reference tests	Description	Outcomes Overall risk of bias/applicability (low/high/unclear)
(2011). Feasibility and yield of screening in relatives from familial pancreatic cancer families. The American journal of gastroenterology, 106(5), 946-954. Country/ies where the study was carried out: USA Study type: Single-centre case series Aim of the study: To evaluate safety and yield of screening for FPC patients Study dates: 12/2002-08/2009 Source of funding: None reported	Inclusion criteria Completed at least one cycle of screening at FPTR centre as of 01/08/2009 ≥35 years-old Informed consent ≥1 FDR with PC <50 years old, or ≥2 relatives with PC (at least 1 FDR), or ≥3 SDR with PC, or Known BRCA1 or BRCA2 mutation with ≥1 relative with PC Exclusion criteria None reported Patient characteristics Mean age (years)=54 (sd=11.4; range 33-86) Male/female=29/80 Jewish religion=36	offered. Screening involved office visit, physical examination and MRCP. Cross-sectional imaging results reviewed by multidisciplinary team (including hepatopancreatobiliary surgeons, gastroenterologists, interventional radiologists, medical and radiation oncologists, and radiologists). If abnormal, then offered radial or curvilinear EUS-FNA using 25-G needle for cytological evaluation and cyst fluid carcinoembryonic antigen as indicated. Surgery for premalignant/malignant lesion determined by patient/surgeon. Abnormal findings consist of: cystic lesion with solid or nodular component pancreatic duct dilation pancreatitis or other lesions deemed of concern by multidisciplinary team Following EUS-FNA, patients recover in day hospital and are discharged on same day. Telephone call day after procedure to identify post-procedural complications. Follow up Annual follow up comprising office visit, physical exam and MRCP.	Total (surgery only)=6/109 >65 years-old=6/17 55-65 years-old-1/31 <55 years-old=2/61 All patients from FPC group without genetic mutation unless otherwise stated. T3N0 pancreatic cancer=1; IPMN=2; PanIN-3=1; PanIN-2=1 Serous cystadenoma=1; Suspected IPMN but declined surgery=3 (1 patient had BRCA mutation) MRCP, n=109 Normal=91 Abnormal=18 EUS, n=15 Normal=6 Abnormal=9 8 of 9 EUS abnormal patients had EUS-FNA; 6 normal had EUS only Surgery, n=6 6 of 9 abnormal EUS patients had surgery, 3 declined. Adverse events No adverse events occurred after cross-sectional imaging studies.

Study details	Participants, index and reference tests	Description	Outcomes Overall risk of bias/applicability (low/high/unclear)
			No patient required intravenous sedation for MRCP. In addition, all EUS ± FNA patients tolerated procedure well and were discharged from surgical day hospital recovery room in stable condition on same day as procedure. No procedure related complications reported on follow up telephone calls. Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of applicability See ROB section below for full details
Full Citation Nicholson, J. A., Greenhalf, W., Jackson, R., Cox, T. F., Butler, J. V., Hanna, T., Raraty, M. G. et al. (2015). Incidence of post-ERCP pancreatitis from direct pancreatic juice collection in hereditary pancreatitis and familial pancreatic cancer before and after the introduction of prophylactic pancreatic	N=60 HRIs (FPC syndrome=48; HP=12) Index test=ERCP Reference test=Surgical pathology, follow up Inclusion criteria Written informed consent Hereditary pancreatitis ≥40 years-old, or FPC and 10 years younger than age at death of youngest PC relative or ≥40 years-old if age	FPC defined as ≥1 FDR or SDR with PC. Recruitment Participants recruited from EUROPAC registry as part of larger screening program at Royal Liverpool Hospital involving imaging, CA 19-9 testing, and ERCP. Screening FPC and HP patients received CT or MRI. FPC patients also received EUS. Option of ERCP given to all patients. Pancreatic juice from ERCP analysed for TP53 and KRAS2 mutations and quantification of CDKN2A promoter methylation. ERCP was performed either with no prophylaxis (patients from 1999-2008), single or dual prophylaxis (patients from 2008-2013). Prophylaxis	Study flow 12 HP patients had 24 ERCP procedures; 48 FPC patients had 56 ERCP procedures. Diagnostic yield Total=2/60 (surgical pathology only) (PanIN1-2=2, both from HP group) Post-ERCP pancreatitis (PEP) (n=48; 56 procedures)

Study details	Participants, index and reference tests	Description	Outcomes Overall risk of bias/applicability (low/high/unclear)
stents and rectal diclofenac. Pancreas, 44(2), 260-265. Country/ies where the study was carried out: UK Study type: Single-centre retrospective review of prospective cohort study Aim of the study: To determine risk of post-ERCP pancreatitis in PC HRIs Study dates: 01/1999-12/2013 Source of funding: National Institute for Health Research, the European Union FP5, Solvay Healthcare (now Abbott), and North West Cancer Research Fund.	of this relative was >50 years-old. Exclusion criteria None reported Patient characteristics Mean age (years)=54 (IQR=45.25-62) Male/female=27/33 Never smoked=33 Previous or current smoker=27	consisted of 3cm 5F self-expelling stent and/or 50mg diclofenac. Patients routinely discharged on same day if no complications. Post-ERCP acute pancreatitis defined as (i) increase in serum amylase level at least 3 times (>450 IU/L) upper limit of normal (150 IU/L) and (ii) abdominal pain within 48 hrs of ERCP. Follow up All patients contacted 6 weeks after ERCP to inform them of results and check for any complications. If stent had been inserted, plain abdominal x-ray 6-weeks after ERCP undertaken to determine if stent expelled. Newcastle-Ottawa Scale quality assessment of study for post-ERCp pancreatitis (Yes/no/unclear) Selection Representative of exposed cohort (with prophylaxis)? Yes (UK residents of EUROPAC registry) Selection of non-exposed cohort (without prophylaxis)? Yes (same community as exposed cohort) Sufficient ascertainment of exposure: Yes (blood or genetic marker tests) Outcome of interest not present at start of study? Yes Comparability Cohorts comparable on basis of design/analysis? Unclear (non-exposed group not matched; not controlled) Outcome Sufficient assessment? Yes (serum amylase levels/self-report of abdominal pain) Adequate follow up for outcome to occur? Yes (within 48 hours of ERCP)	Total=13/56 procedures, all in FPC cohort No prophylaxis group (1999-2008) FPC=7 PEP cases in 16 procedures; HP=No PEP cases in 18 procedures. Single and dual prophylaxis groups (2008-2013) FPC=6 PEP cases in 40 (15 in single group; 25 in dual group) procedures; HP=No PEP cases in 6 procedures. Four of 6 PEP cases were from dual prophylaxis group; 1 each from single groups (diclofenac only, stent only) Other adverse events 1 case of post-ERCP duodenal perforation manged conservatively. Quality of study assessed using QUADAS-2 (diagnostic yield): Overall low risk of bias. Overall low risk of applicability Quality of study for post-ERCP pancreatitis Overall very low quality.

Study details	Participants, index and reference tests	Description	Outcomes Overall risk of bias/applicability (low/high/unclear)
		Adequate follow up of cohort? Yes (post-ERCP pancreatitis defined as occurring within 48 hours of ERCP).	Unclear whether groups are comparable (13 year period of study, changes in diagnostic tests [e.g. accuracy], not controlled); data provided in terms of # of adverse events relative to # of ERCP procedures rather than # of people who had adverse events.
Full Citation Poley, J. W., Kluijt, I., Gouma, D. J., Harinck, F., Wagner, A., Aalfs, C., Fockens, P. et al. (2009). The yield of first-time endoscopic ultrasonography in screening individuals at a high risk of developing pancreatic cancer. The American journal of gastroenterology, 104(9), 2175-2181. Country/ies where the study was carried out: Netherlands Study type: Multicentre case series Aim of the study: To report results of EUS screening for PC HRIs	N=44 HRIs (FPC=21, FAMM=13; BRCA=1; BRCA2=2; PJS=2' HP=2; Li-Fraumeni syndrome=1) Index test=EUS; if abnormal, CT and/or MRI Reference test=Surgical pathology, clinical follow up Inclusion criteria ≥40 years-old or ≥5 years younger than youngest affected family member Asymptomatic for signs/symptoms of PC At least two family members with PC and Hereditary breast and ovarian cancer syndrome (BRCA1/BRCA2) Lynch syndrome Li-Fraumeni syndrome (p53)	Familial pancreatic cancer defined as 2 or more FDR with PC. Recruitment First-time EUS screening study. Screening All participants received radial or curvilinear EUS. If abnormal EUS, then followed by CT and/or MRI and discussed by multidisciplinary team. Abnormal findings consist of: Mass or cystic lesions Duct aberrations Signs of chronic pancreatitis Follow up Twice-yearly intensive follow up with EUS and MRI for small cystic lesions with no sign of malignancy.	Study flow All 44 participants received EUS. Diagnostic yield Total=10/44 (23%) PDAC=3 (FAMMM=2; BRCA2=1) IPMN=7 (FAMMM + HMMM/CDKN2A=1; FPC=3; FAMMM=2; BRCA1=1) EUS, n=40 Normal=30 Abnormal=10 Solid lesion=3; IPMN=7 Unclear how many participants received CT and/or MRI. Adverse events All participants left hospital maximum 2h after procedure.

Study details	Participants, index and reference tests	Description	Outcomes Overall risk of bias/applicability (low/high/unclear)
Study dates: 04/2005-10/2007 Source of funding: None reported	Mutation carriers of known pathogenic mutations Informed consent Exclusion criteria Abdominal imaging by CT, MRI or EUS in past 3 years Patient characteristics Mean age (years)= (range 32-75) Male/female=18/26 All participants were Caucasian.		No EUS-related complications occurred. Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of applicability See ROB section below for full details
Full Citation Potjer, T. P., Schot, I., Langer, P., Heverhagen, J. T., Wasser, M. N., Slater, E. P., Bargello, M. et al. (2013). Variation in precursor lesions of pancreatic cancer among high-risk groups. Clinical cancer research, 19(2), 442-449. Country/ies where the study was carried out: Netherlands; Germany Study type: Multicentre prospective cohort Aim of the study: (1) To compare frequency of precursor lesions and pancreatic duct	N=241 IARs (FPC=125 [high risk=59, moderate=66]; p16=116) FPC cohort includes high- and moderate- risk individuals [High risk=individuals ≥3 FDRs with PC or with BRCA2/PALB2 mutation; Moderate risk=individuals with 2 FDRs with PC] Index test=MRI/MRCP Reference test=Surgical pathology, clinical follow up Inclusion criteria Informed consent P16 mutation and aged 45-70 years-old, and able to undergo major surgery, or Aged 40 years –old or 10 years younger than youngest age of onset of PC in family and	FPC defined as ≥2 FDRs with confirmed PDAC. Recruitment P16 cohort from Leiden University Medical Centre screening/surveillance programs. FPC cohort from Philipps-University of Marburg (FaPcCa) screening/surveillance programs. Screening For FPC cohort, screening consisted of annual MRI/MRCP and EUS±FNA; for p16 cohort, screening consisted of annual MRI/MRCP with or without EUS. Data only for MRI/MRCP here. Surgical specimens investigated at each centre and reassessed by single pathologist. Follow up If normal MRI, then annual follow up. If abnormal, multidisciplinary team recommended either close follow up with MRI/MRCP and EUS or surgery. For p16 group, MRI/MRCP was repeated within 2-4 months if the results were unclear. For FPC group, if abnormal MRI/MRCP, EUS±FNA repeated after 6 weeks; if still suspicious, close follow-up after 6 weeks. If stable, repeat evaluation after 6 months, then every 12 months. Criteria for surgery were:	Study flow All 241 participants received MRI/MRCP. Diagnostic yield P16 cohort Total=7/116 (surgical histology only, baseline + follow up) (PDAC=6; BD-IPMN+PanIN1-2=1) FPC cohort Total=7/125 (surgical histology only; baseline + follow up) (PDAC=1; BD-IPMN=1; BD-IPMN + PanIN≥2=4; PanIN2=1) Adverse events No data reported

Study details	Participants, index and reference tests	Description	Outcomes Overall risk of bias/applicability (low/high/unclear)
adenocarcinoma between p16 and familial pancreatic cancer cohorts; (2) to compare features and natural course of precursor lesions; (3) to discuss implications for surveillance protocol. Study dates: 01/2000-12/2011 Source of funding: Supported by grants from Deutsche Krebshilfe (no. 109126 to D.K. Bartsch) for the FaPaCa project; ZonMW, an independent organization supported by the government, for the p16-Leiden cohort.	≥2 FDRs with confirmed PC, or Member of FPC family and BRCA2 or PALB2 mutation Exclusion criteria Significant comorbidity for p16 group Evidence of other inherited tumour syndrome for FPC group Did not receive MRI/MRCP Patient characteristics for FPC group Median age (years)=47 (range 27-73) Male/female=54/71 Patient characteristics for p16 group Median age (years)=54 (range 38-72) Male/female=50/66	Cystic lesion >3 cm with solid component Inhomogenous hypoechoic lesions with irregular boundaries in HRIs with strong family history (e.g. ≥3 affected FDRs) Positive of highly suspicious EUS-FNA Significant change in size and morphology during follow up Patient preference	Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of applicability See ROB section below for full details
Full Citation Sud, A., Wham, D., Catalano, M., & Guda, N. M. (2014). Promising outcomes of screening for pancreatic cancer by genetic testing and endoscopic ultrasound. Pancreas, 43(3), 458-461. Country/ies where the study was carried out:	N=30 HRIs (FPC=19; BRCA1/BRCA2 and ≥1 relative with PC=7; PJS=2; HMMM and family history of PC=1; Lynch syndrome and family history of PC=1) [Note that this includes 14 patients that did not have initial EUS] Index test=EUS; if abnormal, EUS-FNA	'High-risk' defined as lifetime risk ≥5% for PC (with exception of Lynch syndrome) Recruitment Participants recruited for genetic counselling by (i) primary care providers or oncologists due to personal and/or family history of malignancy, or (ii) referral due to family history of PC. Screening Genetic counselling provided to all potential HRIs consisting of hereditary cancer risk assessment and, if indicated, genetic testing. Eligible patients referred to gastroenterologist. Patients had initial EUS and repeat	Study flow 14 patients did not have EUS for various reasons (e.g. treated for other cancers; lost to FU) Diagnostic yield Total=3/16 (pathology only, baseline + follow up) PDAC=2 (BRCA2=1); IPMN with low grade dysplasia=1 (PJS=1)

Study details	Participants, index and reference tests	Description	Outcomes Overall risk of bias/applicability (low/high/unclear)
USA Study type: Single-centre case series Aim of the study: To determine if initially screening patients for PC by genetic counselling followed by EUS ± FNA in HRI leads to early detection. Study dates: 2008-2011 Source of funding: None reported	Reference test=surgical pathology, clinical follow up Inclusion criteria 2 FDRs on same lineage with PC, or ≥3 relatives on same lineage with PC, or Mismatch Repair Gene syndrome (Lynch syndrome) and ≥1 relative with PC, or Hereditary Pancreatitis, or Peutz-Jeghers syndrome, or Hereditary multiple mole and melanoma syndrome (p16) and ≥1 relative with PC Exclusion criteria None reported Patient characteristics (n=30) Mean age (years)=51.28 (range 20-75) Male/female=unclear (paper reports 4 males and 28 females)	EUS±FNA if abnormality detected. Further imaging and/or surgical evaluation determined by cytology and appearance of abnormality. Note: No definition of 'abnormality' provided. Follow up Annual follow up if no abnormalities detected; otherwise, determined by clinical judgment.	EUS, n=16 Normal=13 Abnormal=3 Nodule=1; mass=1; mass+cystic component=1 EUS-FNA, n=3 Normal=0 Abnormal=3 Initial EUS-FNA on one patient was normal, but revealed to be malignant at 6-mo FU EUS-FNA. (PDAC=1; atypical ductal cells=1; mucinous neoplasm with mild cytologic atypia) Surgery All 3 abnormal EUS patients had surgery. Adverse events No EUS-related complications reported. Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of applicability See ROB section below for full details
Full Citation Vasen, H., Ibrahim, I., Ponce, C. G., Slater, E. P.,	N=178 HRIs (CDKN2a positive=1/p16-Leiden mutation carriers=177)	Recruitment Participants from Leiden registry PC surveillance program. Screening	Note: Data from CDKN2A/p16 cohort only; more recent data for FPC and BRCA cohorts (Leiden

Study details	Participants, index and reference tests	Description	Outcomes Overall risk of bias/applicability (low/high/unclear)
Matthäi, E., Carrato, A., Bonsing, B. A. et al. (2016). Benefit of surveillance for pancreatic cancer in high-risk individuals: outcome of long-term prospective follow-up studies from three European expert centers. Journal of Clinical Oncology, 34(17), 2010-2019. Country/ies where the study was carried out: Germany, Netherlands, and Spain Study type: Multicentre prospective cohort Aim of the study: To assess whether (1) surveillance of individuals at risk of PC leads to detection of early-stage PC or precursor lesions and (2) this leads to prognostic improvements. Study dates: 2000-2015 Source of funding: Supported by ZonMW, Deutsche Krebshilfe (Grant No. 111092), the	Index test=MRI, MRCP and/or EUS Reference test=Surgical pathology, clinical follow up Inclusion criteria Asymptomatic 40 years-old or 10 years younger than youngest relative with PC Informed consent Proven CDKN2A mutation or personal history of melanoma and known mutation in family Exclusion criteria Significant comorbidity Unable to undergo major surgery Patient characteristics Median age (years)=56 (range 37-75) Male/female=72/106 Mean FU (months)=53 (range 0-169)	From 2000-2011, annual MRI/MRCP was offered to HRIs. From 2012, EUS was also offered in addition to MRI/MRCP. All cases of suspicious lesions discussed by multidisciplinary team, who determined whether surgery required. Criteria for surgery: Multiple cystic lesions >1cm (in particular, cystic lesions that show significant growth or solid component) Solitary cystic lesions >3cm Solid lesions >0.5cm confirmed by MRI, EUS and CT (especially those that increase in size) Dilated main pancreatic duct >1cm Positive biopsy results Follow up If lesion was small, MRI repeated 3-6 months later; if suspicion of PC, additional EUS and CT performed	and PanGen-Fam registries) presented in Bartsch et al. 2016. Study flow 17 patients were lost to follow up. Diagnostic yield Total=15/178 (pathology only, baseline + follow up) PDAC=13; Multifocal PanIN1-2 + BD-IPMN=1; IPMN with low-grade dysplasia=1 Overall survival Overall 5-year survival for p16/CDKN2A PDAC patients=24% (Symptomatic sporadic PDAC=4-7%) Screening efficiency: 14 patients to detect one PDAC; 67MRIs to detect one PDAC. Overall resection rate p16/CDKN2A PDAC patients =75% (sporadic PDAC=15-20%; historical controls of CDKN2A/p16 carriers with symptomatic PDAC=15%) Adverse events No procedure-related complications were reported.

Study details	Participants, index and reference tests	Description	Outcomes Overall risk of bias/applicability (low/high/unclear)
Institute of Health Carlos III (Grants No.PI09/ 02221 and PI12/01635), the Red Tematica de Investigacion Cooperativa en Cancer (Grants No. RD12/0036/0034 and RD12/0036/0073), and the European Cooperation in Science and Technology action (Grant No. BM1204).			Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of applicability See ROB section below for full details
Full Citation Verna, E. C., Hwang, C., Stevens, P. D., Rotterdam, H., Stavropoulos, S. N., Sy, C. D., Frucht, H. et al. (2010). Pancreatic cancer screening in a prospective cohort of high-risk patients: a comprehensive strategy of imaging and genetics. Clinical cancer research, 16(20), 5028-5037. Country/ies where the study was carried out: USA Study type: Single-centre prospective cohort Aim of the study:	N=51 high, low or normal risk individuals (includes 32 HRIs, 14 moderate- and 5 normal-risk individuals) Index test=Blood tests (normal risk); EUS or MRI/MRCP and CA 19-9 and oral glucose tolerance test (OGTT) (moderate risk); EUS, MRI, CA 19-9, and OGTT Reference test=Surgical pathology, clinical follow up Inclusion criteria Referred due to family history of PC and interest in risk of disease Average, moderate or high risk of PC (see description) Informed consent Exclusion criteria None reported	FPC defined as ≥3 relatives with PC, 2 FDR with PC, or 1 FDR and ≥1 SDR with PC (at least one of these <55 years old). Individuals with BRCA mutation categorised as FPC if ≥1 FDR or SDR with PC. 'High-risk' defined as family history and/or genetic testing consistent with associated syndromes (PJS, BRCA1/BRCA2, FAMMM, HP, Hereditary nonpolyposis colorectal cancer [HNPCC])) or FPC 'Moderate risk' defined as not meeting high-risk criteria and >1 family member with PC or ≥1 FDR with PC <55 years-old. 'Average risk' defined as 1 family member with PC >55 years old. Recruitment All patients referred to Pancreas Cancer prevention and Genetics Program at Columbia University Medical Center/New York Presbyterian Hospital. Screening Detailed physical examination, personal and family history, and hereditary risk assessment. Patients offered genetic testing at discretion of clinician and genetic counsellor, and	Study flow 10 patients did not receive EUS nor MRI/MRCP (3 in high-risk group, 5 in moderate risk group, 2 in average risk group); 21 patients had genetic testing Diagnostic yield, n=51 (include normal risk group) Total=6/51 (baseline only; 4 from high-risk group; 2 from moderate risk) Metastatic adenocarcinoma=1 (FPC); pancreatic adenocarcinoma with adjacent IPMN and PanIn-2=1 (FPC + BRCA2) IPMN with moderate dysplasia and multifocal PanIN-2=4

Study details	Participants, index and reference tests	Description	Outcomes Overall risk of bias/applicability (low/high/unclear)
To determine if screening high-risk PC individuals is effective Study dates: 2005-2008 Source of funding: Grant from Hirschberg Foundation for Pancreatic Cancer Research	Patient characteristics Mean age (years)=52 (sd=12.3; range 29-77) Male/female=18/33 Non-Hispanic White=46; other=6 Ashkenazi Jewish=25 History of smoking=17 History of other types of cancer=15	subsequent genetic counselling. Average risk group received basic blood tests and other tests if indicated; moderate risk group received curvilinear EUS±FNA or MRI/MRCP, oral glucose tolerance test (OGTT) and CA 19-9 serum cancer antigen test; high-risk group received curvilinear EUS±FNA and MRI/MRCP, OGTT and CA 19-9 test. ERCP conducted at discretion of endoscopist generally for ductal irregularities or changes consistent with IPMN. Abnormal findings consisted of: Mass or cystic lesions IPMN Parenchymal changes indicative of chronic pancreatitis Follow up Findings discussed at weekly multidisciplinary team (inc. surgeon, gastroenterologist, oncologist, radiologist, geneticist). EUS recommended for all patients with abnormal test who do not receive EUS. Patients with resectable mass lesion/suspicion of MD-IPMN, or abnormal EUS-FNA cytology considered for surgery. Patients not undergoing surgery risk stratified and had annual follow up. High-risk group within 10 years age of youngest family member with PC, and any patient who had partial pancreatectomy, seen at 6-month interval.	High- and moderate-risk groups only Total=6/46 EUS, n=31 Normal=4 Abnormal=27 (High risk [normal/abnormal]=3/21; Moderate risk=1/4; Average risk=0/2) 6 patients also had EUS-FNA. Changes of CP=9; BD-IPMN=5; Other cysts=7; solid lesion=2 MRI/MRCP, n=33 Normal=22 Abnormal=11 (High risk [normal/abnormal] =16/7; Moderate risk=4/3; Average risk=2/1) Both masses seen on EUS were detected by MRI. IPMN=1, Other cysts=6, Solid lesion=3, irregularities=1 ERCP, n=7 Normal=4 Abnormal=3 (High risk [normal/abnormal]=3/2;

Study details	Participants, index and reference tests	Description	Outcomes Overall risk of bias/applicability (low/high/unclear)
			Moderate risk=1/0; Average risk=0/1) BD-IPMN=2, irregularities=2 Adverse events No procedure-related events reported. Quality of study assessed using QUADAS-2: Overall risk of bias. Overall risk of applicability See ROB section below for full details
Full Citation Zubarik, R., Gordon, S. R., Lidofsky, S. D., Anderson, S. R., Pipas, J. M., Badger, G., Vecchio, J. et al. (2011). Screening for pancreatic cancer in a high-risk population with serum CA 19-9 and targeted EUS: a feasibility study. Gastrointestinal endoscopy, 74(1), 87-95. Country/ies where the study was carried out: USA Study type: Multicentre case series Aim of the study: To examine effectiveness of screening PC HRIs	N=546 IARs (FPC=540; FPC+BRCA mutation=6) Index test=CA 19-9; if abnormal, then EUS±FNA Reference test=Surgical pathology, clinical follow up Inclusion criteria Aged 50-80 years-old and ≥1 FDR with PC (enrolment at 45-years old if 2 FDRs with PC) PJS or BRCA2 and >40 years-old Exclusion criteria Known pancreatic mass or disease Weight loss Clinically-apparent jaundice Patient characteristics Mean age (years)=59.2 (7.4)	Recruitment Participants were patients undergoing routine endoscopic evaluation and their family members, recruited from (i) University of Vermont and (ii) Dartmouth-Hitchcock Medical Center, or (iii) self-referral via community and local advertisement. Source of referral was 46% endoscopy, 25% physician referral and 29 self-referral. Screening All patients had serum CA 19-9 test: if CA 19-9 >37 U/ml then patient offered radial EUS. If normal EUS or CA 19-9≤37 U/ml then patient followed up by telephone or by checking electronic record 1 year after enrolment, or if no documentation available Social Security Death Index searched. Patients with abnormal EUS received linear EUS-FNA using 25G needle: patients with suspicious or confirmatory cells for carcinoma or high-risk cystic lesion then referred for surgery; if no suspicious or confirmatory cells for carcinoma or low-risk cystic lesion on EUS-FNA then repeat CA 19-9 test performed after 3 months.	Study flow 1 patient with elevated CA 19-9 levels refused EUS. Diagnostic yield Total=5/546 (pathology only, baseline and follow up) PAC=1; Pancreatic NET=1; PanIN-1=1; No pathology detected=2 All 5 patients had only 1 FDR with PC. CA 19-9, n=546 Normal=519 Abnormal=27 EUS, n=26 Normal=14 Abnormal=12

Study details	Participants, index and reference tests	Description	Outcomes Overall risk of bias/applicability (low/high/unclear)
using CA 19-9 testing and targeted EUS Study dates: 09/2006-07/2009 Source of funding: None reported	Male/female=219/327 History of smoking=300 Current smoker=45	Abnormal EUS findings consisted of: cystic or hypoechoic (solid) lesions Follow up 1 year FU for patients with normal CA 19-9 levels; 3-mo FU for patients with normal EUS-FNA.	EUS-FNA performed on 8 participants that received EUS. Adverse events Not reported. Quality of study assessed using QUADAS-2: Overall risk of bias. Overall risk of applicability See ROB section below for full details

F.5 Referral to specialist multidisciplinary teams

Not applicable to this review.

F.6 Staging

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
Full Citation Connor, S., Bosonnet, L., Alexakis, N., Raraty, M., Ghaneh, P., Sutton, R., & Neoptolemos, J. P. (2005). Serum	N=159 patients with potentially resectable PC Inclusion criteria Resectable according to contrast-enhanced CT or unclear Exclusion criteria	Index test 1=CA 19-9 Reference test=Laparoscopy + LUS TNM staging classification used: not reported Procedure All patients had CT where CT-unresectable defined as presence of metastatic disease, superior mesenteric-portal vein encasement of >50% circumference or >2 cm in length, loss of	Study flow No excluded patients. Diagnostic test accuracy data 95%CIs calculated by technical team from raw data.	Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of indirectness

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
CA19-9 measurement increases the effectiveness of staging laparoscopy in patients with suspected pancreatic malignancy. Digestive surgery, 22(1-2), 80-85. Country/ies where the study was carried out: UK Study type: Retrospective review of prospective database Aim of the study: To determine if serum carbohydrate antigen (CA19-9) levels can be used to improve the selection of patients for staging laparoscopy. Study dates:	Unresectablility according to CT criteria. No preoperative laparoscopic assessment No CA 19-9 level performed Characteristics Median age (years)=66 (96%CI 64-67) Male/female=89/70 Median time to surgery (days)=27 (range 5-48) Resectability according to laparoscopy Resectable=135; Unresectable=24 (liver metastases=15; peritoneal metastases=9) Final histological diagnosis PDAC=62; metastatic peripancreatic AC=28; ampuallary AC=27; intrapancreatic cholangiocarcinoma=	the fat plane between the superior mesenteric artery or the coeliac axis. Laparascopy Standard inspection of peritoneal cavity and intraoperative US, separate procedure to planned resection unless specific contraindications (extensive previous surgery, comorbidity preventing surgical intervention, presence of gastric outlet obstruction, necessitating gastric bypass, even if resectable tumour). CA-19-9 Patients further categorised as resectable if CA 19-9 ≤150 U/ml or if >150 U/ml then further categorised thus: if bilirubin ≤35 µmol/l then deemed unresectable. If bilirubin >35 µmol/l (i.e. patients were jaundiced) then deemed resectable if CA 19-9≤300 kU/l, otherwise unresectable.	CA 19-9 ≤ 150 kU/l for resectability according to laparoscopic assessment (n=159)* (TP=60, FP=3, FN=75 TN=21) Sens=0.44 (95%CI, 0.36-0.53) Sp=0.88 (95%CI, 0.68-0.97) PPV=0.95 (95%CI, 0.87-0.98) NPV=0.22 (95%CI, 0.18-0.26) Laparoscopy could have been avoided in 63 patients (40%), resection avoided in 21 of 96 patients *Discrepancy in published results CA 19-9 ≤ 150 kU/l or ≤300 kU/l if bilirubin level >35µmol/l) for resectability according to laparoscopic assessment (n=145) (TP=76, FP=4, FN=49, TN=16)	See ROB Appendix section for full details.

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
1997-2004 Source of funding: Not reported	19; Other malignant tumours=13; Benign pancreatic tumours=8; Suspected periampullary malignancy=2.		Sens=0.61 (95%CI, 0.52-0.69) Sp=0.8 (95%CI,0.56-0.94) PPV=0.95 (95%CI, 0.89-0.98) NPV=0.25 (95%CI, 0.19-0.31) Laparoscopy could have been avoided in 80 of 145 (55%) patients, resection avoided in 16 of 65 patients CA 19-9 ≤300 kU/l if bilirubin level >35µmol/l) for resectability according to laparoscopic assessment (n=71) (TP=16, FP=1, FN=39, TN=15) Sens=0.29 (95%CI, 0.18-0.43) Sp=0.94 (95%CI, 0.7-1.0) PPV=0.94 (95%CI, 0.7-0.99) NPV=0.28 (95%CI, 0.24-0.32)	

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
			Laparoscopy could have been avoided in 17 of 71 (24%) patients, resection avoided in 15 of 54 patients Adverse events Not reported	
Full Citation DeWitt, J., Devereaux, B., Chriswell, M., McGreevy, K., Howard, T., Imperiale, T. F., LeBlanc, J. et al. (2004). Comparison of endoscopic ultrasonography and multidetector computed tomography for detecting and staging pancreatic cancer. Annals of internal medicine, 141(10), 753-763. Country/ies where the study was carried out:	N=120 patients with suspected or recently diagnosed PC Inclusion criteria Agreed to have EUS, CT and surgery if necessary Referred to Indiana University Hospital within 8 weeks for clinically suspected or recently diagnosed PC Written informed consent Exclusion criteria Previous ERCP or EUS at Indiana University Hospital for suspected PC Declined or undecided about receiving surgical intervention	Index test 1=EUS Index test 2=CT Reference test: When resection attempted, pathologic assessment of tumour stage (T1-3) and nodal stage (N0 or N1); Splenic (T3) and non-splenic (T4) vascular involvement defined as lack of adequate surgical plane of dissection. Pathological confirmation of vascular invasion by tumour not routinely performed. TNM staging classification used: AJCC 1997 Procedure All enrolled patients responded to initial health and medical questionnaire, followed by same day EUS. CT performed within 1 week. Within 3 weeks of CT, surgeon examined patient and reviewed EUS/CT to determine potential for resection. Quality of life assessed at 1 month, 3 months, and every 6 months until death or 24 months if clinical disease remained stable. EUS All patients examined with radial echoendoscope then linear echoendoscope by 1 of 3 experienced gastroenterologists. Conscoius sedation performed with various combinations of propofol, meperidine, fentanyl or midazolam. Operator not blinded to previous radiographic data. EUS-FNA with 22G needle performed if cancer not previously confirmed. Cytotechnologist/cytopathologist was onsite for preliminary	Study flow 16 excluded for protocol violations (7 no CT, 9 surgery elsewhere). Of 104 patients remaining, 63 had surgery (10 of which were excluded for not having PC). Information on staging not available for 8 unresectable patients with malignancy due to incomplete laparotomy or resection. T-Staging (n=49) EUS Accuracy=0.67 (95%CI, 0.52-0.8) (33/49) Overstaged=9/49 Understaged=7/49	Quality of study assessed using QUADAS-2: Overall high risk of bias. Overall low risk of indirectness See ROB section below for full details.

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
USA Study type: Prospective cohort Aim of the study: To compare EUS and MDCT for detection, staging and resectability of known or suspected locoregional pancreatic cancer Study dates: 07/2000-10/2002 Source of funding: Two grants from American Society of Gastrointestinal Endoscopy and 1 grant from National Institute of Diabetes and Digestive and Kidney Diseases/	Referred by surgeons outside hospital system. Pregnant Incarcerated Inability to provide informed consent High surgical risk Known or suspected periampullary masses, cholangiocarcinoma, cancer with locally advanced arterial (superior, mesenteric, hepatic or celiac) involvement or metastatic disease (ascites, suspicious liver or pulmonary lesions, distant enlarged lymph nodes) detected by previous imaging. Characteristics, n=104 Mean age (years)=61 (sd 12) Male/female=59/45 White=99; Black=4; Hispanic=1	interpretation of aspirations. Immediately after EUS examination, endosonographer classified visualized mass as resectable or unresectable and assigned TNM staging. MDCT MDCT performed with quad-channel scanner using 0.5s gantry rotation time and acquisition of 4 sections per rotation. Examination in dual-ohase mode. No 3D postprocessing used. One of 3 experienced gastrointestinal radiologists, blinded to EUS results but not to information about symptoms, previous CT results and previous ERCP/pathology results, interpreted CT scans. Surgery One of 2 pancreatobiliary surgeons performed all consultations and operations. Decision to operate based on preop evaluation of surgical risk and EUS/CT findings. Before tumour resection, all patients had complete abdominal exploration by laparoscopy or laparotomy. Pathology Gastrointestinal pathologist evaluated all resected pancreatic masses. If malignant, tumour and node stage assigned. Definition of surgical resectability R0 resection considered resectable; R1 and R2 considered unresectable despite gross tumour removal. Unresectable tumours, evaluated surgically, also defined as any T4 vascular invasion, pathologically confirmed liver or peritoneal metastatic lesions, invasion of the transverse mesocolon or stomach, or metastasis to distant lymph nodes.	CT Accuracy=0.41 (95%CI, 0.27-0.56) 20/49) Overstaged=7/49 Understaged=22/49 Diagnostic test accuracy data 95%CIs, PPV and NPV calculated from raw data by technical team Resectability EUS Sens=0.88 (95%CI, 0.69-0.97) Sp=0.68 (95%CI, 0.44-0.81) PPV=0.71 (95%CI, 0.58-0.81) NPV=0.86 (95%CI, 0.68, 0.95) MDCT (TP=23, FP=10, FN=2, TN=18) Sens=0.92 (95%CI, 0.74-0.99) Sp=0.64 (95%CI, 0.44-0.81) PPV=0.7 (95%CI, 0.58-0.79)	

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
	Location (surgery group): 45 head, 3 body, 1 tail, 1 head and body, 3 body and tail. Mean time to surgery (days) – resectable group: 14.4 (sd 8.1; range 1-35) Mean time to surgery (days) – unresectable group: 12.4 (sd 7.4, range 2-33) Patients with unresectable tumours significantly larger masses than resectable tumours (p=0.012) Final diagnosis after intraoperative/histopathologic exam (n=63) Resectable PC=25 Unresectable PC=28 CP=5; benign IPMN=1; macrocystic seros cystadenoma=1; benign PNET=1; accessory spleen=1; ampullary cancer=1.		NPV=0.9 (95%CI, 0.7-0.97) N staging EUS Sens=0.25 (95%CI, 0.11-0.43) Sp=0.92 (95%CI, 0.64-1.0) PPV=0.89 (95%CI, 0.53-0.98) NPV=0.33 (95%CI, 0.28-0.39) MDCT Sens=0.28 (95%CI, 0.14-0.47) Sp=0.92 (95%CI, 0.64-1.0) PPV=0.9 (95%CI, 0.56-0.98) NPV=0.34 (95%CI, 0.29-0.41) Adverse events No EUS or CT complications occurred	

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
	Diagnosis of no surgery group (n=41) PAC=26, Neuroendocrine cancer=1 Diagnosis confirmed by: malignant cytology from EUS-FNA=24; previously placed stent=1; atypical EUS-FNA and subsequent clinical FU=2 24/26 PAC patients died, mean time to death 196 days (range 24-676).			
Full Citation Doucas, H., Sutton, C. D., Zimmerman, A., Dennison, A. R., & Berry, D. P. (2007). Assessment of pancreatic malignancy with laparoscopy and intraoperative ultrasound. Surgical endoscopy, 21(7), 1147-1152.	N=100 patients with suspected PC Inclusion criteria Radiological diagnosis of PC + no evidence of metastasis Exclusion criteria None reported Characteristics Mean age (years)= 62.9 Male/female=52/48	Index test 1= CT Reference Test 1= Laparoscopy + LUS, surgery + clinical FU Index test 2=Laparoscopy + LUS Reference test 2=Surgical histopathology + clinical FU TNM staging classification used: not reported Procedure CT Spiral CT until 2003, multichannel CT after using i.v. contrast and dedicated pancreatic CT protocol using 1-2mm slices. Scans assessed by specialised radiologist. Some patients referred from other centres with repeat imaging only if prior scan not satisfactory. Diagnostic laparoscopic US (DLUS)	Study flow 6 patients excluded from CT results (did not have surgery=1; unsuccessful laproscopy=2; unfit for exploration=3); further 5 patients excluded from laparoscopy+LUS results (non-PC pathological diagnosis=5). Diagnostic test accuracy data	Quality of study assessed using QUADAS-2: Overall high risk of bias. Overall low risk of indirectness See ROB section below for full details.

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
Country/ies where the study was carried out: UK Study type: Prospective cohort Aim of the study: To assess the efficacy of laparoscopy with intraoperative ultrasound in management of patients with PC Study dates: 01/2001-10/2004 Source of funding: None reported	Surgically resectable (n=89) Resectable=42 Unresectable=47	Performed using 0◦ laparoscope by open insertion of 10mm port at umbilicus and establishment of CO2 pneumoperitoneum; 2nd port placed in either left-upper quadrant or right-lower quadrant and US probe inserted. Additional ports used if necessary for retraction or biopsy. Thorough laparoscopic exam used to assess peritoneal cavity and anterior/posterior liver surfaces; US assessment performed of liver, pancreas, bile duct and vessels. Biopsies of suspicious masses taken and metastatic disease histologically confirmed. Further surgery performed at later date.	Calculated from published raw data. Resectability CT (n=94) (TP=15, FP=54, FN=19, TN=6) Sens=0.44 (95%CI, 0.27-0.62) Sp=0.1 (95%CI, 0.04-0.21) PPV=0.28 (95%CI, 0.16-0.29) NPV=0.24 (95%CI, 0.12-0.42) Laparoscopy + LUS (n=64) (TP=15, FP=21, FN=0, TN=28) Sens=1.0 (95%CI, 0.78-1.0) Sp=0.57 (95%CI, 0.42-0.71) PPV=0.42 (95%CI, 0.34-0.5) NPV=1.0 Adverse events No laparoscopic-related complications.	
Full Citation Fang, C. H., Zhu, W., Wang, H.,	N=80 patients with pancreatic and	Index test 1=MDCT-3D Index test 2=MDCT without 3D	Study flow 3 patients preoperatively ruled	Quality of study assessed using QUADAS-2:

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
Xiang, N., Fan, Y., Yang, J., zheng Zhong, S. et al. (2012). A new approach for evaluating the resectability of pancreatic and periampullary neoplasms. Pancreatology, 12(4), 364-371. Country/ies where the study was carried out: PR. Of China Study type: Prospective cohort Aim of the study: To compare MDCT with and without 3D visualisation in assessing resectability of pancreatic and periampullary neoplasms. Study dates: 1/2008-08/2010 Source of funding:	periampullary tumours Inclusion criteria Pathologically confirmed pancreatic or periampullary neoplasm Exclusion criteria Distant metastasis (e.g. liver or bone) Not surgically explored Characteristics Mean age (years)=57.9 (range 15-91) Male/female=49/31 Final diagnosis Pancreatic head tumours=45 (PDAC=43; Solid psuedopapillary tumours=2); ampullary adenocarcinomas=14 ; pancreatic body and tail tumours=21 (of the pancreas (PDAC=14; solid pseudopapillary tumours=3; serous	Reference test=Surgery TNM staging classification used: not reported Procedure Preoperative resectability assessment for the patients was performed using the results of CTA imaging (referenced by radiologists' reports) and MI-3DVS 3D (MDCT-3D) reconstruction. CTA imaging reported by two radiologists. MDCT with 3D imaging reported by other two radiologists. All of the radiologists blind to clinical outcomes and other radiologist reports. All 80 cases examined surgically. All cases in this study were subject to multislice CT examination. Resectability based on CTA imaging (referenced by reports issued by radiologists). Criteria for unresectability was (1) tumour intricately associated with the celiac trunk and its main branches, the abdominal aorta, the inferior vena cava, the portal vein, the superior mesenteric artery, the inferior mesenteric vein such that there is no apparent space in between them; (2) a low-density tumour completely surrounding its neighbouring blood vessels without causing lumen changes; and 3) a low-density tumour that causes occlusion or stenosis by vascular invasion. Surgical resectability defined as R0 (negative margin). MDCT The data were collected using a Philips Brilliance 64-MDCT scanner. Enhanced CT scanning was performed as follows: dynamic abdominal triphasic tomography and thin slice scanning were performed for the patients after non-ionic Iopamiro, an intravenous contrast agent, was administered. Each patient received 80e100 mL of the vascular contrast agent. The contrast was injected at a rate of 5 mL/s, followed by vascular flushing with 40e50 mL of normal saline at the same rate. Arterial-phase scanning of the pancreas was achieved by contrast agent tracing; specifically, the scanning was automatically triggered 8 s after the vascular CT value in the diaphragmatic section of the abdominal	out as having advanced and unresectable PC. Diagnostic test accuracy data Sens/Sp/predictive values, and 95%CIs, calculated using raw data. Data shown only for PAC patients. Resectability MDCT without 3D* (n=57 PAC patients only) (TP=30, FP=2, FN=8, TN=17) Sens=0.79 (95%CI, 0.63-0.9) Sp=0.89 (95%CI, 0.67-0.99) PPV=0.94 (95%CI, 0.8-0.98) NPV=0.68 (95%CI, 0.53-0.8) *Discrepancy in reported raw data and reported sens/sp/PPV/NPV MDCT with 3D (n=57 PAC patients only) (TP=38, FP=0, FN=0, TN=19)	Overall low risk of bias. Overall low risk of indirectness See ROB section below for full details.

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
The National High Technology Research and Development Program of China (863 Program) (Grant No. 2006AA02Z346); the Natural Science Foundation of Guangdong Province, China (Grant No. 6200171); the Science and Technology Project of Guangzhou City (Grant No. 2008Z1-E611); the integration project of industry, education and research jointly funded by Guang-dong Province and the Ministry of Education of P. R. China (Grant No. 2009B080701077) ; the strategic cooper-ation	cystadenomas=3; malignant interstitial tumour=1).	aorta reached 100 HU. Portal venous phase scanning was initiated by the same criterion but with a 60 s delay; the scanning covered the area from the diaphragm to the lower poles of the kidneys. The scanning parameters included a voltage of 120 kV, a current of 200 mA, a slice thickness of 0.67 mm, an interval of 0.5 mm, a detector combination of 0.625 mm x 64, a pitch of 0.891, a bed speed of 47.5 mm/s, and a rotation time of 0.5 s. The MDCT-3D system allowed the segmentation and 3D reconstruction of the CT images, in which thin-sliced CT data were imported into the software to facilitate their automatic registration. Subsequently, regions of interest were extracted based on threshold values. An adaptive region-growing method was employed to reconstruct the abdominal organs and blood vessels. Important structures such as the pancreas, tumours, and peripancreatic vessels were extracted from CT images by segmentation and were used to generate 3D models using a surface-rendering algorithm. The reconstructed 3D models were scaled, rotated, and displayed separately or in combination to comprehensively evaluate the anatomical structure and determine the structural details. The diagnosis and evaluation of tumour resectability were performed alongside an evaluation of the patient's medical history. The main elements examined in the 3D model included the tumour shape, size, and location; the distribution of related vessels; the luminal morphology of large vessels; the distribution and morphology of the small peripancreatic veins; the morphology, degree of dilation, and obstructive sites of the bile and pancreatic ducts; and the morphology of adjacent organs. Surgery Experienced pancreatic surgeons, who do not know the reports issued by radiologists and results of MI-3DVS evaluation, performed the surgical exploration and resection of tumours that had been classified as resectable or potentially resectable, and	Sens=1.0 (95%CI, 0.91-1.0) Sp=1.0 (95%CI, 0.82-1.0) PPV=1.0 NPV=1.0 Adverse events Not reported	

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
project jointly funded by Guangdong Province and the Chinese Academy of Sciences (Grant No.201000032); the Science and Technology Project of Guangdong Province, China (Grant No. 2011B031800088); and the National Natural Science Foundation of China (Grant No. 81072439).		each surgery was videotaped. The surgical specimens were then submitted for pathological examination. No resection of tumour (palliative surgery) or resection of tumour with venous resection were defined as surgical unresectablility.		
Full Citation Farma, J. M., Santillan, A. A., Melis, M., Walters, J., Belinc, D., Chen, D. T., Malafa, M. et al. (2008). PET/CT fusion scan enhances CT staging in patients with pancreatic neoplasms. Annals	N=83 patients with suspected PC Inclusion criteria Referred to H.Lee Moffitt Cancer Center and Research Institute Presumed pancreatic neoplasm Preoperative PET/CT scans Pancreatic lesion	Index test 1=CT Index test 2=PET/CT Index test 3=CT + PET/CT Reference test=Surgery, biopsy from percutaneous or EUS, clinical, imaging and pathologic follow up TNM staging classification used: not reported Procedure Standard treatment schema for patients with suspected pancreatic cancer evaluated at our institution includes a three-phase computed tomography angiogram (CTA) with pancreas protocol, CT of the chest, and CA 19–9. Patients with metastatic disease are treated with systemic chemotherapy. Those with	Study flow 1 patient excluded (reason not stated). 72 patients had EUS. Diagnostic test accuracy data 95%CIs calculated by technical team M-Staging CT (TP=13, FP=5, FN=10, TN=54)	Quality of study assessed using QUADAS-2: Overall unclear risk of bias. Overall low risk of indirectness See ROB section below for full details.

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
of surgical oncology, 15(9), 2465-2471. Country/ies where the study was carried out: USA Study type: Retrospective review of prospective cohort Aim of the study: To determine if addition of PET/CT to CT affects treatment in patients with pancreatic mass. Study dates: 01/2006-12/2007 Source of funding: None reported	Exclusion criteria x Characteristics Mean age (years)=69 (range 24-88) Male/female=43/89 Location: 49 head, 22 body, 7 tail, 4 multifocal.	locally advanced disease are treated with neoadjuvant chemo-radiotherapy with restaging prior to resection. Patients with potentially resectable disease are referred for endoscopic ultrasound and surgical consultation. Metabolic tracer imaging was perform-ed with 2-deoxy-2-[18F] fluoro-D-glucose positron emission tomography integrated with computed tomography, using either a Siemens Biograph Classic PET/CT or a General Electric Healthcare Discovery PET/CT scanner. Imaging was initiated at 90 min after i.v. injection of 296–555 MBq (8–15 mCi) of radiotracer. All patients were discussed in our multidisciplinary gastrointestinal tumour board prior to definitive treatment planning. Outside biopsies were re-evaluated by our pathologists to confirm definitive diagnosis. All patients in this series had a preoperative biopsy performed by percutaneous or endoscopic means. Clinical, radiographic, and pathologic follow-up was evaluated for each patient.	Sens=0.57 (95%CI, 0.34-0.77) Sp=0.92 (95%CI, 0.81-0.97) PPV=0.72 (95%CI, 0.51-0.87) NPV=0.84 (95%CI,0.77-0.9) PET/CT (TP=14, FP=0, FN=9, TN=59) Sens=0.61 (95%CI, 0.39-0.8) Sp=1.0 (95%CI, 0.94-1.0) PPV=1.0 NPV=0.91 (95%CI, 0.8-0.92) CT + PET/CT (TP=20, FP=5, FN=3, TN=54) Sens=0.87 (95%CI,0.66-0.97) Sp=0.92 (95%CI, 0.81-0.97) PPV=0.8 (95%CI, 0.63-0.9) NPV=0.93* *Discrepancy in published NPV results Adverse events	

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
			Not reported	
Full Citation Fischer, U., Vosshenrich, R., Horstmann, O., Becker, H., Salamat, B., Baum, F., & Grabbe, E. (2002). Preoperative local MRI-staging of patients with a suspected pancreatic mass. European radiology, 12(2), 296. Country/ies where the study was carried out: Germany Study type: Prospective cohort Aim of the study: To evaluate value of MRI for preoperative local staging of patients with suspected pancreatic mass Study dates: 01/1997-12/1999	N=94 patients with suspected PC Inclusion criteria Suspected pancreatic tumour after clinical examination, US, and/or CT Exclusion criteria Did not have MRI Characteristics Mean age (years)=56 (range 32-87) Male/female=53/41 Range from MRI to surgery=1-15 days	Index test 1=MRI Reference test=Surgical pathology TNM staging classification used: not reported Procedure All MRI exams performed on 1.5T MRI system, maximum gradient strength 25 mT/m using 4 channel body phased array coil, according to protocol. The protocol included three different imaging modalities: non-enhanced and contrast-enhanced (CE) MRI of the upper abdomen, MR cholangiopancreatography (MRCP), and CE MR angiography (MRA) of the abdominal aorta and the visceral arteries, the abdominal veins, and the portal vein. The evaluation of the images was performed by two experienced readers in agreement modality. The readers did not know the results of the CT if performed before. Evaluation criteria included the detection of a pathologic pancreatic or extrapancreatic change (yes/no) and, if so, an assessment of the tumour entity (benign lesion/malignant lesion). Tumours with an infiltration (i.e., tumour encasement, occlusion of the vessel) of the arterial [celiac trunk, a. lienalis, a. hepatica, mesenteric artery (AMS)], and/or portal-venous vessels [portal vein (VP), mesenteric vein (VMS)] on CE MRA subtraction images were classed as “probably unresectable”. An encasement or occlusion of the v. lienalis was not assessed as a sign of non-resectability MRI MRI of upper abdomen: Non-enhanced T1-weighted and additional T2-weighted images of the upper abdomen were performed in different orientations. The sequence parameters were kept constant in all patients. After CE MRA, additional CE T1-weighted images were acquired in transversal and coronal	Study flow Four patients eligible for study excluded (did not have MRI=4) Diagnostic test accuracy data 95%CIs, Sens/Sp, NPV calculated from raw data. Resectability Pancreatic head tumours (n=29) [used in analysis] (TP=12, FP=22, FN=5, TN=7) Sens=0.71 (95%CI, 0.44-0.9) Sp=0.78 (95%CI, 0.4-0.97) PPV=0.86 (95%CI, 0.63-0.95) NPV=0.58 (95%CI, 0.38-0.76) Patients with solid tumours who had surgery, n=36) (TP=14, FP=2, FN=5, TN=15) Sens=0.74 (95%CI, 0.49-0.91)	Quality of study assessed using QUADAS-2: Overall high risk of bias. Overall low risk of indirectness See ROB section below for full details.

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
Source of funding: None reported		orientation with fat suppression. Fat saturation was obtained with a time penalty of 2 s (acquisition time=22s). MRCP: A T2-weighted turbo spin-echo sequence was used for imaging the biliary tract and pancreatic duct. Three single slices of different thickness (30, 50, 70 mm) were acquired in coronal–oblique planes parallel to the long axis of the extrahepatic biliary tract and pancreatic duct. Different slice thickness was chosen in all patients to allow the presentation of possibly anatomic variants, and best documentation of the biliary tract and pancreatic duct was evaluated. CE MRA: In all cases non-enhanced and dual-phase contrast-enhanced examinations were performed using the same unchanged fast imaging with steady-state precession sequence in a sequential k-space order. The sequence parameters were kept constant for all. Gadopentetate dimeglumine (Magnevist, Schering, Berlin, Germany) was used in a dosage of 0.15 mmol gadopentetate dimeglumine per kilogram of body weight followed by a saline solution flush of 20 ml through an 18-G venous catheter positioned in an antecubital vein. The contrast material was injected by using an MR-compatible power injector at an injection rate of 2 ml/s. For the visceral arterial perfusion phase, the tailoring of the contrast material bolus to the contrast-sensitive low-frequency lines of k space was achieved individually by means of a transit-time evaluation. For this purpose a test bolus of 2 ml of gadopentetate dimeglumine followed by a saline solution flush of 20 ml was used, again with a flow rate of 20 ml/s. The transit time of the contrast material to the celiac artery was measured repetitively by using a fast-low-angle-shot (TurboFLASH, Siemens, Erlangen, Germany) sequence (TR=8.5 ms, TE=1.4 ms, flip angle=10°) with an imageacquisition time of 1 s over a period of 45 s at the same location of the abdominal aorta in a transversal plane. The portal venous phase was acquired with the same imaging parameters after a fixed delay of 12 s after the completion of the arterial phase. During that interval	Sp=0.88 (95%CI, 0.64-0.99) PPV=0.88 (95%CI, 0.65-0.96) NPV=0.75 (95%CI, 0.58-0.87) Adverse events Not reported	

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
		the patient received breathing instructions so that a second breath-hold acquisition could be achieved for the portal venous phase.		
Full Citation Fristrup, C. W., Mortensen, M. B., Pless, T., Durup, J., Ainsworth, A., Hovendal, C., & Nielsen, H. O. (2006). Combined endoscopic and laparoscopic ultrasound as preoperative assessment of patients with pancreatic cancer. HPB, 8(1), 57-60. Country/ies where the study was carried out: Denmark Study type: Prospective cohort Aim of the study: To evaluate combined EUS and LUS in staging of pancreatic cancer	N=146 patients with potentially resectable PC Inclusion criteria Histologically-verified PC Referred to Department of Surgical Gastroenterology, Odense University Hospital from 01/2002-02/2004 Exclusion criteria Known metastasis Non-resectability on previous CT or US Poor performance status and reevalaution after down-staging with chemoradiotherapy Characteristics Median age (years)=66 (range 22-89) Male/female=97/86	Index test 1=Laparoscopy+LUS Reference test=Surgery or surgical pathology TNM staging classification used: not reported Procedure All patients had CT or abdominal US before referral. Patients with carcinosis, non-regional lymph nodes and live metastasis considered incurable. All metastatic lesions histologically verified by FNA. Unresectability defined as local tumour infiltration of portal vein, superior mesenteric vessels, coeliac trunk and transverse mesocolon. Patients with carcinosis, non-regional lymph nodes and liver metastasis were considered incurable. Regional metastatic lymph nodes were not considered as unresectable. All metastatic lesions were histologically verified by fine needle aspiration Patients categorised using EUS or LUS into (1) resectable, (2) possibly resectable or (3) non-resectable. EUS/LUS performed by experienced surgeons. All patients had EUS first: if judged resectable by EUS then definitely resectable scheduled for laparoscopy/LUS and resection on same day; if possibly resectable by EUS, then laparoscopy/LUS performed separately. If non-resectable by EUS referred onto/discussed with oncologists for best supportive care, chemotherapy or chemoreadiotherapy. Surgical bypass offered to patients in which endoscopic or radiological palliation failed.	Study flow 179 patients referred: 33 patients excluded (31 from surgery due to poor performance status, and 2 referred for biopsy only due to metastasis on initial CT). Diagnostic test accuracy data Sens/Sp/PPV/NPV + 95%CIs calculated from raw data. Laparoscopy + LUS Resectability (TP=38 (R0 resection), FP=14 (exploration only=6, surgical bypass=3, R1 or R2-resection=5), FN=0, TN=94) Sens=1.0 (95%CI, 0.91-1.0) Sp=0.87 (95%CI, 0.79-0.93) PPV=0.73 (95%CI, 0.62-0.82)	Quality of study assessed using QUADAS-2: Overall high risk of bias. Overall low risk of indirectness See ROB section below for full details.

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
Study dates: 01/2002-02/2004 Source of funding: None reported			NPV=1.0 Adverse events No procedure-related complications.	
Full Citation Furukawa, H., Uesaka, K., & Boku, N. (2008). Treatment decision making in pancreatic adenocarcinoma: multidisciplinary team discussion with multidetector-row computed tomography. Archives of Surgery, 143(3), 275-280. Country/ies where the study was carried out: Japan Study type: Tertiary care prospective cohort Aim of the study: To evaluate usefulness of MDCT in	N=213 patients with confirmed PDAC Inclusion criteria Referred to hospital for treatment of invasive PDAC Informed consent Exclusion criteria Endocrine tumour, IPMN, solid or pseudopapillary tumour Received surgical or medical treatment at another hospital Characteristics Mean age (years)=64 (range 32-82) Male/female=136/77	Index test 1=MDCT Reference test=Histopathology for vascular invasion and nodal status TNM staging classification used: IUAC 2002 Procedure Every patient had MDCT and lab tests and was discussed within multidisciplinary team. Diagnostic radiologists looked for signs of unresectability including extrapancreatic tumour spread, particularly into the celiac axis and the root of the superior mesenteric artery; para-aortic massive lymph node involvement; and the presence of distant metastases and ascites. When MDCT images showed direct contact greater than 90° between the portal vein and the tumour, the case was diagnosed as positive for portal vein invasion by the tumour. Lymph nodes were considered positive for disease when the short axis was greater than 1 cm in diameter or there were clusters of 3 or more smaller nodes (each <1 cm). Encasement of the portal vein and regional lymphadeno-pathy not considered a surgical contraindication. Probably resctable defined as TNM≤2; Definitely resectable defined as TNM≥3; if suspect but inconclusive findings of 1 or more signs present, tumour considered probably unresectable. At multidisciplinary meeting, patients divided into resectable and unresectable groups: patients with tumours considered certainly unresectable were referred to the division of gastrointestinal medical oncology and chemotherapy, and chemotherapy or radiation therapy (or best supportive care) was given. Patients with tumours considered probably resectable were admitted to a surgical ward and underwent surgery. Patients with tumours	Diagnostic test accuracy data 95%CICIs calculated from raw data by technical team MDCT Resectability (n=213) (TP=68, FP=11, FN=0, TN=134) Sens=1.0 (95%CI,0.95-1.0) Sp=0.92 (95%CI, 0.87-0.96) PPV=0.86 (95%CI, 0.78-0.92) NPV=1.0 N staging (n=68) (TP=12, FP=3, FN=26, TN=27) Sens=0.32 (95%CI, 0.18-0.49) Sp=0.9 (95%CI, 0.73-0.98) PPV=0.8 (95%CI, 0.55-0.93)	Quality of study assessed using QUADAS-2: Overall high risk of bias. Overall low risk of indirectness See ROB section below for full details.

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
determining treatment of PC Study dates: 09/2002-03/2005 Source of funding: Supported by Foundation for Promotion of Cancer Research, Tokyo, Japan.		considered probably unresectable were also referred to a surgical ward, and laparotomy was performed. If no factors prohibiting resection were found at laparotomy, curative resection was attempted. A biliary or enteric bypass graft was constructed based on the surgeon's judgment. The treatment plan decided on at the conference was presented to the patient, and informed consent was obtained. CT Performed using CT scanner (Aquiline; Toshiba Medical Systems Co, Ltd, Tokyo, Japan) with 16 high-resolution central detectors. 1-mm section thickness selected and data reconstructed at 1-mm intervals (0.5-mm overlap). Other parameters were a 0.5-second helical rotation time, 135 kV (peak), and 350 to 400 mA-s. Study protocol was 4-phase acquisition that consisted of early arterial phase images beginning at 20 seconds, late arterial phase images beginning at 40 seconds, pancreatic phase images beginning at 70 seconds, and a delayed phase beginning at 120 seconds after the start of contrast medium injection. Early arterial images were used to reconstruct CT arteriography. Disease was primarily evaluated using late arterial and pancreatic images. Delayed phase images were used to detect the presence of fibrous tissue and for upper abdominal survey; 150 mL of iopamidol injected (Iopamiron; Nihon Schering Co, Ltd, Tokyo, Japan) through a peripheral venous line at 4 mL/s by using a power injector (Auto Enhance A-50; Nemoto Kyorindo, Tokyo, Japan). Multiplanar reformation and CT angiographic findings reconstructed using a freestanding workstation (Zaio Corp, Tokyo, Japan) if the diagnostic radiologists considered it necessary. Images were sent to a picture archiving and communication system (Synapse; Fujifilm Medical Co, Tokyo, Japan) that enables interactive analysis.	NPV=0.51 (95%CI, 0.45-0.57) Portal vein invasion (n=68) (TP=13, FP=3, FN=12, TN=40) Sens=0.52 (95%CI, 0.31-0.72) Sp=0.93 (95%CI, 0.81-0.99) PPV=0.81 (95%CI, 0.58-0.93) NPV=0.77 (95%CI, 0.69-0.83) Adverse events Not reported	

<table>
<tr><th>Study details</th><th>Participants</th><th>Index and reference tests
Description</th><th>Outcomes</th><th>Overall Risk of bias/Indirectness (Low/High/Unclear)</th></tr>
<tr>
<td>Full Citation
Ghaneh P, Hanson R, Titman A, Lancaster G, Plumpton C, Lloyd-Williams H, et al. (2018) PET-PANC:
multicentre prospective diagnostic accuracy and health economic analysis study of the impact of
combined modality ^{18}fluorine-2-fluoro-2-deoxy-d-glucose positron emission tomography with computed tomography scanning in the diagnosis and management of pancreatic cancer.
Health Technology Assessment 22(7)

Country/ies where the study was carried out:</td>
<td>Participants
N=393 patients with suspected PC

Inclusion criteria
Written informed consent
Able to have MDCT scan and attend PET/CT scan
Able to attend 12-mo FU
Patients with suspected pancreatic malignancy, defined as: (1) Focal lesion in pancreas/bulky pancreas/dilated pancreatic duct (with or without metastases) detected by MDCT (without or without MRI/EUS/ultrasound), or (2) Jaundice due to distal obstruction of common bile duct or ampulla (not due to calculi) [defined as serum bilirubin > 35 µmol/l] or (3) Serum CA 19-9>37 kU/l</td>
<td>Index test 1=PET/CT
Index 2=MDCT
Reference test=Histology (biopsy or resection) or 12-mo clinical FU

TNM staging classification used: UICC 2009 (7th edition)

Procedure
Study comprised 18 major pancreatic centres. All participants received standard diagnosis and staging with MDCT. Patients then underwent PET/CT with reference standard diagnosis within 2 weeks following informed consent. Follow up was 12 months. For 18-F-FDG PET/CT, patients fasted for 6 hours before scan; accurate SUV measurements obtained using calibrated class III device with blood glucose recorded using calibrated Boehringer Mannheim glucometer. Patients hydrated before scan; scan started 90 minutes after FDG injection. All PET/CT scans transferred to central reporting centre and reviewed by independent expert. Scans also additionally reviewed by 4 other centres.

Stage 0/IA/IB/IIA at D4 (reference standard)
<table>
<tr><th></th><th colspan="4">PET/CT at D2</th></tr>
<tr><th>MDCT at D1</th><th>Stage 0/IA/IB/IIA</th><th>Stage IIB</th><th>Stage III</th><th>Stage IV</th></tr>
</table>
</td>
<td>Study flow
910 patients screened, 619 registered, 589 underwent PET/CT scan.

MDCT
Accuracy
Overall=60%
Overstaged=7%
Understaged =34%

PET/CT
Accuracy
Overall=70%
Overstaged=8%
Understaged 22%

See description of study for additional results.

Adverse events
No events related to study procedure. One case of lymphangitis carcinomatosis, related to patient's original condition.</td>
<td>Quality of study assessed using QUADAS-2:
Overall low risk of bias.
Overall low risk of indirectness

See ROB section below for full details.</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Index and reference tests
Description</th><th>Outcomes</th><th>Overall Risk of bias/Indirectness (Low/High/Unclear)</th></tr>
<tr>
<td>UK
Study type:
Multicentre prospective cohort study
Aim of the study:
To determine incremental diagnostic accuracy and impact of PET/CT on standard diagnostic work-up in patients with suspected pancreatic cancer.
Study dates:
01/2011-05/2014
Source of funding:
Funded by HTA project # 08/29/02; DC funded by NIHR Biomedical Research Centre at Royal Marsden and Institute of Cancer Research.</td>
<td>Exclusion criteria
Patients <18 years
Pregnant
Poorly controlled diabetes

Characteristics (ITT population, n=583)
Median age (years)=66, range 21-87)
Male/female=328/255
Eligibility criteria:
Focal lesion=538; jaundice=159
CA 19-9 >37=127</td>
<td>
<table>
<tr><td>Stage 0/IA/IB/IIA</td><td>171</td><td>3</td><td>1</td><td>4</td></tr>
<tr><td>Stage IIB</td><td>4</td><td>4</td><td>0</td><td>0</td></tr>
<tr><td>Stage III</td><td>2</td><td>0</td><td>4</td><td>1</td></tr>
<tr><td>Stage IV</td><td>0</td><td>0</td><td>0</td><td>2</td></tr>
</table>
Stage IIB at D4 (reference standard)
<table>
<tr><td></td><td colspan="4">PET/CT at D2</td></tr>
<tr><td>MDCT at D1</td><td>Stage 0/IA/IB/IIA</td><td>Stage IIB</td><td>Stage III</td><td>Stage IV</td></tr>
<tr><td>Stage 0/IA/IB/IIA</td><td>50</td><td>21</td><td>1</td><td>3</td></tr>
<tr><td>Stage IIB</td><td>3</td><td>19</td><td>0</td><td>2</td></tr>
<tr><td>Stage III</td><td>0</td><td>1</td><td>3</td><td>0</td></tr>
<tr><td>Stage IV</td><td>2</td><td>0</td><td>0</td><td>2</td></tr>
</table>
Stage III at D4 (reference standard)
<table>
<tr><td></td><td colspan="4">PET/CT at D2</td></tr>
<tr><td>MDCT at D1</td><td>Stage 0/IA/IB/IIA</td><td>Stage IIB</td><td>Stage III</td><td>Stage IV</td></tr>
</table>
</td>
<td></td>
<td></td>
</tr>
</table>

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)

Stage 0/IA/IB/IIA	9	0	0	0
Stage IIB	1	6	0	0
Stage III	0	0	10	0
Stage IV	0	0	1	0

Stage IV at D4 (reference standard)

	PET/CT at D2			
MDCT at D1	**Stage 0/IA/IB/IIA**	**Stage IIB**	**Stage III**	**Stage IV**
Stage 0/IA/IB/IIA	10	0	0	15
Stage IIB	0	4	0	5
Stage III	0	0	0	7
Stage IV	1	0	0	21

Full Citation Imbriaco, M., Megibow, A. J., Ragozzino, A., Liuzzi, R., Mainenti, P., Bortone, S., Salvatore, M. et al. (2005). Value of the single-phase technique in	N=71 patients with suspected PC Inclusion criteria Suspected pancreatic mass based on clinical symptoms, lab findings, results of ERCP or sonography Informed consent	Index test 1=MDCT Reference test=Histopathology (n=42) or percutaneous FNA biopsy+1-year clinical follow up (n=29) TNM staging classification used: not reported Procedure Clinical findings, history of prior surgery and patient data recorded. If tumour confirmed as unresectable at lapartomoy, surgical biopsy followed by surgical bypass. Surgical resectability defined as completely removable by surgery; unresectability defined as presence of distant metastases in liver or peritoneal	Study flow 31 patients had CP and were not assessed for resectability. Diagnostic test accuracy data 95%CIs PPV and NPV calculated from raw data by technical team; Average of raw	Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of indirectness See ROB section below for full details.

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
MDCT assessment of pancreatic tumours. American Journal of Roentgenology, 184(4), 1111-1117. Country/ies where the study was carried out: Italy Study type: Prospective cohort Aim of the study: To evaluate diagnostic value of single-phase MDCT in suspected PC Study dates: 09/2001-02/2003 Source of funding: None reported	Exclusion criteria None reported Characteristics Mean age (years)= 63 (sd 12) Male/female=41/30 Tumour size (cm)=2.4 (sd 0.8; range 1-4) CA 19-9 (U/mL)=728 (sd 24) CEA (ng/mL)=6.2 (2.1) Jaundice=17 Pain=26 Final diagnosis PC=40 (22 head, 11 body, 7 tail) ; chronic pancreatitis=31	cavity or direct extension into surrounding organs or adjacent tissue, involvement of major arteries and veins (superior mesenteric vein and artery, celiac axis), lymphadenopathy>1.5cm. MDCT Performed using MDCT scanner (MX8000, Marconi) with 0.5s gantry rotation and acquisition of 4 slices per rotation. Ten to fifteen minutes before the examination, patients were given 500 mL of water for demarcation of the stomach and duodenum and delineation of the pancreatic head region. An 18- or 20-gauge catheter was placed in an antecubital vein. Glucagon was not administered. Unenhanced scanning of the pancreas was initially performed to define the craniocaudal extent of the pancreas using the following parameters: 4 × 2.5 mm detector configuration, 3-mm reconstruction interval, pitch of 1, 120 kVp, 200 mAs, and 35-cm field of view. Then one acquisition through the pancreas and upper abdomen was performed using the following parameters: caudocranial direction (from the inferior hepatic margin to the diaphragm), 4 × 1 mm detector configuration, 1.25-mm reconstruction interval, pitch of 1, 120 kVp, 260–280 mAs, and 35-cm field of view; with a scanning delay of 60 sec after the IV injection of 150 mL of nonionic contrast material (Ultravist [iopromide], Schering) with an iodine content of 370 mgI/mL delivered at 3 mL/sec. Mean scanning time from the inferior hepatic margin to the diaphragm was 18.4 ± 5 sec (range, 10–28 sec). Imaging interpretation was performed directly at a dedicated workstation (Kayak PC, Hewlett Packard) using a software package with a volume-rendering algorithm (Vitrea 2.2, Vital Images). Two reviewers independently evaluated the images for the presence of tumour and assessment of resectability. In addition, attenuation values of the tumour, the normal pancreatic parenchyma, the	data from both reviewers used in analysis; Resectability Reviewer 1 (TP=8, FP=2, FN=1, TN=29) Sens=0.89 (95%CI, 0.52-1.0) Sp=0.94 (95%CI, 0.79-0.99) PPV=0.8 (95%CI, 0.11-0.38) NPV=0.97 (95%CI, 0.82-0.99) Reviewer 2 (TP=7, FP=3, FN=2, TN=28) Sens=0.78 (95%CI, 0.4-0.97) Sp=0.9 (95%CI, 0.74-0.98) PPV=0.7 (95%CI, 0.43-0.88) NPV=0.93 (95%CI, 0.8-0.98) Adverse events Not reported	

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
		liver, the hepatic veins, Two reviewers independently (and without knowledge of results of prior imaging tests, clinical history, surgical or histopathological findings) evaluated images for presence of tumour and resectability assessment and the superior mesenteric artery and vein were also measured.		
Full Citation Klauss, M., Mohr, A., von Tengg-Kobligk, H., Friess, H., Singer, R., Seidensticker, P., Grenacher, L. et al. (2008). A new invasion score for determining the resectability of pancreatic carcinomas with contrast-enhanced multidetector computed tomography. Pancreatology, 8(2), 204-210. Country/ies where the study was carried out: Germany Study type: Prospective cohort Aim of the study:	N=80 patients with suspected PC Inclusion criteria Strong clinical suspicion of PC based on icterus, prior CT or US scan, unspecific weight loss, or elevated CA 19-9 Informed consent Exclusion criteria Renal impairment with creatinine value>2 mg/dl Manifest hyperthyroidism Known contrast medium allergy Failure to consent Characteristics Mean age (years)=64.9 (range 37-89) Male/female=43/37 Final diagnosis	Index test 1= CT Reference test=Intraoperative findings for resectability; histology or biopsy, or 1-year clinical follow up for benign findings who did not have surgery. TNM staging classification used: not reported Procedure All patients received CT. Images evaluated by 2 radiologists blinded to prior evaluations (inc. previous CT, MRI and US results, final diagnosis, surgical findings). Clearly unresectable cases were followed up with imaging during radio- or chemotherapy every 3 months. Invasion of vessels evaluated using 2 variables (length of tumour contact and circumferential involvement) for arterial invasion and 3 variables (same as for arteries + other abnormalities) for veins. Score of 11 or more calculated as having highest sensitivity and specificity. CT A 16-row multislice hydro-CT (Siemens Somatom Sensation 16, Erlangen, Germany) was performed on all the patients, and Ultravist 370 (Schering, Berlin, Germany) was administered. First, a non-contrast-enhanced spiral CT of the abdomen was performed. Then, examinations were performed in the arterial phase (delay of 8 s after the threshold) and in the portal venous phase (delay of 35 s after the threshold) using the Care bolus technique with 120 ml contrast medium (5 ml/s, Ultravist 370, Schering), resulting in an iodine dose of 44.4 g and an iodine delivery rate of 1.85 g/s. The attenuation value for bolus triggering was 100 Hounsfield units; the attenuation was	Study flow Vascular invasion not evaluable in 18 of the 45 patients with tumour because they did not have surgery. Diagnostic test accuracy data Resectability (TP=21, FP=0, FN=1, TN=6) Sens=0.95 Sp=1.0 PPV=1.0 NPV=0.86 Vascular invasion* (total invasion score≥11 (n=9) to indicate infiltration; TP=7, FP=2, FN=1, TN=18) Sens=0.88 Sp=0.9 PPV=0.78 NPV=0.95	Quality of study assessed using QUADAS-2: Overall high risk of bias. Overall low risk of indirectness See ROB section below for full details.

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
To determine value of vascular invasion score to determine resectability in staging Study dates: 03/2005-08/2006 Source of funding: None reported	Malignant, n=45 [histology=43; 2 FU] (PAC=35, IPMN=3; pancreatic metastases=5; other=2) Benign, n=35 (CP=11)	measured in the aorta at the height of the superior mesentery artery. Dual-phase imaging, because in some cases, it is helpful to analyze the etiology of a pancreatic tumour. A curved MPR of the examination in the venous phase was generated in all cases and blinded image review, but was not evaluation criterion for the study.	*Discrepancy in reported data Superior mesenteric vein (TP=4, FP=1, FN=0, TN=23) Sens=1.0 Sp=0.96 PPV=0.8 NPV=1.0 Splenic vein (TP=2, FP=0, FN=1, TN=25) Sens=0.67 Sp=1.0 PPV=1.0 NPV=0.96 Portal vein (TP=2, FP=1, FN=0, TN=25) Sens=1.0 Sp=0.96 PPV=0.67 NPV=1.0 Celiac trunk (TP=1, FP=0, FN=0, TN=27) Sens=1.0 Sp=1.0 PPV=1.0	

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
			NPV=0.96 Superior mesenteric artery (TP=1, FP=0, FN=0, TN=27) Sens=1.0 Sp=1.0 PPV=1.0 NPV=0.96 Adverse events Not reported	
Full Citation Klek, S., Kulig, J., Popiela, T., Kotodziejczyk, P., Szybinski, P., Popiela, T. J., & Urbanik, A. (2004). The value of modern ultrasonographic techniques and computed tomography in detecting and staging of pancreatic carcinoma. Acta Chirurgica Belgica, 104(6), 659-667.	N=140 patients with suspected PC Inclusion criteria Written informed consent Operated on for PC Exclusion criteria x Characteristics Mean age (years)=59.6 (range 37-81) Male/female=77/63 Final diagnosis, n=140 PC=126; Endocrine tumours=10; CP=4 WHO classification	Index test 1=CT Index test 2= Power-Doppler US Reference test=Post-operative histopathology TNM staging classification used: WHO Procedure All patients had surgery for suspected PC. Hitachi EUB 6000, Elscint Helicat Flash and Siemens Somatom Sensation 10 used to perform US and CT exams. Helical, multirow CT performed ~3hr after oral contrast (1000 ml 2% urographin) and addition i.v. contrast (Uropolinum or Omnipaque, Polpharma and Nycomed, respectively) by 2 physicians. If technical problems during US, repeated following day.	Study flow 14 patients without final diagnosis of PC (CP=4; endorince tumours=10) excluded from analysis Diagnostic test accuracy data Data only shown for best US technique; results for routine US, Colour Doppler US and 3D-US not shown. Data not shown for T-staging as there are substantial discrepancies in the	Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of indirectness See ROB section below for full details.

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
Country/ies where the study was carried out: Poland Study type: Prospective cohort Aim of the study: To assess value of CT, 3DUS, Routine US, and Colour-/Power-Doppler US in detection and staging of pancreatic cancer. Study dates: 01/2000-02/2004 Source of funding: None reported	T1=9; T2=21; T3=41; T4=54.		published results in text and table. N-Staging (n=70) CT* Sens=0.75 Sp=0.95 PPV=0.78 NPV=0.94 *Discrepancy in published results Power Doppler US Sens=0.75 Sp=0.91 PPV=0.81 NPV= 0.88 Vascular invasion (n=126) CT Sens=0.91 Sp=0.96 PPV=0.94 NPV=0.93 Power Doppler US Sens=0.91 Sp=0.96 PPV=0.94 NPV= 0.93 Adverse events	

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
Full Citation Koelblinger, C., Ba-Ssalamah, A., Goetzinger, P., Puchner, S., Weber, M., Sahora, K., Schima, W. et al. (2011). Gadobenate dimeglumine–enhanced 3.0-T MR imaging versus multiphasic 64–detector row CT: prospective evaluation in patients suspected of having pancreatic cancer. Radiology, 259(3), 757-766. Country/ies where the study was carried out: Austria Study type: Prospective cohort Aim of the study: To compare diagnostic performance of	N=89 patients with suspected PC Inclusion criteria Written informed consent Referred to hepatobiliary-pancreatic department for suspected PC on basis of clinical examination (n=62; e.g. jaundice, increased CA 19-9 levels, rapid weight loss) or previous US or CT from other institution (n=27) Exclusion criteria No pancreatic malignancy Characteristics Mean age (years)= 65.5 (sd 10.7) Male/female=41/48 # patients with focal lesions=63 Mean tumour size (cm)=3.4 (sd 1.8) Tumour location: 53 head, 10 body, 7 tail. Final diagnosis	Index test 1=MDCT Index test 2=MRI Reference test= Surgery, surgical histopathology, CT-/US-guided biopsy, imaging or clinical FU TNM staging classification used: not reported Procedure All patients had MDCT and MRI within 1 week of each other; images interpreted independently by 2 radiologists who were blinded to all clinical info and final diagnosis. Reading sessions separated by at least 8 weeks and presented to both readers in different randomised order. Assessment of vascular invasion according to criteria of Li et al. 2005. MDCT All CT examinations performed with a 64–detector row CT scanner (Sensation 64; Siemens, Erlangen, Germany) with a gantry rotation speed of 0.5 second and a detector configuration of 64 x 0.6 mm. All scans were acquired in a cephalocaudal direction with a pitch of 1 by using an automatic dose adaptation system provided by the manufacturer (Caredose, Siemens). Twenty minutes before undergoing CT, the patients drank 1000 mL of water to distend the stomach and duodenum. After an unenhanced scan was obtained of the upper abdomen, the upper abdomen was scanned in the pancreatic parenchymal phase and the abdomen and pelvis were scanned in the portal venous phase. One hundred fifty milliliters of non-ionic contrast material (iomeprol [300 mg iodine per milliliter]; Iomeron 300, Bracco, Milan, Italy), warmed to room temperature, was administered with a power injector (Ohio Tandem; Ulrich Medical, Ulm, Germany) at a flow rate of 5 mL/sec via an 18- or 20-gaugediameter intravenous catheter placed in a cubital or antecubital vein; this was followed by a 40-mL saline flush. A bolus tracking program	Study flow Of 112 eligible patients, 23 were excluded (CT/MRI contraindication=7; time constraints=5; not contactable/refusal to participate=11); 38 patients (normal pancreas=26; benign findings=12) were excluded due to lack of pancreatic malignancy. Diagnostic test accuracy data 95%CIs, PPV and NPV calculated from raw data by technical team; average of reader 1 and reader 2 used in analysis; data for vascular invasion not shown since given in terms of number of vessels rather than number of patients. Resectability MDCT Reader 1	Quality of study assessed using QUADAS-2: Overall high risk of bias. Overall low risk of indirectness See ROB section below for full details.

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
multiphasic 64-detector row CT with gadobenate dimeglumine-enhanced 3.0T MRI in suspected PC Study dates: 09/2006-11/2007 Source of funding: None reported	Malignant, n=56 (PC=43; other=8) Benign, n=14	provided by the CT unit manufacturer was used to monitor contrast enhancement after initiation of contrast medium administration by using a region of interest placed in the aorta at the level of the diaphragm. The pancreatic parenchymal phase was started 25 seconds after the trigger threshold of 100 HU was reached in the abdominal aorta. The portal venous phase was started after an interscan delay of 23 seconds. Multidetector CT was performed at 120 kVp. All images were recon-structed with a section thickness of 3 mm and a section increment of 2 mm for transverse viewing and at a section thickness of 1 mm and a section increment of 0.7 mm for 3D reconstructions. Coronal multiplanar reconstructions of images obtained in the pancreatic parenchymal and venous phases were routinely acquired (section thickness, 3 mm; section increment, 2 mm). Curvedplanar reconstructions were created along the pancreatic duct and, if necessary, the peripancreatic vessels. MRI All MR examinations were performed with a 3.0-T unit (Trio Tim, Siemens) equipped with a phased-array coil (which was placed ventrally on the upper abdomen) and a spine coil (for the dorsal part of the abdomen). All patients received injection of a bolus of 0.1 mmol/kg (0.2 mL per kg gram body weight) gadobenate dimeglumine (MultiHance, Bracco) into a cubital or antecubital vein at 2–3 mL/sec, followed by a 10-mL saline flush. Dynamic transverse T1-weighted GRE volumetric interpolated breath-hold images were then acquired in the pancreatic parenchymal phase (30 seconds after injection), portal venous phase (65 seconds after injection), equilibrium phase (5 minutes after injection), and hepatobiliary phase (60–90 minutes after injection). In addition, coronal volumetric interpolated breath-hold and transverse T1-weighted 2D GRE sequences were used in the equilibrium and hepatobiliary phases. The field of view was 350–400 x 350 mm	Sens=0.75 (95%CI, 0.35-0.97) Sp= 0.87 (95%CI, 0.60-0.98) PPV=0.75 (95%CI, 0.44-0.92) NPV=0.87 (95%CI, 0.66-0.96) Reader 2 Sens=0.63 (95%CI, 0.25-0.91) Sp=0.87 (95%CI, 0.6-0.98) PPV=0.71 (95%CI, 0.38-0.91) NPV=0.81 (95%CI, 0.63-0.92) Average of reader 1 and 2 used in analysis (TP=6, FP=2, FN=2, TN=13) Sens=0.75 (95%CI, 0.35-0.97) Sp=0.87 (95%CI, 0.6-0.98) PPV=0.75 (95%CI, 0.44-0.92) NPV=0.87 (95%CI, 0.66-0.96) MRI	

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
		for all transverse sequences and 400–450 x 450 mm for all coronal sequences, with individual adjustment dependent on patient size. Except for the navigator triggered sequences, all sequences were performed with a breath-hold technique (duration, 18–21 seconds). All sequences, except for T2-weighted single-slab 3D turbo spin echo (SPACE, or sampling perfection with application-optimized contrast using different flip angle evolutions), were performed with one signal acquired.	Reader 1 Sens=0.75 (95%CI, 0.35-0.97) Sp=0.93 (95%CI, 0.68-1.0) PPV=0.86 (95%CI, 0.46-0.98) NPV=0.88 (95%CI, 0.68-0.96) Reader 2 Sens=0.5 (95%CI, 0.16-0.84) Sp=0.93 (95%CI, 0.68-1.0) PPV=0.8 (95%CI, 0.35-0.97) NPV=0.78 (95%CI, 0.63-0.88) Average of reader 1 and 2 used in analysis (TP=5, FP=3, FN=1, TN=14) Sens=0.83 (95%CI, 0.36-1.0) Sp=0.82 (95%CI, 0.57-0.96) PPV=0.63 (95%CI, 0.36-0.83) NPV=0.93 (95%CI, 0.7-0.99)	

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
			Adverse events Not reported	
Full Citation Kwon, A. H., Inui, H., & Kamiyama, Y. (2002). Preoperative laparoscopic examination using surgical manipulation and ultrasonography for pancreatic lesions. Endoscopy, 34(06), 464-468. Country/ies where the study was carried out: Japan Study type: Prospective cohort Aim of the study: To determine contribution of laparoscopy and laparoscopic US to diagnosis and/or staging of pancreatic lesions. Study dates: 07.1996-09/2000	N=118 patients with suspected PC Inclusion criteria Written informed consent Radiologically resectable lesion Exclusion criteria Not radiologically resectable Characteristics (n=52) Mean age (years)=59 (range 40-74) Male/female=32/20 Tumour location: 39 head, 13 body.	Index test 1=Laparoscopy + LUS Reference test= Surgery, surgical histopathology or LUS TNM staging classification used: not reported Procedure All patients had previous US, CT, ERCP and/or angiography. Surgical procedure indicated in 52 patients but no diagnostic certainty and/or assessment of whether lesion resettable possible preoperatively on basis of histology. Laparoscopic US carried out immediately prior to planned surgical intervention for pancreatic lesion. Laparoscopy +LUS Under satisfactory general anesthesia, the abdomen was filled with carbon dioxide until the intraperitoneal pressure reached 10–12 mmHg. This can be performed via an open approach with a Hasson trocar through a periumbilical incision. Surgeon's approach always tailored to the individual patient. After an inspection of the peritoneal cavity, a careful search was made for any free fluid, for peritoneal or serosal deposits of tumour cells, and for lesions on the surface of the liver. A flexible 7.5-MHz linear-array ultrasound probe with a maximum diameter of 10mm (LAP-703SL, Machida, Tokyo, Japan or PEF-704LA, Toshiba Medical, Tokyo, Japan) was inserted through this port, and the resulting images were viewed on a scanning machine (SSA-260A, Toshiba Medical, Tokyo, Japan). The liver, bile duct, and pancreas can be scanned in the transverse and sagittal planes with careful manipulation of the probe. A laparoscopic examination for lesions of the head of the pancreas, using a retroduodenal approach, was also performed. Mobilization	Study flow 66 patients excluded from laparoscopy+LUS results due to CT-unresectable results. Diagnostic test accuracy data Sens/Sp/PPV/NPV calculated using raw data. Resectability CT (n=118) (TP=33, FP=19, FN=0, TN=66) Sens=1.0 (95%CI, 0.89-1.0) Sp=0.78 (95%CI, 0.67-0.86) PPV=0.63 (95%CI, 0.54-0.72) NPV=1.0 Laparoscopy+LUS (n=52) (TP=39, FP=3, FN=0, TN=10) Sens=1.0 (95%CI, 0.91-1.0)	Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of indirectness See ROB section below for full details.

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
Source of funding: None reported		of the duodenum and the head of the pancreas was achieved using the Kocher manoeuver. The duodenum was grasped with Babcock forceps, and retracted medially as the peritoneum along the lateral wall of the duodenum was incised. Ligation of the vessels in this area was not usually necessary. Blunt or gauze dissection was used to push the posterior wall of the pancreas away from the underlying vena cava and the right kidney. However, an avascular cleavage plane can easily be developed. An attempt was made to detect any enlarged lymph nodes and to trace the vessels in the region of the pancreas and portal vein, while paying particular attention to the presence of any displacement or invasion of the portal and superior mesenteric veins using LUS. Alternatively, an infragastric approach was used to examine for lesions of the body and tail of the pancreas. The stomach was grasped and lifted with the forceps, and the transparent window close to the greater curvature was dentified. This window was divided by scissors, and the opening was enlarged by ligation and division of the adjacent gastric vessels supplying the greater curvature from the gastroepiploic arcade. Excellent close-up visualization of the entire lesser sac, and of the body and tail of the pancreas, can be obtained in this manner. The linear-array probe was placed directly on the body and tail of the pancreas, which was irrigated with warm normal saline to enhance the acoustic contact between the pancreas and the transducer. Biopsies of any suspicious lesions were taken under direct laparoscopic and/or ultrasonic guidance, using either a direct-core biopsy needle or biopsy forceps. Specimens obtained were immediately sent for frozen-section examination. Cautery and laparoscopic argon beam coagulation were used to significantly reduce post-biopsy bleeding. The surgical field was then washed out with normal saline, and no drainage was required. Criteria for unresectability: (i) presence of liver, serosal or peritoneal metastases; (ii) mesocolic involvement; (iii) celiac or	Sp=0.77 (95%CI, 0.46-0.95) PPV=0.93 (95%CI, 0.83-0.97) NPV=1.0 Adverse events No laparoscopic-related complications.	

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
		portal node involvement; (iv) invasion or encasement of celiac axis or hepatic artery; (v) encasement by tumour of portal or superior mesenteric veins and/or artery.		
Full Citation Lemke, A. J., Niehues, S. M., Hosten, N., Amthauer, H., Boehmig, M., Stroszczynski, C., Felix, R. et al. (2004). Retrospective digital image fusion of multidetector CT and 18F-FDG PET: clinical value in pancreatic lesions—a prospective study with 104 patients. Journal of nuclear medicine, 45(8), 1279-1286. Country/ies where the study was carried out: Germany Study type: Prospective cohort	N=104 patients with suspected PC Inclusion criteria Suspected pancreatic lesion Exclusion criteria Blood glucose level>110 mg/dL for PET Characteristics Median age (years)= 64 (range 23-84) Male/female=51/53 Median time to histological confirmation=16 days (range 5-35) Final diagnosis (n=100) Malignant=64 (PAC=57; other=7) Benign=36 (CP=28; other=8)	Index test 1=CT Index test 2=PET-CT Reference test=Surgical resection (n=53), exploratory surgery (n=25), percutaneous needle aspiration biopsy (n=16) TNM staging classification used: not reported Procedure Median time interval between CT and PET=3 days (range 1-6). PET-CT fusion retrospectively performed using AVS Express program. CT Triple-phase with quadruple-line multislice CT scanner with patients in prone position and arms raised above head. CT performed in respiratory midposition and without gastric filling. Nonconstrast study of abdomen acquired (120 kV; 165 mA; collimation, 4 x 5 mm; table feed, 20 mm; pitch, 1; reconstruction interval, 8 mm). Eighteen seconds after initiating the intravenous administration of 100 mL iopromide (Ultravist 370; Schering AG), a contrast-enhanced acquisition was started during both the arterial phase (collimation, 4 x 1 mm; table feed, 4 mm; pitch, 1; reconstruction interval, 5 mm) and the venous phase 80 s after beginning with the intravenous administration of the contrast agent (collimation, 4 x 1 mm; table feed, 4 mm; pitch, 1; reconstruction interval, 8 mm). Image fusion was based on the arterial phase. PET The PET scans were performed with an ECAT EXACT 47 scanner (Siemens AG). The blood glucose level of each patient was determined before he or she underwent PET scanning.	Study flow Image fusion not technically possible in 4 patients due to differences in body position. Diagnostic test accuracy data 95%CIs calculated by technical team from raw data; data for PET not shown. N staging CT (TP=8, FP=4, FN=23, TN=12) Sens=0.26 (95%CI,0.12-0.45) Sp=0.75 (95%CI, 0.48-0.93) PPV=0.67 (95%CI, 0.41-0.85) NPV=0.34 (95%CI, 0.27-0.43) PET-CT (TP=10, FP=4, FN=21, TN=12)	Quality of study assessed using QUADAS-2: Overall unclear risk of bias. Overall low risk of indirectness See ROB section below for full details.

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
Aim of the study: To evaluate clinical benefit of PET/CT image fusion in diagnostic workup of pancreatic cancer Study dates: 08/1999-12/2001 Source of funding: Grants from Deutsche Forschungsgemeinschaft Graduier-tenkolleg 331 and National Science Foundation		Patients whose blood glucose level exceeded 110 mg/dL were excluded from the study. Scans were performed in prone position and no breathing commands were given throughout the scan. Intravenous administration of 5 MBq 18F-FDG per kilogram of body weight was followed by a 2-dimensional (2D) whole-body PET scan with integrated transmission measurement and iterative image reconstruction. An uptake period of 60–90 min was adhered to before the actual image acquisition. Contrary to the CT studies, the patients kept their arms alongside the body. Glucose uptake was quantified by the standard uptake value (SUV), with an SUV of >3.5 considered as indicative of malignancy. For definite assessment of a pancreatic mass, both the SUV value and visual aspects were considered. After inclusion of the last patient, a receiver operating characteristic (ROC) analysis of SUV values was performed to verify the cutoff point between benign and malignant lesions. PET-CT Two radiologists evaluated original CT and PET images, and fused image in randomised order in 3 different settings with interval of 2 weeks each. Using a standardized questionnaire, the following aspects were assessed and compared with the gold standard: (i) Presence of a benign or malignant lesion; (ii) Possible infiltration of tissue adjacent to the pancreas (fuzzy outline of the organ, infiltration of peripancreatic fatty tissue or duodenum) or infiltration of one of the following vessels (tumour encasement ≥ 50% (7)) to assess resectability: superior mesenteric vein; confluence of the superior mesenteric, splenic, and portal vein; superior mesenteric artery; splenic artery; common hepatic artery; celiac axis (8–10); (iii) presence of any locoregional lymph node metastasis (CT criterion: diameter, >1 cm; PET criterion: focal tracer hot spots); (iv) Presence of any	Sens=0.32 (95%CI, 0.17-0.51) Sp= 0.75 (95%CI, 0.48-0.93) PPV=0.71 (95%CI, 0.48-0.87) NPV=0.36 (95%CI, 0.28-0.45) Vascular invasion (n=47) CT (TP=21, FP=0, FN=23, TN=3) Sens=0.48 (95%CI,) Sp=1.0 (95%CI,) PPV=1.0 (95%CI,) NPV=0.12 (95%CI,) PET-CT (TP=30, FP=1, FN=14, TN=2) Sens=0.68 (95%CI, 0.52-0.81) Sp=0.67 (95%CI, 0.09-0.99) PPV=0.97 (95%CI, 0.86-0.99) NPV=0.13* (95%CI, 0.05-0.26) *reported as 0.013 in article Adverse events	

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
		other manifestation of the tumour—for example, liver metastases or other abdominal metastases.	Not reported	
Full Citation Liu, R. C., & Traverso, L. W. (2005). Diagnostic laparoscopy improves staging of pancreatic cancer deemed locally unresectable by computed tomography. Surgical Endoscopy And Other Interventional Techniques, 19(5), 638-642. Country/ies where the study was carried out: USA Study type: Retrospective review of prospective cohort Aim of the study: To evaluate staging contribution of	N=74 patients with CT-locally advanced and CT-non-metastatic PAC Inclusion criteria Histologically documented PAC Exclusion criteria CT-resectable or CT-metastatic tumour Characteristics Mean age (years)= Male/female=	Index test 1=CT Reference test=Diagnostic laparoscopy TNM staging classification used: not reported Procedure All patients, unless high quality CT scan at referring hospital (n=9), evaluated by double-helix, early arterial/late portal venous phase thin-cut 'pancreas protocol' CT with oral water. No CT scans used to determine clinical stage. CT scans interpreted by multidisciplinary team. Determination of local extension as 'unresectable' made by surgeon. ERCP, EUS, CT- or US-guided biopsies performed if appropriate for diagnosis and relief. If percutaneous biopsy performed before diagnostic laparoscopy, then association with peritoneal lavage cytology examined. CT-unresectable if CT showed involvement of contiguous organ or adjacent blood vessel; lymph node enlargement not indicator of unresectability. Diagnostic laparoscopy Laparoscopy was performed with the patient under general anesthesia in an outpatient setting. The patient was placed in the supine position and access was obtained with a Veress needle through an infraumbilical site. Carbon dioxide pneumoperitoneum was established at 15 mmHg. A safety-shielded 5-mm port and then a 5-mm 30laparoscope were inserted. All four quadrants were inspected. An additional 5-mm port was inserted for lavage and possible biopsy. The site of insertion depended on where potential metastatic disease was observed and was always lateral to the rectus sheath to avoid the epigastric vessels. After inspection and before biopsy, the upper abdomen was filled with 400 ml of 0.9% saline for PLC. The fluid was distributed throughout the peritoneal cavity by external agitation of the	Diagnostic test accuracy data M Staging (no evidence of metastases on CT for all patients) (TP=0, FP=0, FN=25, TN-49) Sens=na Sp=1.0 (0.93-1.0) PPV=na NPV=0.66 [management changed in 25 patients] Adverse events Intraoperative complication rate=4% (liver laceration=1; serosal tear=1). No post-procedural complications.	Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of indirectness See ROB section below for full details.

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
laparoscopy in locally advanced PC patients deemed CT-unresectable. Study dates: 04/2000-02/2004 Source of funding: None reported		abdominal wall and tilting of the operating table up and down. Then all possible fluid was aspirated for cytologic examination. The PLC results were considered positive if malignant cells or cells highly suspicious for malignancy were found at cytologic examination [6]. After the PLC, a biopsy of grossly suspicious liver or peritoneal lesions was performed with cold-cut scissors and biopsy forceps. Hemostasis was obtained with electrocautery. The primary purpose of the diagnostic laparoscopy was to detect metastatic disease. Therefore, the primary tumour, pancreas, and lesser sac were not examined. Laparoscopic ultrasound was not used.		
Full Citation Maithel, S. K., Maloney, S., Winston, C., Gönen, M., D'Angelica, M. I., DeMatteo, R. P., Allen, P. J. et al. (2008). Preoperative CA 19-9 and the yield of staging laparoscopy in patients with radiographically resectable pancreatic adenocarcinoma. Annals of surgical oncology, 15(12), 3512-3520.	N=491 patients with potentially resectable PC Inclusion criteria Radiologically resectable PC Had staging laparoscopy Exclusion criteria Borderline resectable Findings consistent with metastatic disease Characteristics Median age (years)=69 (range 41-91) Male/female=238/253 Tumour location: 373 head; other=118	Index test 1=CA 19-9 Reference test= Laparoscopy/surgery TNM staging classification used: not reported Procedure Radiographic resectability was determined with a detailed examination of preoperative axial imaging, which included either a high-quality CT scan or MRI. CT scans obtained at institution were pancreas dedicated with dynamic contrast enhancement and multidetector thin-section (5 mm) imaging. Patients with ''borderline resectable'' disease, as defined by tumour extension to the celiac axis, abutment of the superior mesenteric artery, or short-segment involvement of the portal vein or the superior mesenteric vein were excluded from analysis. Patients with any suspicious findings for distant metastatic disease were also excluded from the study. Staging laparoscopy and resection were generally performed under the same anaesthetic. Although the technique of staging laparoscopy varied slightly according to surgeon preference, the standard exploration included a detailed examination of the liver, peritoneal surfaces, and transverse colon mesentery for the presence of disease.	Study flow CA 19-9 values not available for 229 patients, who were excluded. Diagnostic test accuracy data Calculated from raw data (TP=105, FP=13, FN=106, TN=38) CA 19-9 Resectability (indicated by CA 19-9 <130 U/ml) Sens=0.5 (95%CI, 0.43-0.57) Sp=0.75 (95%CI, 0.6-0.86) PPV=0.89 (95%CI, 0.83-0.93)	Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of indirectness See ROB section below for full details.

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
Country/ies where the study was carried out: USA Study type: Retrospective review of prospective database Aim of the study: To analyse influence of CA 19-9 on laparscopic yield in resectable pancreatic adenocarcinoma. Study dates: 01/2000-12/2006 Source of funding: None reported	Preoperative symptoms: weight loss=195; pain=231; jaundice=174; pain and weight loss=299.		NPV=0.26 (95%CI, 0.23-0.31) Laparoscopy could be avoided in 118 out of 262 patients, and resection avoided in 38 of 144 patients. Adverse events Not reported	
Full Citation Maluf-Filho, F., Sakai, P., Cunha, J. E. M., Garrido, T., Rocha, M., Machado, M. C. C., & Ishioka, S. (2004). Radial endoscopic ultrasound and spiral computed	N=61 patients with suspected pancreatic or periampullary cancer Inclusion criteria Informed consent Suspected pancreatic or periampullary cancer based on clinical	Index test 1=Spiral CT Index test 2=EUS Reference test=Surgical histopathology or intraoperative biopsy from laparotomy or EUS-FNA TNM staging classification used: UICC 1997 Procedure All patients underwent EUS examination of the biliary ducts and pancreas and abdominal SCT within 1 week. Both exams were performed	Study flow One EUS exam incomplete. 92% underwent surgical exploration. Diagnostic test accuracy data T Staging (n=27 pancreatic cancer patients only)	Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of indirectness See ROB section below for full details.

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
tomography in the diagnosis and staging of periampullary tumors. Pancreatology, 4(2), 122-128. Country/ies where the study was carried out: UK Study type: Prospective cohort Aim of the study: To evaluate the accuracy of EUS and spiral CT for the diagnosis and staging of localregional pancreatic malignancy and ampullary adenocarcinoma Study dates: 06/1997-12/1999 Source of funding: None reported	symptoms and biochemical results compatible with cholestatic jaundice, associated with biliary duct dilation seen on abdominal US in patients without concomitant stone disease Exclusion criteria Patients with neuroendocrine pancreatic tumours and with distant organ metastatic disease demonstrated by spiral CT Characteristics Mean age=56.8 years (range 14-100) Male/female: 28/33 Final diagnosis Pancreatic adenocarcinoma=27; Other cancer=25, other=9	and interpreted without previous knowledge of the result of other image methods except by US. Tumour staging for both PA and AA was performed by the TNM system. Results of both EUS and SCT were double-blinded. Spiral CT Quadruple phase spiral SCT scan examination performed using GE, model Hi-Speed and Pro-Speed (Milwaukee, Wisc.,USA). After the administration of negative contrast medium (water), 5-mm-thick slices were taken, with a pitch of 1.4 s followed by reconstructions every 5 mm. This phase was aimed for the detection of stones in the biliary tract. After this, about 1,500 ml of diluted iodated contrast medium (meglumine iodamide 2%) was given orally, over approximately 60 min and another set of 5-mm-thick slices accomplished, with a pitch of 2.0 s, using breath-hold technique. The organs were studied in the arterial phase 25–40 s after i.v. injection of approximately 150 ml of non-ionic iodated contrast medium. The rate of i.v. contrast administration was 3 ml/s. Portal phase imaging followed 20 s after the arterial phase. After another rest of 30–60 s, new slices were taken in the additional late phase imaging. The slices obtained at the end of examination aimed to assess the behaviour of hepatic lesions eventually found in previous phases. The images were obtained from the diaphragm to the brim of the pelvis in each phase and they were interpreted by a senior radiologist. Lesions were characterized according to size, location, solid or cystic component and attenuation by contrast medium in different phases (arterial, portal and intermediate). Lymph nodes 610 mm were considered malignant when associated with images compatible with a tumour. Vascular tumour invasion was considered in the presence of one of the following findings: (1) deformity of more	CT Accuracy=59% Overstaged=7% Understaged=33% EUS Accuracy=89% Overstaged=7% Understaged=4%	

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
		than 90% of the vessel circumference by the expansible lesion; (2) circumferential vascular involvement by the tumour ('vascular encasement') and (3) the presence of a vascular thrombus. Dilation of tributary vessels and presence of collateral circulation were considered suspicious of tumour venous infiltration. EUS Gastroechoendoscope with frequencies of 7.5 and 12.0 MHz, model GF-UM20 used, coupled to an ultrasonographic processor of models EUM-20 or 30 (Olympus Optical Co. Ltd, Tokyo, Japan). Patients were under conscious intravenous sedation. One single endoscopist accomplished all echoendoscopic exams. The expansive lesions were characterized regarding location, size, contour, echogenicity and predominant aspect (solid, cystic or mixed). The hypoechoic lymph nodes (LN) were considered metastatic when one or more of the following findings were present: (1) size 610 mm; (2) homogeneous LN; (3) sharply demarcated borders; (4) location within 15 mm of the primary lesion, and (5) grouped LN, that is, more than two LN clumped together. Hyperechoic LN were considered malignant when two or more of the following criteria were fulfilled: (1) size 610 mm; (2) homogeneous LN; (3) next to the primary lesion, or clumped. Portal (PV), superior mesenteric (SMV) and splenic veins (SV) were considered free of tumour involvement by EUS in two situations: (1) presence of a hyperechoic plane between the tumour and the vessel wall or (2) disappearance of this plane, but with preservation of a smooth vascular contour along the region of tumour interface. Echoendoscopic signs of neoplastic vascular invasion were loss of hyperechogenic interface between the vascular structure and the tumour, associated to irregular vascular contour, or the presence of a thrombus in the vessel lumen, or disappearance of the vessel contiguous to mass associated with the presence of collateral circulation.		

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
Full Citation Mansfield, S. D., Scott, J., Oppong, K., Richardson, D. L., Sen, G., Jaques, B. C., Charnley, R. M. et al. (2008). Comparison of multislice computed tomography and endoscopic ultrasonography with operative and histological findings in suspected pancreatic and periampullary malignancy. British Journal of Surgery, 95(12), 1512-1520. Country/ies where the study was carried out: UK Study type: Prospective cohort Aim of the study:	N=84 suspected pancreatic tumours Inclusion criteria Referred for assessment to Freeman Hospital, Newcastle upon Tyne. Had clinically indicated EUS and MDCT at Freeman Hospital Exclusion criteria EUS performed for sole purpose of gathering FNA cytology Characteristics Median age (years)=67 Male/female=39.45 Clinical symptoms: obstructive jaundice=59 Final diagnosis Malignant, n=60 (PAC=47; other=13) Benign, n=24	Index test 1=MSCT Index test 2=EUS Reference test=Consensus diagnosis by multidisciplinary team using clinical imaging, histology, and biochemical markers. TNM staging classification used: not reported Procedure Assessment of vascular invasion and resectability, operative assessment with histological assessment of resected specimens where available; malignant lymphadenopathy assessed using histology. Analysis within 8 weeks of imaging. Patients with benign disease followed up for at least 12 months. Unresectability defined as peritoneal, liver or other distant metastases; tumour invading the portal vein/SMV when it would not be possible to obtain clear resection margins; arterial involvement of the coeliac, hepatic and superior mesenteric arteries; and malignant lymphadenopathy distant to the peripancreatic nodes confirmed on histological or cytological examination. MSCT All scans were performed using a Siemens Volume Zoom MSCT scanner (Siemens, Erlangen, Germany) which has four detector arrays. Dynamic triple-phase scans were performed using a standard pancreatic imaging protocol. All scans were reported by a single consultant radiologist with a special interest in axial imaging of the pancreas, reporting 400–500 pancreatic CTs per year, who was blinded to the findings of other investigations. Standard criteria for diagnosis and staging, including vascular invasion and assessment of lymphadenopathy, used EUS EUS was performed without blinding to other investigations to maintain the normal clinical scenario. All EUS examinations were	Study flow No patients were excluded Diagnostic test accuracy data 95%CIs calculated from raw data. Resectability (n=35) MSCT* Sens=0.96 Sp=0.5 PPV= 0.89 NPV=0.75 *Discrepancy in reported results EUS Sens=0.81* Sp=0.43 PPV=0.85 NPV=0.38 *Discrepancy in reported results N-staging (malignant lymphadenopathy) (n=31) MCST Sens=0.4 (95%CI, 0.05-0.85)	Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of indirectness See ROB section below for full details.

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
To compared multislice CT and EUS in diagnosis and management of pancreatic and periampullary malignancy and to determine whether it is possible to restrict number of imaging tests required for certain patients. Study dates: 06/2002-06-2004 Source of funding: None reported		performed by a single consultant gastroenterologist with an interest in pancreatic endoscopy or a single consultant radiologist with an interest in EUS, both of whom had undergone formal training in EUS (combined volume of pancreatic cases was 150–200 per year). Echoendoscopes used were either the OlympusGFUM20 mechanical/radial scanning scope with 7·5- and 12-MHz transducers (Olympus, Tokyo, Japan), a Pentax 100° curved/linear EG-3630U scope with 5- and 7·5-MHz transducers (Pentax, Tokyo, Japan), or a Pentax radial 270° EG-3630UR scope with 5-, 7·5- or 10-MHz transducers. The choice of endoscope (or combinations thereof) was purely at the discretion of the operator.	Sp=1.0 (95%CI, 0.87-1.0) PPV=1.0 NPV=0.9 (95%CI, 0.81-0.95) EUS* Sens=0.3 Sp=0.9 PPV=0.75 NPV=0.56 *Discrepancy in reported results Portal vein/SMV invasion (n=31) MSCT* Sens=0.88 (95%CI,) Sp=0.92 (95%CI,) PPV=0.78 (95%CI,) NPV=0.96 (95%CI,) *Discrepancy in reported results EUS Sens=0.5 (95%CI, 0.16-0.84) Sp=0.83 (95%CI, 0.61-0.95) PPV=0.5 (95%CI, 0.24-0.76) NPV=0.83 (95%CI, 0.7-0.91)	

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
			SMA invasion (n=29) MSCT* Sens=0.4 Sp=1.0 PPV=1.0 NPV=0.9 *Discrepancy in reported results EUS* Sens=0 Sp=0.95 PPV=0 NPV=0.8 *Discrepancy in reported results Adverse events Not reported	
Full Citation Minniti, S., Bruno, C., Biasiutti, C., Tonel, D., Falzone, A., Falconi, M., & Procacci, C. (2003). Sonography versus helical CT in identification and staging of pancreatic ductal adenocarcinoma. Journal of clinical	N=108 patients with suspected PC Inclusion criteria Suspected PC on basis of incidental findings of sonography, CT, or MRI of upper abdomen or relevant symptoms (abdominal pain, weight loss, obstructive jaundice)	Index test 1=CT Index test 2=Transabdominal US Reference test=Surgical histology for resectability and vascular involvement; for hepatic metastases, intraoperative US for radical resection patients, and surgery for palliative surgery patients. TNM staging classification used: not reported Procedure All patients had sonography and helical CT, which were performed by 2 independent radiologists. Intraoperative US of liver also performed by another independent radiologist in patients who had radical resection. Diagnostic irresectability=presence of 1 or more hepatic metastases and/or involvement of peripancreatic vessels	Study flow 44 patients excluded (inadequate US=8; no evidence of PAC on histopathological examination=36) Diagnostic test accuracy data 95% CIs calculated from reported raw data Resectability (n=43)	Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of indirectness See ROB section below for full details.

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
ultrasound, 31(4), 175-182. Country/ies where the study was carried out: Italy Study type: Prospective cohort Aim of the study: To compare sonography with helical CT in identification/staging of pancreatic ductal adenocarcinoma Study dates: 11/2000-10/2001 Source of funding: Not reported	Referred to hospital from 11/2000-10/2001 Oral informed consent Exclusion criteria Inadequate US examination No evidence of PC on histopathology Characteristics (n=64) Mean age (years)=64.7 (range 40-83) Male/female=36/28 Mean tumour size on US (cm)=3.2 (range 1.5-6.8) Tumour location=50 head, 11 body, 3 tail. Had laparotomy=43 (radical resection=18; palliative surgery=25)	(obstruction, thrombosis, encasement by tumoural tissue more than half circumference of any vessel). Final diagnosis made on basis of histopathologic examination of surgical specimen if laparotomy conducted, or percutaneous FNA biopsy otherwise. CT Performed using Somatom Plus 4 CT scanner (Siemens AG, Erlangen, Germany) using helical technique and bolus administration (4 ml/second), via a 20-gauge needle inserted into a forearm vein, of 140 ml of the nonionic contrast medium Iopamiro 370 (Bracco, Milan, Italy), which has an iodine concentration of 370 mg/100 ml. Images were obtained in a slightly delayed (“pancreatic”) arterial phase (ie, 30–35 seconds after injection of the contrast medium) with a 5-mm slice thickness and a pitch of 1 and in the portal phase (ie, 70–75 seconds after the contrast medium injection) with an 8-mm slice thickness and a pitch of 1. Transabdominal US Performed using Sonoline Elegra US scanner equipped with 2.7-5.1 MHz convex-array transducer, with occasional use of tissue harmonic imaging and Doppler techniques. All data collected prospectively in real time. Surgery Surgeon precisely determined during both radical and palliative surgeries, the presence and extent of neoplastic involvement of each vessel. During the palliative surgeries, in which intraoperative transabdominal US was not performed, the surgeon also determined whether hepatic metastases were present.	CT (TP=16, FP=4, FN=2, TN=21) Sens=0.89 (95%CI, 0.65-0.99) Sp=0.84 (95%CI, 0.64-0.91) PPV=0.8 (95%CI,0.62-0.91) NPV=0.91 (95%CI, 0.74-0.98) Transabdominal US (TP=16, FP=6, FN=2, TN=19) Sens=0.89 (95%CI, 0.65-0.99) Sp=0.76 (95%CI, 0.55-0.91) PPV=0.73 (95%CI, 0.57-0.85) NPV=0.91 (95%CI, 0.72-0.97) Adverse events Not reported	
Full Citation Phoa, S. S., Tilleman, E. H., Delden, O. M. V.,	N=72 patients with suspected PC Inclusion criteria	Index test 1=CT Reference test=Surgery or surgical histopathology TNM staging classification used: not reported Procedure	Study flow 1 patient excluded due to lack of follow up	Quality of study assessed using QUADAS-2:

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
Bossuyt, P. M., Gouma, D. J., & LamÉris, J. S. (2005). Value of CT criteria in predicting survival in patients with potentially resectable pancreatic head carcinoma. Journal of surgical oncology, 91(1), 33-40. Country/ies where the study was carried out: Netherlands Study type: Prospective cohort Aim of the study: To establish prognostic value of CT in patients with pancreatic head carcinoma. Study dates: 02/1997-07/1999 Source of funding: None reported	Pancreatic head carcinoma Exclusion criteria Distal cholangiocarcinoma, cysticor endocrine tumour Characteristics Mean age (years)=62 (range 42-76) Male/female=33/38	(Local) Irresectability defined as presence of any infiltration, any vessel showing involvement >180◦ or tumour convexity grade D or E. CT All patients were prospectively included to undergo a pre-operative CT according to protocol, using a dual slice technique (CT Twin Flash, Elscint, Haifa). Collimation was 2x2.5 mm, 120 kVp, 199 mAs, table speed 7.5 mm/sec. Intravenous contrast injection was given at a rate of 3.5 ml/sec (130 ml Omnipaque 300, Nycomed, Oslo, Norway). A dual phase scan was performed, the pancreatic phase of the scan had a delay of 50 sec. The CT scans were retrieved after surgery and reviewed on a workstation by two experienced abdominal radiologists, separately. The only information given to the radiologist was that patients had been explored for suspected pancreatic cancer. If there was disagreement between readers, a third consensus reading was held. (Decisions whether to operate patients had been made in multidisciplinary meetings with all clinical and imaging data available.) Local resectability combined several CT criteria: a tumour was regarded as locally not resectable if any infiltration was present, or if any vessel showed involvement of >180 degrees or if tumour convexity was scored as grade D or E. The CT variable local resectability was also compared to whether surgical resection was done and the histopathology of resected tumours. Completeness of the resection (whether resection margins were tumour negative) was established by reviewing histopathology reports.	Diagnostic test accuracy data 95%CIs, PPV and NPV calculated from raw data by technical team Resectability (surgery as reference) (TP=26, FP=10, FN=15, TN=20) Sens=0.63 (95%CI, 0.47-0.78) Sp=0.67 (95%CI, 0.47-0.83) PPV=0.72 (95%CI, 0.6-0.82) NPV=0.57 (95%CI, 0.45-0.68) Resectability (used in analysis) (histopathology/R0 vs R1 or R2 as reference) (TP=18, FP=18, FN=6, TN=29) Sens=0.75 (95%CI, 0.53-0.9) Sp=0.62 (95%CI, 0.46-0.75) PPV=0.5 (95%CI, 0.39-0.61)	Overall low risk of bias. Overall low risk of indirectness See ROB section below for full details.

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
			NPV=0.83 (95%CI, 0.7-0.91) Adverse events Not reported	
Full Citation Roche, C. J., Hughes, M. L., Garvey, C. J., Campbell, F., White, D. A., Jones, L., & Neoptolemos, J. P. (2003). CT and pathologic assessment of prospective nodal staging in patients with ductal adenocarcinoma of the head of the pancreas. American Journal of Roentgenology, 180(2), 475-480. Country/ies where the study was carried out: UK Study type: Prospective cohort Aim of the study:	N=62 patients with suspected PC Inclusion criteria Suspected PC based on clinical symptoms, lab findings (inc. tumour markers) and results of ERCP or sonography Exclusion criteria Not resectable due to proven metastasis or vascular occlusion according to CT or laparoscopic sonography Characteristics (PC patients only) Male/female=3/6 Mean age=67 years (range 53-78) Final diagnosis Pancreatic ducal adenocarcinoma=9, other=53	Index test 1=Helical CT Reference test=Histopathology of resected lymph nodes in patients whose final histologic diagnosis was pancreatic ductal adenocarcinoma. TNM staging classification used: not reported Procedure All potentially eligible patients had dual-phase helical CT of pancreas and staging laparoscopy (inc. laparoscopic sonography). One pathologist with a special interest in pancreatic carcinoma examined all pathologic specimens. The pathologist was unaware of the results of all other investigations. The lymph nodes were dissected from the specimen, and the specimen and nodes were examined separately. Resected lymph nodes were identified individually according to the Japan Pancreas Society classification, and a TNM classification was determined. Helical CT After preliminary unenhanced axial scans were acquired for localization, dual-phase helical CT scanning was performed (HiSpeed Advantage scanner General Electric Medical Systems, Milwaukee, WI). An IV bolus of at least 100 mL of iopromide (Ultravist 300; Schering, Berlin, Germany) was administered via a pump injector at 3 mL/sec. The first phase through the pancreas began at 30 sec after initiation of the bolus, and 3-mm slices were obtained using a pitch of 2 to optimize visualization of the primary tumour, peripancreatic nodes, and vessels. The second phase began at 75 sec after initiation of the bolus, with 5-mm slices obtained using a pitch of 2 to cover the liver and pancreas—	Study flow 24 had unresectable tumours on preoperative assessment; one died from unrelated causes before surgery could be performed; two were considered unfit to undergo major surgery. At surgery, seven patients were found to have unresectable tumours (six pancreatic carcinoma, one gall-bladder carcinoma). The remaining patients underwent a standard pancreato-duodenectomy. Diagnostic test accuracy data	Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of indirectness See ROB section below for full details.

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
To compare the assessment of peri-pancreatic lymph nodes using CT with the gold standard of detailed histopatho-logic assessment of resected specimens in patients with pancreatic ductal adeno-carcinoma Study dates: 12/1998-6/2000 Source of funding: None reported		mainly to show liver metastases. Dilute meglumine diatrizoate (2%) (Gastrografin; Schering, Berlin, Germany) was administered orally to opacify the stomach and duodenum. Image analysis Three experienced radiologists interpreted each CT scan before the histologic diagnosis was made. The observers were unaware of all other investigations, and agreement was reached by consensus. Analysis involved evaluation of the primary tumour characteristics, vessel encasement, stenosis or invasion (including the superior mesenteric–portal venous system and the superior mesenteric, splenic, and hepatic arteries), and assessment of distant metastases. Particular attention was paid to nodal involvement, especially specific node groups as described by the Japan Pancreas Society. Nodes were measured and categorized into three groups by short-axis diameter: less than 5 mm, 5–10 mm, and greater than 10 mm. The observers commented on nodal morphology, including ovoid versus spherical shape, whether or not the nodes appeared in clustered groups of three or more, and the presence or absence of a lucent fatty hilum. For the purposes of TNM classification, only lymph nodes with a short-axis diameter greater than 10 mm were considered positive; morphology was not used for staging. After the TNM classification was determined, each tumour was labeled as resectable or unresectable on the basis of CT findings. Criteria for unresectability included peritoneal metastases, liver metastases, or ascites; extrapancreatic invasion of adjacent tissues and organs other than the duodenum or bile duct; and occlusion or stenosis of the major pancreatic vessels. Encasement of the portal vein was not considered a deterrent to attempted curative surgery, provided that less than half of the vessel circumference and less than 1 cm of its length were affected. The presence of enlarged lymph nodes per se, in the	95%CIs, PPV and NPV calculated from raw data. CT N Staging (data given by number of lymph nodes rather than by number of patients) (40 nodes, 9 patients with PDAC) Sen=0.14 (95% CI, 0-0.58) Sp=0.85 (95% CI, 0.68-0.95) PPV=0.17 (95% CI, 0.03-0.59) NPV=0.82 (95% CI, 0.77-0.87)	

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
		absence of any other evidence of unresectability, was not considered a contraindication to attempted resection. Surgery Surgeons were aware of the study design and the necessity to accurately label all specimens. In particular, lymph node specimens were identified according to the Japan Pancreas Society classification. The site and extent of tumour, including local invasion, local vessel involvement (encasement, stenosis, or invasion, and the need for portal vein resection), and the presence or absence of liver or other metastases, were noted at surgery. Patients deemed to have resectable disease underwent a standard Kausch-Whipple pancreatoduodenectomy.		
Full Citation Schachter, P. P., Avni, Y., Shimonov, M., Gvirtz, G., Rosen, A., & Czerniak, A. (2000). The impact of laparoscopy and laparoscopic ultrasonography on the management of pancreatic cancer. Archives of Surgery, 135(11), 1303-1307. Country/ies where the study was carried out:	N=67 patients with suspected PC Inclusion criteria Scheduled for explorative laparotomy Exclusion criteria Metastatic/advanced disease Characteristics Mean age (years)= 63.3 (range 30-88) Male/female=31/36 Tumour location: 48 head, 19 body and tail.	Index test 1=Laparoscopy + LUS Reference test=Laparotomy TNM staging classification used: not reported Procedure All patients had transabdominal US, contrast-enhanced CT and, in some cases, ERCP. Patients with inconclusive CT had EUS. Surgical candidates (n=67; those judged resectable or probably resectable by imaging) offered laparoscopy and LUS as separate procedures before final decision regarding treatment. Patients judged to have resectable tumours on laparoscopy and LUS had explorative laparotomy. Irresectability criteria: any metastatic spread in peritoneal cavity or liver and involvement of superior mesenteric artery or vein; regional lymph node involvement contraindication for resection. Laparoscopy with LUS Laparoscopy performed under general anaesthetic as separate procedure using standard technique. Two disposable 10mm cannuylas introduced, one at umbilicus for 30◦ telescope, other at right upper abdominal quadrant for US probe. Additional ports	Study flow No exclusions reported Diagnostic test accuracy data 95%CIs calculated from raw data by technical team Resectability (TP=33, FP=4, FN=0; TN=30) Sens=1.0 (95%CI, 0.89-1.0) Sp=0.88 (95%CI, 0.73-0.97) PPV=0.89 (95%CI, 0.77-0.95) NPV=1.0	Quality of study assessed using QUADAS-2: Overall high risk of bias. Overall low risk of indirectness See ROB section below for full details.

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
Israel Study type: Prospective cohort Aim of the study: To examine impact of laparoscopic US on staging and surgical decision making in patients with pancreatic tumours. Study dates: 04/1996-03/1999 Source of funding: Not reported	Average time of operation(s): 30 min (range 17-65)	entered as needed. LUS performed with 10mm, 8 MHz sectoral contact US probe, which uses simultaneous view of laparoscopic and US images; has capability of lateral US view up to 90◦; Doppler system to differentiate between vein vs artery, and bile ducts or cysts; LUS guided biopsy system using 18G core biopsy needle. Laparoscopic and US examination of body and tail of pancreas performed through aperture in gastrocolic ligament and entrance in lesser sac. Laparotomy Enlargement of sporadic lymph nodes per se not considered contra-indication for laparotomy. Tumours>5cm and no other irresectabilty variables not considered absolute contraindication for exploration.	Adverse events No post-operative complications	
Full Citation Shah, D., Fisher, W. E., Hodges, S. E., Wu, M. F., Hilsenbeck, S. G., & Brunicardi, F. C. (2008). Preoperative prediction of complete resection in pancreatic cancer. Journal of Surgical Research, 147(2), 216-220.	N=88 patients with confirmed PAC Inclusion criteria Confirmed PAC Surgical consultation at Elkins Pancreas Center, Baylor College of Medicine Informed consent Exclusion criteria Other pancreatic neoplasms (e.g. ampullary adenocarcinoma, pancreatic endocrine	Index test 1=Laparoscopy + LUS Reference test=Surgery TNM staging classification used: Not reported Procedure When referred, patients have repeat abdominal CT using MDCT; EUS performed only when unclear involvement of mesenteric vessels. Staging laparoscopy recommended when tumour>4cm, weight loss>20% of body weight, ascites, or a marked elevated CA 19-9 (<1000 U/mL). Patients had staging laparoscopy if preoperative CT scan shows questionable evidence of small liver or peritoneal metastases that are too small to fully characterize by CT and too small to biopsy percutaneously. Preoperative irresectability= definite evidence on CT, EUS or preoperative diagnostic laparoscopy of (i) extra-pancreatic disease (e.g. liver, omental, or peritoneal metastases), (ii) bulky (>2 cm) celiac	Study flow 69 patients did not meet criteria for staging laparoscopy and were excluded (unresectable due to metastatic/locally advanced=35; medically unfit=1; suspect vascular involvement=3; did not satisfy staging laparoscopy criteria=30). 2 patients were excluded from	Quality of study assessed using QUADAS-2: Overall high risk of bias. Overall low risk of indirectness See ROB section below for full details.

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
Country/ies where the study was carried out: USA Study type: Retrospective review of prospective cohort Aim of the study: To evaluate efficacy of MDCT and staging laparoscopy in staging of PC Study dates: Not reported, 2 year period Source of funding: None reported	tumours, cystic neoplasms) Characteristics Increased C19-9>1000 U/mL=4; Tumour.4cm=6; Wight loss?20% body weight=10; ascites=4; questionable liver lesions=9	adenopathy, (iii) malignant ascites, (iv) loss of a patent portosplenic confluence, or 360° encasement of the portal or superior mesenteric veins or, (v) any contact between the tumour and the hepatic artery or superior mesenteric artery. Staging laparoscopy (laparoscopy + LUS) Included a general exploration of the abdominal surfaces including palpation of the liver with two instruments. The hilum of the liver visualized and foramen of Winslow examined. The transverse colon and omentum reflected cephalad and the base of the transverse mesocolon examined for tumour with particular attention to the mesocolic vessels. Gastrocolic ligament/ omentum incised and lesser sac examined. Laparoscopic ultrasound used to improve the accuracy of staging laparoscopy by permitting an assessment for intraparenchymal hepatic metastasis and to evaluate the retroperitoneal tumour-vessel relation-ships. Primary tumour, peripancreatic, or periportal lymph nodes not biopsied because these would be excised en bloc with the specimen. However, if tissue diagnosis not yet achieved and evidence of unresectable disease discovered at laparoscopy, biopsies of liver lesions or other easy targets performed with frozen section histology to make every effort to obtain tissue diagnosis before leaving operating room. Typically, staging laparoscopy performed in same procedure prior to pancreatic resection but use of selective criteria increased the frequency that laparoscopy changed the operative plan.	staging laparoscopy due to being medically unfit. Diagnostic test accuracy data 95%CIs calculated from raw data. Resectability (R0 as resectable; TP=6, FP=2, FN=0, TN=9) Sens=1.0 (95%CI, 0.54-1.0) Sp=0.8 (95%CI, 0.48-0.98) PPV=0.75 (95%CI, 0.46-0.91) NPV=1.0) Adverse events Not reported	
Full Citation Shami, V. M., Mahajan, A., Loch, M. M., Stella, A. C., Northup, P. G., White, G. E., Kahaleh, M. et al.	N=127 patients with confirmed PC Inclusion criteria Had both EUS-FNA and MRI Informed consent	Index test 1=EUS-FNA Index test 2=MRI Reference test=Surgical pathology or cytologic tissue confirmation of metastatic disease. TNM staging classification used: UICC 1997 Procedure	Study flow 79 patients did not have surgery. Diagnostic test accuracy data Overall TNM Stage	Quality of study assessed using QUADAS-2: Overall high risk of bias.

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
(2011). Comparison between endoscopic ultrasound and magnetic resonance imaging for the staging of pancreatic cancer. Pancreas, 40(4), 567-570. Country/ies where the study was carried out: USA Study type: Prospective cohort Aim of the study: To determine differences between EUS-FNA and MRI in staging PC Study dates: Not reported Source of funding: Not reported	Exclusion criteria None reported Characteristics Mean age (years)= 66 (sd 11.4) Male/female=71/56 Surgery=48 Resection=22/48	All patients underwent EUS-FNA by dedicated pancreaticobiliary endoscopists and were captured prospectively in a database. Patients underwent MRI with the radiologist blinded to the EUS result. Final surgical stage was also recorded in patients who went to surgery. EUS Performed using Olympus curvilinear array echoendoscopes (GF-UCT140 or GF-UC140P, Olympus America, Center Valley, Pa). Tumour size, vessel involvement, and the presence of lymphadenopathy were noted on each staging EUS. Any liver lesions or ascites detected were also sampled with FNA. If abnormalities were seen on EUS but FNA proved negative, these abnormalities, such as lymphadenopathy and liver lesions, were not counted to final stage. MRI Performed using Siemens 1.5-T superconducting magnets (Magnetom Sonata, Symphony, and Avanto; Siemens Medical Systems, Buffalo Grove, Ill), with use of a 4-element torso-phased array coil and fast pulse sequences that allowed acquisition of each image set within a single breath hold. Unenhanced images included axial T1-weighted in- and opposed-phase gradient echo (GRE); axial T1-weighted magnetization-prepared gradient-echo (MP-GRE); and coronal, sagittal, and axial T2-weighted half-Fourier acquisition single-shot turbo spin echo (HASTE). Positioning of the images was such that the entire liver and pancreas were included. Magnetic resonance cholangiopancreaticography was performed using sets of single-shot HASTE-type images obtained as (1) a coronal multislice sequence providing thin contiguous T2-weighted images, (2) a single slice sequence providing 40- to 60-mm-thick image, with each slice positioned in a coronal/paracoronal fashion centered around the common bile duct, and (3) a 3-dimensional (3D) image set obtained with	MRI Accuracy=75% (36/48) Overstaged=0% (0/48) Understaged=25% (12/48) EUS-FNA Accuracy=71% (34/48) Overstaged=2% (1/48) Understaged=27% (13/48) Adverse events Not reported	Overall low risk of indirectness See ROB section below for full details.

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
		respiratory gating, providing 1- to 2-m-thick slice. Contrast-enhanced images covering the entire liver and pancreas included dynamically obtained 3- to 5-mm-thick axial T1-weighted 3-dimensional GRE images with fat saturation, obtained in the pancreatic parenchymal phase (35-55s after injection), portal venous phase (70-90s after injection), and late phase (100-120s after injection), with a 15s pause between each acquisition, as well as a delayed phase acquisition obtained at the end of the study, 7 to 10 minutes after initial injection. Intravenous contrast material administration consisted of 10 to 20 cc of gadodiamide (Omniscan; Amersham Health, Harrisburg, Pa) or gadopentetate dimeglumine (Magnevist; Bayer HealthCare Pharmaceuticals, Wayne, NJ). Subsequently, 3 coronal sets with contrast enhancement were obtained in arterial, portal venous, and hepatic venous phase, each requiring a single breath hold and additional 10 to 20 cc of contrast material, using a fast thin slice (1 mm) 3-dimensional GRE sequence for MR angiography covering the pancreas and major peripancreatic vessels as well as the abdominal aorta. In each case, MRI staging was performed by a qualified radiologist covering the study on the day of imaging using the TNM staging guidelines.		
Full Citation Soriano, A., Castells, A., Ayuso, C., Ayuso, J. R., De Caralt, M. T., Ginès, M. À., Feu, F.et al. (2004). Preoperative staging and tumour	N=127 patients with suspected PC Inclusion criteria Pathologically-confirmed PC Fit for curative or palliative surgery Metastatic disease only if palliative surgery indicated or disagreement	Index test 1=EUS Index test 2=CT Index test 3=MRI Index test 4=CT+EUS (all) Index test 5=CT+EUS if CT-resectable Index test 6=EUS+CT if EUS-resectable Reference test=Surgery + histopathology TNM staging classification used: AJCC 1997	Study flow 65 patients excluded (metastatic dissemination (n=25), had less than 3 imaging methods (n=20), neoplasm not confirmed (n=19), no consent (n=1)). Overall TNM Stage (precise staging)	Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of indirectness See ROB section below for full details.

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
resectability assessment of pancreatic cancer: prospective study comparing endoscopic ultrasonography, helical computed tomography, magnetic resonance imaging, and angiography. The American journal of gastroenterology, 99(3), 492-501. Country/ies where the study was carried out: Spain Study type: Prospective cohort Aim of the study: To prospectively evaluate efficacy of EUS, helical CT, MRI and angiography in staging and tumour resectability	between imaging techniques Exclusion criteria Unfit for curative or palliative surgery due to impaired physical condition (ECOG score of 3 or 4) or associated severe diseases. Lesions other than pathologically-confirmed PC Not submitted to surgery (e.g. due to refusal, contraindi-cation, or observation of massive metastatic dissemination) Had less than 3 of the 4 imaging techniques Characteristics (n=62) Mean age (years)=65 (sd 10) Male/female=33/29 Tumour location: 42 head, 6 body, 4 tail, 10 ampullary region. TNM stage	Unresectability= (i) distant metastases; (ii) celiac trunk, hepatic artery or superior mesenteric artery invasion; (iii) portal or superior mesenteric vein invasion not suitable for patching. Procedure All patients had EUS, helical CT, MRI and angiography within a 2 week period before surgery. Each imaging technique performed by single examiner who was aware of suspected diagnosis but blinded to results of other methods. Tests performed depending on availability according to pre-established protocol in clinical setting. After preoperative staging, single investigator summarised all imaging results and evaluated eligibility for study. Summary of results sent to surgery team, who were blinded to imaging source of relevant information and performed all surgery. Unresectability= (i) distant metastases; (ii) celiac trunk, hepatic artery or superior mesenteric artery invasion; (iii) portal or superior mesenteric vein invasion not suitable for patching. EUS Endoscopic ultrasonography was performed with the Olympus GF-UM20 echoendoscope (Olympus Inc., Melville, NY). Ultrasound frequencies of 7.5 and 12 MHz were used. After i.v. sedation with 5–10 mg of midazolam, the instrument was introduced into the descending duodenum. The balloon at the instrument's tip was filled with water to improve ultrasonographic visualization. When retracting the instrument to the duodenal bulb from the second duodenum, the pancreatic head and body, superior mesenteric vein, portal vein with the confluence, and splenic vein were scanned. From gastric antrum, body, and fundus, the pancreatic body and tail, along with the splenic vein and celiac trunk were examined. Endosonographic criteria for nodal involvement were: round shape, homogeneous echogenicity, relative hypoechointensity, and size >10 mm. For vascular invasion, the endosonographic criteria were: loss of the hyperechoic vessel wall/tumour interface, direct visualization of	EUS Accuracy=40% (95%CI, 27-53) Overstaged=5% (95%CI, 0-11) Understaged=56% (95%CI, 43-69) CT Accuracy=46% (95%CI, 33-59) Overstaged=8% (95%CI, 1-15) Understaged=46% (95%CI, 33-59) MRI Accuracy=36% (95%CI, 23-49) Overstaged=7% (95%CI, 0-14) Understaged=57% (95%CI, 44-70) T-Staging EUS (n=52) Accuracy=63% (95% CI, 50-76) Overstaging=0% Understaging=37% (95% CI, 24-50) CT (n=59) Accuracy=73% (95% CI, 62-84)	

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
assessment of pancreatic cancer. Study dates: 10/1995-03/2000 Source of funding: Supported in part by grants from Fondo de Investigaciones Sanitarias (FIS 01/0104-02) from Minsterio de Ciencia y Tecnologia Medica of the Generalitat de Catalunya, and Instituto de Salud Carlos III (RC03.02, RC03/10 and RG03/156).	T1=3, T2=10, T3=26, T4A=26, T4B=12	tumour in the vascular lumen, and nonvisualization of a major portal vessel in the presence of collateral vessels. The presence of metastases in the left hepatic lobe as well as peritoneal involvement was also evaluated. CT Helical CT was performed on a Somatom Plus-4 scanner (Siemens Medical Systems, Erlangen, Germany). Spiral acquisition of the upper abdomen was obtained after oral contrast administration, with 8-mm slice collimation, pitch of 1.5, and reconstruction intervals of 8 mm (8 mm/1.5/8 mm) to localize the pancreas. All patients received 120 ml of i.v. contrast agent (Iohexol 64.75 g, Shering AG, Berlin, Germany or Omnigraf 300, Juste S.A.Q.F, Madrid, Spain). It was delivered with a power injector at a rate of 3.0 ml/s before scanning. A special software ("care bolus") to detect the arrival of the contrast medium to the aorta was used to adjust the delay between the onset of injection and the start of scanning acquisition to obtain the arterial dynamic study of pancreatic area (usually 20 s). A spiral technique for the arterial phase was as follows: 3 mm/1.5/1 mm, 120 kVp, and 280 mAs. Images were obtained during a single breath-hold. The parenchymal phase of the hepatopancreatic area was acquired 60 s after the onset of injection using the next technical parameters: 5 mm/1.5/5 mm, 120 kVp, and 210 mAs. Angiographic reconstructions using volume rendering technique were obtained in selected cases. Lymph nodes greater than 10 mm in diameter were considered as being suspicious for metastasis. Vascular invasion was considered when: (1) the soft tissue mass was partially obliterating the perivascular fat, whether or not the tumour was abutting or displacing a patent vessel (vascular-tumour contiguity); (2) the soft tissue mass was circumferentially obliterating the perivascular fat and CT showed vascular encasement; or (3) total or partial vascular occlusion was present.	Overstaging=2% (95% CI, 0-6) Understaging=25% (95% CI, 14-36) MRI (n=53) Accuracy=62% (95% CI, 49-75) Overstaging=6% (95% CI, 0-12) Understaging=32% (95% CI, 19-45) Diagnostic test accuracy data Data for angiography results not shown. Resectability EUS (n=52) Sens=0.23 (95%CI, 0.12-0.34) Sp=1.0 (95%CI, 0.93-1.0) PPV=1.0 (95%CI, 0.96-1.0) NPV=0.64 (95%CI, 0.51-0.77) CT (n=59) Sens=0.67 (95%CI, 0.55-0.79) Sp=0.97 (95%CI, 0.93-1.0)	

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
		MRI Magnetic resonance exams were performed on a 1.0-T scanner (Magnetom Impact, Siemens Medical Systems, Erlangen, Germany). A body coil was used. The MRI protocol consisted of T2-weighted axial spin-echo sequence through the liver to exclude metastatic disease, with these parameters: TR/TE 2500/90, section thickness 10 mm, gap 10%, number of excitations (NEX) 2, matrix 128 times 256, and field of view (FOV) 35–40 cm. Axial T1-weighted spin-echo sequences with and without fat saturation were obtained through the pancreas and peripancreatic vessels (TR/TE 400-600/15, thickness 5 mm, gap 10%, NEX 4, matrix 128 times 256, and FOV 35–40 cm). Breath-hold axial T1-weighted images were then obtained with a fast low-angle shot (FLASH) sequence (TR/TE 110/4, flip angle 80°, thickness 5 mm, gap 10%, NEX 1, matrix 128 times 256, and FOV 35–40 cm) to cover the same anatomic region, before and 20 s, 1, 2, 3, and 5 min after a bolus injection of 0.1 mmol/kg of gadopentate dimeglumine (Magnevist, Schering, Berlin, Germany, or Gadodiamide, Nycomed, Birmingham, UK) through an antecubital vein. No oral contrast medium was used. Criteria for lymph node involvement and vascular invasion were similar to those mentioned for the CT evaluation	PPV=0.95 (95%CI, 0.89-1.0) NPV=0.77 (95%CI, 0.66-0.88) MRI (n=53) Sens=0.57 (95%CI, 0.44-0.7) Sp=0.9 (95%CI, 0.82-0.98) PPV=0.81 (95%CI, 0.7-0.92) NPV=0.73 (95%CI, 0.61-0.85) CT+EUS (all patients had both)* (n=52) Sens=0.71 (95%CI, 0.62-0.8) Sp=0.97 (95%CI, 0.94-1.0) PPV=0.82 (95%CI,0.74-0.9) NPV=0.94 (95%CI, 0.89-0.99) *Discrepancy in published results CT+EUS if CT resectable (n=52)* Sens=0.97 (95%CI, 0.94-1.0) Sp=0.81 (95%CI, 0.73-0.89)	

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
			PPV=0.98 (95%CI, 0.95-1.0) NPV=0.71 (95%CI, 0.62-0.8) *Discrepancy in published results EUS+CT if EUS resectable (n=52)* Sens=0.63 (95%CI, 0.54-0.72) Sp=0.96 (95%CI, 0.92-1.0) PPV=0.91 (95%CI, 0.85-0.97) NPV=0.82 (95%CI, 0.74-0.9) *Discrepancy in published results N-Staging EUS (n=52) Sens=0.42 (95%CI, 0.28-0.56) Sp=0.97 (95%CI, 0.92-1.0) PPV=0.89 (95%CI, 0.8-0.98) NPV=0.74 (95%CI, 0.62-0.86) CT (n=59) Sens=0.67 (95%CI, 0.55-0.79)	

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
			Sp=0.94 (95%CI, 0.88-1.0) PPV=0.89 (95%CI, 0.81-0.97) NPV=0.8 (95%CI, 0.7-0.9) MRI (n=53) Sens=0.59 (95%CI, 0.46-0.72) Sp=0.84 (95%CI, 0.74-0.94) PPV=0.72 (95%CI, 0.6-0.84) NPV=0.74 (95%CI, 0.62-0.86) Vascular invasion EUS (n=52) Sens=0.42 (95%CI, 0.28-0.56) Sp=0.97 (95%CI, 0.92-1.0) PPV=0.89 (95%CI, 0.8-0.98) NPV=0.74 (95%CI, 0.62-0.86) CT (n=59) Sens=0.67 (95%CI, 0.55-0.79) Sp=0.94 (95%CI, 0.88-1.0)	

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
			PPV=0.89 (95%CI, 0.81-0.97) NPV=0.8 (95%CI, 0.7-0.9) MRI (n=53) Sens=0.59 (95%CI, 0.46-0.72) Sp=0.84 (95%CI, 0.74-0.94) PPV=0.72 (95%CI, 0.6-0.84) NPV=0.74 (95%CI, 0.62-0.86) M Staging EUS (n=52) Sens=0 (95%CI,) Sp=1.0 (95%CI, 0.96-1.0) PPV=n/a NPV=0.85 (95%CI, 0.75-0.95) CT (n=59) Sens=0.55 (95%CI, 0.42-0.68) Sp=0.96 (95%CI, 0.91-1.0) PPV=0.75 (95%CI, 0.64-0.86) NPV=0.9 (95%CI, 0.82-0.98) MRI (n=53)	

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
			Sens=0.3 (95%CI, 0.18-0.42) Sp=0.98 (95%CI, 0.94-1.0) PPV=0.83 (95%CI, 0.73-0.93) NPV=0.87 (95%CI, 0.78-0.96) Locoregional extension EUS (n=52) Sens=0.44 (95%CI, 0.31-0.57) Sp=1.0 (95%CI, 0.96-1.0) PPV=1.0 (95%CI, 0.96-1.0) NPV=0.44 (95%CI, 0.31-0.57) CT (n=59) Sens=0.66 (95%CI, 0.54-0.78) Sp=1.0 (95%CI, 0.96-1.0) PPV=1.0 (95%CI, 0.96-1.0) NPV=0.48 (95%CI, 0.35-0.61) MRI (n=53) Sens=0.53 (95%CI, 0.4-0.66)	

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
			Sp=1.0 (95%CI, 0.96-1.0) PPV=1.0 (95%CI, 0.96-1.0) NPV=0.5 (95%CI, 0.37-0.63) Adverse events Not reported	
Full Citation Taylor, A. M., Roberts, S. A., & Manson, J. M. (2001). Experience with laparoscopic ultrasonography for defining tumour resectability in carcinoma of the pancreatic head and periampullary region. British journal of surgery, 88(8), 1077-1083. Country/ies where the study was carried out: UK Study type: Prospective cohort Aim of the study:	N=51 patients with potentially resectable pancreatic tumours Inclusion criteria Informed consent Potentially resectable PC of head or periampullary region on CT Exclusion criteria Non-resectable on CT Characteristics Mean age (years)=66 (sd 10; range 26-84) Male/female=29/22 Tumour location: 42 head, 9 ampullary lesions Obstructive jaundice=46 Pancreatitis=5	Index test 1=Laparoscopy + LUS Reference test=Surgery for resectability; unresectability supported by biopsy (n=8), EUS showing vascular invasion (n=9), laparotomy with biliary bypass (n=4). TNM staging classification used: not reported Procedure 40 of the 51 patients had clinical suspicion of PC with or without abdominal US, ERCP (+stent if jaundiced). Diagnostic resectability=absence of metastatic disease (liver, peritoneum, lymph nodes), no evidence of local vascular invasion (portal vein, superior mesenteric vein and artery, aorta, inferior vena cava). Surgical resectability defined as complete excision of tumour with disease confined to pancreas or ampulla. CT 40 of the 51 patients had CT using same imaging protocol using CT PACE scanner. Patients starved for 6h before imaging. Oral contrast (1000 ml 2% Gastrografin) administered 1h before imaging. Axial, precontrast images acquired from diaphragm to third party of duodenum (10mm slice thickness (SLT), 10mm gap). Intravascular contrast (Iohexol 350mg/ml) administered in 2 phases, 70 ml at 2 ml/s followed by 80 ml at 0.6 ml/s. Postcontrast images acquired after administration of first 70 ml of	Study flow 2 patients classed as resectable by LUS declined surgery. Diagnostic test accuracy data 95%CIs, Sens/Sp/NPV calculated by technical team. Resectability (n=49) Calculated using TP=27, FP=0, FN=2, TN=22 Sens=0.93 (95%CI, 0.77-0.99) Sp=1.0 (95%CI, 0.83-1.0) PPV=1.0 NPV=0.91 (95%CI, 0.72-0.97) Adverse events	Quality of study assessed using QUADAS-2: Overall high risk of bias. Overall low risk of indirectness See ROB section below for full details.

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
To evaluate efficacy of preoperative laparoscopic US in determining resectability in pancreatic cancer of head and periampullary region. Study dates: 07/1996-03/2000 Source of funding: None reported	Mean time to surgery (days)=17.2 (sd 13.7, range 1-46)	contrast (third part of duodenum to top of pancreas: 5mm SLT, 5 mm gap; top of pancreas to diaphragm: 10mm SLT, 10mm gap). Remaining 11 patients from referring hospitals had variety of scanning techniques and equipment. Laparoscopy + LUS Performed under general anaesthetic with surgeon and radiologist presents. Images acquired using 6.5 MHz convex array transducer type 8555 with medical US scanner type 2002. Two disposable 10mm cannulas inserted at umbilicus and in right upper quadrant just inferior to costal margin in mid-axillary line. 10mm laparoscope inserted via one of the ports and LUS transducer inserted under direct vision via other port. US images acquired of liver, biliary tree, duodenum, pancreas, and adjacent retroperitoneum. Probe inserted via both laparoscopic ports to ensure visualisation of pancreas in two planes. Doppler mode available on US probe.	No LUS-related complications.	
Full Citation Tellez-Avila, F. I., Chavez-Tapia, N. C., López-Arce, G., Franco-Guzmán, A. M., Sosa-Lozano, L. A., Alfaro-Lara, R., Ramírez-Luna, M. A. et al. (2012). Vascular invasion in pancreatic cancer: predictive values for endoscopic ultrasound and	N=50 patients with suspected PC Inclusion criteria Had clinical, biochemical and/or radiological diagnosis (US and CT) of pancreatic lesion at Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran Had EUS Written informed consent	Index test 1=EUS±FNA Index test 2=CT Reference test=Surgery TNM staging classification used: not reported Procedure All CT and EUS performed at same centre. All patients hospitalised after EUS for 2 hours to evaluate any complications. CT vascular invasion defined as tumour contiguous with 75% of the vessel on imaging and the ‘‘teardrop’’ sign and morphologic deformation of the vessel at the tumour site. EUS vascular invasion defined as dilated peripancreatic collateral vessels, loss of vascular interface, or observed tumour within the vessel lumen. EUS Before EUS, complete blood cell count, INR, and prothrombin time obtained from all patients. One endoscopist performed all	Study flow 102 patients were excluded because they did not have surgery to confirm US and CT imaging results. Diagnostic test accuracy data Test data for veins only and arteries only not shown. Vascular invasion (arteries and veins) EUS	Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of indirectness See ROB section below for full details.

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
computed tomography imaging. Pancreas , 41(4), 636-638. Country/ies where the study was carried out: France Study type: Prospective cohort Aim of the study: To evaluate the accuracy of endoscopic ultrasound (EUS) to determine vascular invasion in patients with pancreatic cancer. Study dates: 03/2005-03/2010 Source of funding: None reported	Exclusion criteria No surgery Characteristics Mean age (years)=61 (sd 11.5) Male/female=23/27 Median tumour size (cm)=4 (range 1.2-7) Tumour location= 41 head, 5 body, 2 tail, 2 uncinate process.	linear EUS procedures using deep sedation (midazolam, propofol, fentanyl). When FNA performed, 19G or 22G needle used. FNA samples sent for histo- and cytological analysis. MDCT 16- or 64-slice MDCT. All images analysed by 2 certified radiologists. Images were obtained with section thickness of 3-5 mm with reconstruction interval of 2-2.5 mm. All patients received i.v. contrast, 120 mL of Conray was given 45 seconds before CT examination. Forty milliliters of ioditrast M60 diluted in 1000 mL of water and given to all patients orally 1 hour before CT imaging.	Sens=0.61 (95%CI, 0.39-0.80) Sp=0.9 (95%CI, 0.75-0.97) PPV=0.79 (95%CI, 0.52-0.92) NPV=0.8 (95%CI, 0.64-0.9) Discrepancy in published results CT Sens=0.56 (95%CI, 0.34-0.75) Sp=0.93 (95%CI, 0.78-0.98) PPV=0.83 (95%CI, 0.55-0.95) NPV=0.77 (95%CI, 0.61-0.88) Discrepancy in published results Adverse events No EUS- nor CT-related complications	
Full Citation White, R. R., Paulson, E. K., Freed, K. S., Keogan, M. T., Hurwitz, H. I., Lee, C., Jowell, P. S.et	N=98 patients with confirmed PDAC Inclusion criteria Histologically-confirmed PDAC Exclusion criteria None reported	Index test 1=CE-CT Reference test=Staging laparoscopy TNM staging classification used: not reported Procedure All patients underwent thin-section, contrast-enhanced dynamic CT, which was performed with an incremental or spiral scanner; collimation through the pancreas was not more than 5 mm, and	Study flow No excluded patients Diagnostic test accuracy data Sp/NPV calculated from raw data; data	Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of indirectness

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
al. (2001). Staging of pancreatic cancer before and after neoadjuvant chemoradiation. Journal of gastrointestinal surgery, 5(6), 626-633. Country/ies where the study was carried out: USA Study type: Retrospective review of prospective cohort Aim of the study: (1) To determine utility of staging laparoscopy in patients eligible for neoadjuvant CRT; (2) to evaluate accuracy of restaging CT after CRT in predicting resectability Study dates: 08/1994-11/2000 Source of funding: None reported	Characteristics Median age (years)=64 (range 31-82) Male/female=52/46 Tumour location: 78 head/uncinate process; 20 body/tail. CT resectability Potentially resectable=45, locally advanced=53	images were acquired during the portal predominant phase of enhancement. Many patients underwent CT scanning at referring institutions; CT scans deemed adequate for the purpose of excluding metastatic disease were not repeated. CT evidence of distant metastatic disease included solid focal liver lesions not satisfying the criteria for simple cyst or hemangioma, multiple noncalcified pulmonary nodules, and evidence of peritoneal spread of tumour including fluid, peritoneal thickening and/or nodularity, and mesenteric/omental implants. CT scans were reviewed by one of three radiologists. Localized tumours were categorized as potentially resectable if there was no evidence of direct invasion of the superior mesenteric artery (SMA) and celiac axis, and the superior mesenteric vein (SMV) and portal vein were patent. Tumours were categorized as locally advanced in the presence of soft tissue abutting or encircling the SMA or celiac axis or occlusion of the SMV or portal vein. Staging laparoscopy was performed with patients under general anaesthesia. Pneumoperitoneum was established using an open technique, followed by introduction of a 30-degree angled laparoscope. Two 5 mm trocars were placed in the right upper quadrant. A systematic, 360-degree inspection of the abdomen was performed, beginning with the liver and including the peritoneum, omentum, and entire bowel mesentery. Biopsies were obtained of any suspicious lesions and sent for pathologic examination. No attempt was made to examine or perform a biopsy of the primary tumour, and 72 patients underwent placement of a jejunostomy feeding tube.	not shown for restaging after CRT. M-Staging (n=98 patients deemed potentially resectable or locally-advanced on CT) (TP=0, FP=0, FN=21, TN=77) Sens=na Sp=1.0 (95%CI, 0.95-1.0) PPV=na NPV=0.79 [Management changed in 21 patients; 8 of 45 potentially resectable, 13 of 55 locally advanced] Adverse events Not reported	See ROB section below for full details.

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
Full Citation Yoneyama, T., Tateishi, U., Endo, I., & Inoue, T. (2014). Staging accuracy of pancreatic cancer: comparison between non-contrast-enhanced and contrast-enhanced PET/CT. European journal of radiology, 83(10), 1734-1739. Country/ies where the study was carried out: Japan Study type: Retrospective review of prospective cohort Aim of the study: To clarify diagnostic accuracy of CE PET/CT for staging of pancreatic cancer	N=95 patients with pathologically-confirmed primary or recurrent PC (non-CE PET/CT=52; CE-PET/CT=43) Inclusion criteria Performance status 0 or 1 No concomitant malignancy No history of therapy or >3 weeks after prior therapy for recurrent disease No discernible lesions by PET/CT and MRI in patients whose lesions established only by pathological diagnosis Written informed consent Exclusion criteria Uncontrolled diabetes Pregnant or lactating women Apparent infection	Index test 1=Non-contrast-enhanced PET/CT Index test 2=Contrast-enhanced (CE) PET/CT Reference test=Surgery or biopsy for vascular invasion (n=48 resected patients), dynamic CT for tumour stage (n=47other patients). TNM staging classification used: not reported Procedure Patients assigned to CE or non CE PET/CT group. Patients were clinically evaluated based on general physical examination and laboratory findings: complete blood count, biochemical data, tumour markers, and routine dynamic contrast-enhanced CT. If a pancreatic tumour was resectable, actual pancreatic carcinoma vascular invasion was established by evaluating pathologic (surgery or biopsy) specimens. In patients with unresectable pancreatic carcinoma or unavailable pathological specimens but highly suspected pancreatic cancer (n = 47, 49%), actual tumour stage was re-assessed with dynamic CT performed 2 weeks and one month after non-CE PET/CT or CE PET/CT. PET/CT After fasting at least 6 h and then receiving an intravenous injection of 2.5 MBq/kg of 18F-FDG, patients underwent an uptake phase for 63 ± 5 min and were then placed in a supine, arm-up position for scanning, immediately after bladder evacuation. For the PET/CT, CT data were firstly acquired at 400 mA, 120-kVp using an auto exposure control system, beam pitch of 0.875 or 1, and 2-mm × 16-row mode. Patients were intravenously injected with 100 mL of contrast agent (iopamidol) at a rate of 1.0 mL/s for CE PET/CT. The scan was delayed 120 s after administration of the contrast agent. Data acquisition was performed for each patient from the top of the skull to the mid-thigh. Images were obtained by the following parameters: data	Study flow 3 patients originally assigned to CE PET/CT group assigned to non-CE PET/CT group due to allergy to contrast material. Diagnostic test accuracy data Data not shown for primary staging only or restaging only. N-Staging (overall primary + restaging) Non-CE PET/CT (n=52) Sens=0.73 Sp=0.90 PPV=0.67 NPV=0.93 CE PET/CT (n=43) Sens=0.83 Sp= 0.90 PPV=0.77 NPV= 0.93 M-Staging	Quality of study assessed using QUADAS-2: Overall low risk of bias. Overall low risk of indirectness See ROB section below for full details.

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
compared to the performance of non-contrast-enhanced(non-CE) PET/CT Study dates: 04/2006-11/2009 Source of funding: Partly funded by Grant-in Aid for Scientific Research from Japan Society for the Promotion of Science (Nos. 17209041 and 21390342) and the 21st Century COE Program (Medical Science).	Serious medical disorder Characteristics of whole sample Mean age (years)==67 (range 36-83) Characteristics of non-CE PET/CT group (n=52)* Male/female=27/25 Pathologically proven cases=30 Tumour location: 33 head, 8 body, 11 tail Size (cm)=3.9 (sd 1.7) SUVmax (g/ml)=6.2 (sd 3) Characteristics of CE PET/CT group (n=43)* Male/female=25/18 Pathologically proven cases=23 Tumour location: 23 head, 10 body, 10 tail. Size (cm)=4.5 (sd 1.6)	acquisition, 180 s for one bed; field of view (FOV), 500 mm; number of iterations, 4; subset, 14; matrix size, 128 × 128; filter, Gaussian 5 mm in full-width-half-max (FWHM); reconstruction, ordered subset expectation–maximization (OSEM). Dynamic CT All patients underwent triple-phase (arterial, portal, and venous phases) CT independently. CT scans were acquired using one of the following CT scanners: Aquilion 64 (Toshiba Medical Systems, Tokyo, Japan); Sensation 16 (Siemens Medical Solutions, Forchheim, Germany). The scanning parameters for the 64-channel detector CT scanner were: detector collimation, 0.5 mm; slice thickness, 5 mm; reconstruction interval, 1 mm; table speed for each phase of enhancement, 50.8-mm per rotation. The scanning parameters for the 16-channel detector CT scanner were: detector collimation, 0.75 mm; reconstruction interval, 1 mm; table speed, 12-mm per rotation. A 30–37 cm FOV, 0.5-s gantry rotation time, auto-exposure control, and 120 kVp were used for all the phases on the two types of scanners. For precontrast imaging, 2.5- to 3-mm-thick sections were acquired. Nonionic contrast material (Iopamiron 300, Bayer, Berlin, Germany; Omnipark 300 Daiichi-Sankyo, Tokyo, Japan; Oiparomin 300 Konica Minolta, Tokyo, Japan) was administered with a power injector (Dual Shot, Nemoto-Kyorindo, Tokyo, Japan) at a rate of 3.0 mL/s for a total of 1.5 mL per body weight (kg) through 22-gauge plastic intravenous catheter placed in an antecubital vein. For the arterial phase, the scan delay was determined using an automatic bolus tracking technique provided by the CT manufacturer. Contrast enhancement was automatically calculated by placing the region-of-interest cursor over the abdominal aorta, and the level of the trigger threshold was set at an increase of 130 HU over the baseline for the 16-channel detector, 180 HU over the baseline for the 64-channel detector. Arterial phase scanning was obtained automatically 15 s after the trigger threshold was reached. Portal and venous phase	Non-CE PET/CT (n=52) Sens=0.76 Sp= 0.84 PPV=0.76 NPV= 0.84 CE PET/CT (n=43) Sens=0.91 Sp= 0.91 PPV=0.91 NPV= 0.91 Adverse events Not reported	

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
	SUVmax (g/ml)=6.3 (sd 2.2) *No significant differences between groups at baseline.	scanning were obtained 40 s and 90 s after triggering, respectively. The PET and CT images in all standard planes were reviewed on a workstation (PETSTAT™, AdIn Inc., Tokyo, Japan). Images were analyzed visually and quantitatively by two blinded reviewers (with 8 and 10 years of experience, respectively). The images were reviewed and a diagnostic consensus was reached by two reviewers for evaluation of tumour staging. For the visual analysis, abnormal 18F-FDG uptake was defined as activity substantially greater than in the aortic blood on the attenuation-corrected images. A volume of interest (VOI) was outlined within areas of increased 18F-FDG uptake and measured on each slice. When the lesion was extensively heterogeneous, the VOI was set so as to cover all components of the lesion. PET/CT measurements included largest diameter and maximum standardized uptake value (SUVmax) corrected for the body weight. Pancreatic adenocarcinoma was defined on PET/CT as a low-density lesion with significant accumulation of 18F-FDG, and lesions showed less or little enhancement relative to the normal pancreatic parenchyma. For T-staging, the following targeted vascular structures were evaluated on non-CE PET/CT and CE PET/CT images: celiac artery (CA), common hepatic artery (CHA), splenic artery (SA), and superior mesenteric artery (SMA), portal vein (PV), splenic vein (SV), and superior mesenteric vein (SMV). Two reviewers assessed independently only for vascular invasion. According to the contiguous relationship between vascular and pancreatic lesions, vascular involvement of pancreatic lesions were graded as follows: 1, no contiguity between the tumour and vessel; 2, tumour contiguous with less than one-quarter of the vessel circumference; 3, tumour contiguous with one-quarter to one-half of the vessel circumference; 4, tumour contiguous with between one-half and three-quarters of the vessel circumference; 5, tumour contiguous with greater than three-quarters of the vessel circumference, or		

Study details	Participants	Index and reference tests Description	Outcomes	Overall Risk of bias/Indirectness (Low/High/Unclear)
		any vessel constriction. The cases with grade 4 and 5 were judged to be vascular invasions. 18F-FDG-avid lymph nodes or distant metastases on PET/CT were interpreted as positive for metastases regardless of size. Lymph nodes with abnormal uptake were deemed positive for metastases even when they were smaller than 10.0 mm in short axis nodal diameter. Lung nodules without abnormal uptake but depicting highly suggestive of lung metastases on the CT part of PET/CT were considered to be positive for metastases.		

F.71 Psychological support needs

Study details	Participants	Interventions/Methods	Outcomes and Results	Limitation (risk of bias)
Arthur, A et al. (2016) Pancreatic cancer survivors preferences, barriers and facilitators related to physical activity and diet interventions J Cancer Surviv Aim: To collect data to inform the development of an exercise and diet intervention for newly diagnosed patients. Setting: Follow-up post treatment Country: USA	Survivors previously treated for resectable pancreatic cancer. Stage I-II Treated between October 2011 and August 2014 117 eligible patients 46 could not be contacted 71 were contacted 51 agreed to participate Response rate was 71.8%	Healthy lifestyle program to help newly diagnosed pancreatic patients manage their diet and exercise through working with a dietician and exercise specialist. Telephone Survey 12 multiple choice questions and four open ended items	Primary Outcome: To establish survivor's level of interest in, preferences for and perceived barriers and facilitators to participating in such an intervention program. Secondary Outcome: to establish survivors acceptability of and comfort with a technology based intervention using visual communication tools such as Skype™ and FaceTime® Participant Characteristics and program interest Mean Age: 69 years White: 84% Female: 57% At least a 4 year college degree: 34% Median driving time to academic medical centre: 90 mins (12-720) Median time since surgery: 13 months Chemotherapy: 65% Radiotherapy: 45% Chemo/Rad data unavailable: 25% Perception of the intervention Interest in exercise and diet programming 69% of participants indicated interest in participating in a non-research exercise and diet intervention within 3-6 months after diagnosis. 66% of participants would participate in a research study to test the benefits of this exercise and diet intervention. Perceived barriers/facilitators	Clear Aims: Yes Clear & appropriate design: Yes Clear description of context: Yes Existing tools used: Likert Scale Items Clear Description of survey population and time frame: Yes Representative population: Unclear Full spectrum of the population of interest: Unclear. Only stage I-II patients were included and it is not clear whether this was the intention. Study large enough (sample size estimate): Unclear, no sample size estimates All subjects accounted for: Yes All appropriate outcomes considered: Yes Ethical Approval: Yes Response Rate: 71.8% Clear what is being measured: Yes

			32% of participants reported no perceived barriers to program participation. 56% of participants reported no perceived facilitators to program participation. The most commonly reported barriers included physical issues, personal issues, distance and chemo/radiation The most commonly reported facilitators included awareness of a program (18%). Patients would like to be informed of such a program immediately after diagnosis and adequately educated on the potential benefits of participation. Location was another commonly reported facilitator (8%) with patients wanting easily accessible or home-based programs. Intervention preferences 50% of participants indicated they would prefer to exercise alone 30% indicated a preference for supervised exercise 20% indicated no preference 56% of participants preferred to exercise at home Participants preferred to have the exercise information provided personally (34%) or over the phone (22%) and diet information personally (48%) or over the phone (16%). Comfort with technology 54% of participants reported using a smartphone or tablet and 58% reported they would be happy to use a loaned tablet. 62% of participants reported using Wi-Fi at home and of these, 81% reported they were comfortable using Wi-Fi. 44% of participants reported feeling comfortable using visual communication	Valid Measurement: Yes Reliable Measurement: Yes Reproducible measurement: Yes Basic data adequately described: Yes Results presented clearly: Partly, some data not presented Internally consistent: No (reports 51 participants and 50 responses) Data suitable for analysis: Yes Clear description of the methods of analysis: Yes Appropriate methods: Yes Correctly performed/interpreted: Yes Method for calculating response rate: Partly, details of how participants were approached, contacted, recorded were included. Method for handling missing data: No Information on how non-respondents differ from respondents: No

			technology such as Skype™ and FaceTime®. Pancreatic Cancer Research 86% of participants reported a belief that research which improves quality of life, physical functioning, and fatigue/tiredness in survivors is important (quite important/very important). Outcomes they felt were important to include in research consisted of psychological support/help coping with side effects (n=6), diet and exercise (n=5), treatment/cure (n=4), etiology (n=4) and screening (n=3). Differences in responses by participant characteristics Participants aged ≥65 years were significantly less likely to report interest in non-research exercise and diet interventions, comfort with a loaned tablet and/or comfort using a visual communication tool.	Results discussed in relation to existing knowledge: Yes, discussed in context of other cancer types Limitations of the study reported: Yes Can the results be generalised: Partly, likely only to stage I-II patients Attempts to establish reliability of validity: Unclear Authors Conclusions Justified: Yes
Andersson T et al. (2012) Health is belonging: Lived experiences during recovery after pancreaticoduoden ectomy ISRN Nursing Aim: to explore the lived experience of the symptoms, health and illness reported by patients recovering after pancreaticoduoden ectomy ad modum	Patients who had undergone pancreaticoduode nectomy ad modum Whipple for a pancreatic or periampullary tumour; no other major surgery or reoperation; no mental disorder; no alcohol or drug abuse; time since discharge not less than 30 days.	Interviews (six took place in the surgical unit and seven took place in participants own home) Naïve Reading: interviews were read several times to become familiar Structural Analysis: texts were divided into meaning units in accordance with the aim of the study and grouped into themes and subthemes Comprehensive Understanding: text was read again and the themes reflected on.	Naïve Understanding Participants had a strong desire to recapture everyday life but were aware there was process of recovery. Themes: Common themes which emerged included: Recapturing everyday life Being healthy Looking to the future Recapturing everyday life Participants were forced to confront everyday life on their own for the first time since surgery. Food and drink were associated with negative experiences due to symptoms	Clear Aims: Yes Clear & appropriate design: Yes Clear description of context: Yes Existing tools used: Unclear, only brief details of the interview questions are described. Clear Description of survey population and time frame: Yes Representative population: Unclear,

Whipple due to pancreatic or periampullary cancer Setting: Post surgery follow-up Country: Sweden	N=17 approached about participation N=13 (9 female) agreed to participate Response Rate: 76.5%		such as altered taste. Eating was no longer pleasant and considered merely necessary for the recovery process: "The most difficult part was coming home and finding that food was not tasty and that I was not hungry. I think it is fair to say that it was like being tired of food" As a result of difficulties with food intake, weight did not stabilise for a while and bodily changes resulted in various emotional problems: "I do not want to have close contact with other people. I realise that I do not like my own body at present. It was a shock that I should think I was so repulsive" Decrease in physical functioning was experienced as difficult to master, required a lot of adaptation and made participants more dependent on other people: "I was completely dependent on my husband for help, because I was very weak" Symptoms impacted on everyday life initially which lead to participants experiencing isolation or needing to adapt to negative changes in bodily functioning. Participants mastered these experiences through self-care and pharmacological control of symptoms (analgesics or enzyme replacements). Recapturing everyday life required planning, including meal planning and in some cases finding out the location of the nearest toilet. This unavoidable planning was considered limiting. Prior to discharge participants had access to health care professionals continuously providing them with attention and care. It was a shock to some participants that they	more females than males with no discussion around whether this is a true reflection. Full spectrum of the population of interest: No, study carried out in a single hospital so represent and single medical/nursing approach Study large enough (sample size estimate): Unclear (no sample size calculations provided) All subjects accounted for: Yes All appropriate outcomes considered: Yes Ethical Approval: Not required according to Swedish law at the time the study was conducted Response Rate: 76.5% Clear what is being measured: Yes Valid Measurement: Yes Reliable Measurement: Yes Reproducible measurement: Yes

			no longer had someone to rely on post discharge or to discuss their self-care experiences with: "It may be that that's it. Now that I have been discharged they do not care about me as much as before. So now I'm discharged, written off somehow." Participants highlighted the importance of support from health care staff after discharge as they felt it gave them a chance to discuss symptom management and self-care needs. "As soon as a problem arose, I phoned her. She always took the time and talked. If she wasn't in, she would phone back. It was nice to know that I could contact her." Participants with enjoyable hobbies or who were still working were eager to regain their strength and return to their former lives. A gradual increase in activity as well as social support helped many participants through this period: "I have had tremendous support from family and friends as well as colleagues, but I suppose I am the sort of person who finds it easy to talk about it (my illness)." Participants with no close relatives or support person experienced difficulties with all participants describing the value of social support in the recovery process, not just with practical matters but also for encouragement: "It is tremendously important to me and means so much. I do not think I would have coped without that support because then I would have had to go into a home or something." Being Healthy	Basic data adequately described: Yes Results presented clearly: Yes Internally consistent: Unclear, no tables to ensure all participants answered all questions. Data suitable for analysis: Partly – qualitative, open ended questions, analysis took the form of identifying themes. Clear description of the methods of analysis: Yes Appropriate methods: Yes Correctly performed/interpreted: Yes Method for calculating response rate: No, response rate not reported (calculated for the review based on information provided) Method for handling missing data: No Information on how non-respondents differ from respondents: Partly – mentions the possibility that only

			Participants described themselves as healthy with the most important aspects of healthy being the ability to play an active part in everyday life and feel that they have contributed both socially and professionally: “I have accompanied my son and worked a lot with him on different jobs. I find it great fun and being able to participate in equivalent to health”. Being healthy did not equate to being symptom free with participants who experienced debilitating symptoms coping by using successful symptom management: “Good health may not necessarily mean that I am in top form but that I feel well, can manage my everyday life and think that living is great fun” The importance of being needed at work and in their social network was highlighted. Participants reported feeling angry and frustrated about the initial experience of social isolation due to symptoms and that readjustment took time. Participants never described themselves as sick, rather that they experienced good health in view of their condition and associated this with being independent. “Because I can, that I’m feeling will and can go out, can do various things without having to ask for help, just the fact that I am able to do it gives you a kick, being able to manage a thing” Looking to the future All participants’ perceptions of their future varied. Some had a cautious, short term perspective, making the most of each day. Their approach was to not dwell on the disease or future relapse, coping through	well patients might participate Results discussed in relation to existing knowledge: Yes Limitations of the study reported: Yes Can the results be generalised: No Attempts to establish reliability of validity: Yes Authors Conclusions Justified: Yes

			adopting a positive way of thinking and focusing on the good aspects of their lives: “Sometimes I think about what causes a relapse to occur, I mean how big is the risk of a new cancer in the pancreas, or some other form of cancer. But I have not bothered to ponder or read up about it as if it happens, it happens.” Older participants felt that having reached a considerable age, there was no point speculating about life expectancy. All participants brooded and expressed uncertainty about the future with some of those uncertainties relating to the information provided by the healthcare staff or obtained by the participant themselves. Reappearing symptoms tended to give rise to negative thoughts about the future and sometimes to frustration and anger. The perception that health care staff had not provided straightforward and honest information contributed to these feelings. Participants might search for their own information but had difficulty understanding the content. Participants tended to seek support, consolation and motivation from family members when they worried about the future. Interpreted Whole Participants had a positive view of the future yet were aware of the risk of relapse. Improvements in health and recovery gradually contributed to a positive feeling and inspired them further in the healing process: “it was really fantastic that I recovered so quickly, which may explain why my self-	

			confidence improved, not that it was lacking before but…strengthened self-confidence, strengthened belief [in one's ability] and all that…"	
Akizuki N. (2016) Prevalence and predictive factors of depression and anxiety in patients with pancreatic: a longitudinal study Japanese Journal of Clinical Oncology 46;1:71-77 Aims: to determine the prevalence of depression and anxiety among pancreatic cancer patients before and 1 month after the start of anticancer treatment and identify factors which predict their occurrence Setting: Secondary care (patients being treated for pancreatic cancer) Country: Japan	N=130 consecutively diagnosed patients in a single centre between August 2003 and May 2004. N=110 were assessed at baseline N=91 were assessed at follow-up Inclusion Aged 18 years or older Clinical diagnosis of pancreatic cancer Awareness of the pancreatic cancer diagnosis No history of anti-pancreatic cancer treatment Ability to speak and read Japanese Not too ill to complete the questionnaires and participate in the interviews	Structured Interviews /Questionnaires (NCCH DSM-III-R (SCID) (18)) Baseline questionnaire before treatment started Questionnaire and interview one month after treatment began (if the patient was deemed eligible) Baseline assessments were performed on inpatients only. Follow-up assessments included both inpatients and outpatients.	Presence of depression and anxiety (assessed by a trained psychiatrist) Time of onset of depression and anxiety Validity Reliability of interview ratings was assessed based on concordance rate with the SCID conducted by an independent trained clinical psychologist in 39 cases. Kappa coefficient was 0.76 for any psychiatric diagnosis, 0.79 for major depression and 0.69 for adjustment disorders. Prevalence of depression and anxiety 15 patients were diagnosed with depression and anxiety (13.6%; 95% CI: 7.2-20%) at the baseline assessment 15 patients were diagnosed with depression and anxiety at follow-up assessment (16.5%; 95% CI: 8.9-24.1%) Time of onset of depression and anxiety compares with time to onset of first physical symptoms 3/15 patients diagnosed with depression and anxiety at baseline had psychiatric symptoms before onset of somatic symptoms 12/15 patients experienced their first psychiatric symptoms concomitant with or after the onset of somatic symptoms (median 1 months after onset; 0-5 months). OF the 15 patients diagnosed with depression and anxiety at baseline, 12 completed follow-up assessments. 4/12 continued to have psychiatric disorders	Clear Aims: Yes Clear & appropriate design: Yes Clear description of context: Yes Existing tools used: Yes (NCCH DSM-III-R (SCID) (18)), relevant sections translated to Japanese as required Clear Description of survey population and time frame: Yes Representative population: Unclear, single centre however all pancreatic patients were included. Full spectrum of the population of interest: Unclear, all pancreatic patients were eligible but patients too ill to participate were excluded at follow-up. Study large enough: Yes, sample size calculation indicate 107 patients were required and the study included 130 All subjects accounted for:

	Absence of cognitive impairment Exclusion Patients subsequently proven to have non-malignant tumours after biopsy or surgery		5/6 patients with adjustment disorders at baseline and ¾ patients with major depression at baseline had improved at follow-up. Predictive factors for depression and anxiety 79/91 patients at follow-up had no psychiatric diagnosis at baseline Higher sadness scores on the MDASI, lower KPS and experience with a relative dying due to cancer were significant predictive factors for newly diagnosed psychiatric disorder at follow-up.	All appropriate outcomes considered: Ethical Approval: Yes Response Rate: Clear what is being measured: Yes Valid Measurement: Yes Reliable Measurement: Yes Reproducible measurement: Yes Basic data adequately described: Yes Results presented clearly: Yes Internally consistent: Yes Data suitable for analysis: Yes Clear description of the methods of analysis: Yes Appropriate methods: Yes Correctly performed/interpreted: Yes Method for calculating response rate: No Method for handling missing data: Yes – researchers checked questionnaires and asked to fill out any blanks

				Information on how non-respondents differ from respondents: No, not relevant as consecutive patients were enrolled Results discussed in relation to existing knowledge: Yes Limitations of the study reported: Yes Can the results be generalised: No, not to palliative care as the study included patients who had not yet undergone anticancer treatment Attempts to establish reliability of validity: Yes Authors Conclusions Justified:
Beesley V et al. (2016) A tsunami of unmet needs: pancreatic and ampullary cancer patients supportive care needs and use of community and allied health services Psycho-oncology 25;150-157 Aim: To describe people's needs and use of support	N=136 patients (13 had ampullary cancer) Patients aged 18 years or older with a suspected or confirmed diagnosis of primary pancreatic cancer between January 2007 and June 2011.	Patients were given an information sheet, consent form, questionnaire and reply-paid envelope. Patients who did not return the questionnaire and consent form were followed up by telephone after 10 and 17 days.	At the time of completing the questionnaire median time after diagnosis was 3 months. 47% had stage II-IV disease 82% of participants had received chemotherapy 56% of participants did not have a completed surgical resection (inoperable locally advanced disease, age and/or comorbidities or aborted resection). Prevalence of needs within domains Median standardised score was highest for physical/daily living needs (M=35; IQR 15-60)	Clear Aims: Yes Clear & appropriate design: Yes Clear description of context: Yes Existing tools used: Yes Supportive care needs survey short form Clear Description of survey population and time frame: Yes Representative population: Unclear,

services and to examine whether these differed according to whether or not patients had undergone surgical resection. Setting: Secondary Care, patients being treated for pancreatic cancer Country: Australia			Median standardised score was M=25 for psychological (IQR 8-53), health system/information (IQR 18-35) and patient care (IQR 10-30). 96% of participants reported having some needs (met and unmet) and 69% reported moderate to high unmet levels. More than 80% of participants reported at least one met or unmet need in four of the five domains. More than 50% of participants reported a moderate to high unmet physical/daily living (54%) or psychological (52%) need. 32% of participants reported moderate to high unmet needs for help with health system/information 21% of participants reported moderate to high unmet needs for patient care needs. 16% or participants reported moderate to high level sexuality needs. No statistically significant difference in needs were observed when comparing participants following a palliative group or surgical resection pathway. Most prevalent 'moderate to high' unmet supportive care need items The most commonly reported 'moderate to high' unmet need was participants 'not being able to do things they used to do' (41%). 37% of participants reported 'moderate to high' unmet need relating to 'concerns about the worries of those close'. Other moderate to high unmet needs included: Uncertainty about the future (30%) Lack of energy/tiredness (28%)	single centre however all stages of pancreatic cancer were included. Full spectrum of the population of interest: Unclear, a number of patients declined to take part but there is no information about these patients' reasons for refusing consent. Study large enough: Unclear (no sample size calculations) All subjects accounted for: Partly – numbers of participants refusing consent/died before participation is listed. All appropriate outcomes considered: Yes Ethical Approval: Yes Response Rate: 54% Clear what is being measured: Yes Valid Measurement: Yes Reliable Measurement: Yes Reproducible measurement: Yes Basic data adequately described: Yes

			Work around the home (28%) Fear of cancer spreading (26%) Pain (26%) Participants with non-resectable disease were significantly more likely to report to some health information/system needs: Being given information (written, diagram and drawings about aspects of managing your illness and side effects at home (22%) Being given explanations for tests for which explanations are requested (22%) Being informed about your test results as soon as possible (22%). Use of community and allied health services The most frequently used services (information and education) and providers (dieticians, complementary medicine practitioners and psychological practitioners) did not differ b yresection. Consultation with a physiotherapist or exercise physiologist was higher in participants who had a resection. Participants without resection were more likely access respite care and palliative care access was higher in participants who did not have a resection (59% versus 27%; p<0.05). Psychological need for help and corresponding self-reported consultation with psychological health professionals 90% of patients reported at least one psychological need. Of these 3% reported having all their needs met and 76% reported having at least one psychological need satisfied.	Results presented clearly: Yes Internally consistent: Yes Data suitable for analysis: Yes Clear description of the methods of analysis: Yes Appropriate methods: Yes Correctly performed/interpreted: Yes Method for calculating response rate: No Method for handling missing data: No Information on how non-respondents differ from respondents: No Results discussed in relation to existing knowledge: Yes Limitations of the study reported: Yes Can the results be generalised: Unclear Attempts to establish reliability of validity: Yes Authors Conclusions Justified:

			Only 16% of participants consulted a psychologist, psychiatrist, social worker or telephone counsellor.	
Beesley V et al. (2016a) Risk factors for current and future unmet supportive care needs of people with pancreatic cancer: A longitudinal study Support Care Cancer 24;3589-3599 Aim: to determine whether the supportive care needs of people with pancreatic cancer change over time and to identify factors associated with current and future unmet needs. Setting: Follow-up post diagnosis Country: Australia	N=136 patients completed the baseline Response rate 54% of those approached) N=20 participants with unusable data N=116 participants contributing data Patients were excluded if they were more than 8 months after diagnosis or if they were physically or mentally unable to take part in the study.	Self-administered mail questionnaire at recruitment and every two months thereafter until loss to follow up or 8 months after diagnosis. Supportive Care needs survey short for (SCNS-SF34) assesses needs across five domains: Physical/daily living Health system/information Patient care/support Sexuality 1=not applicable (no need) 2= satisfied (need was met) 3=low unmet need 4=moderate unmet need 5=high met need	At baseline 70% of participants reported at least one moderate to high unmet need, 53% reported physical or psychological needs at moderate to high levels. 29% reported health system/information, 17% patient care and 13% sexuality needs Prevalence of an change in unmet needs over time There were no significant changes over time in the proportion reporting moderate to high unmet needs Baseline=70% to four months 75% (adjusted OR=0.9; 95% CI 0.3-2.1) The odds of having needs in the future did not differ significantly at baseline or at the 2-month follow-up (OR=1.2; CI 0.5-2.7) In unadjusted stratified analysis there was an indication of a reduction in needs over time for patients who had a complete resection and an increase in needs over time in patients with locally advanced (73 to 85%) or metastatic disease (66 to 88%). Factors associated with having at least one current or future moderate to high unmet need In bivariate analysis, no significant associations were found between reporting moderate to high unmet needs and age, sex, marital status, education, place of residence, initial place of treatment, having a resection, comorbidities, chemotherapy, social support, having a care coordinator or accessing palliative care.	Clear Aims: Yes Clear & appropriate design: yes Clear description of context: Yes Existing tools used: SCNS-SF34 Clear Description of survey population and time frame: Yes Representative population: Full spectrum of the population of interest: Unclear Study large enough: Unclear – no sample size calculation All subjects accounted for: Yes All appropriate outcomes considered: Yes Ethical Approval: Yes Response Rate: 54% Clear what is being measured: Yes Valid Measurement: Yes Reliable Measurement: Yes Reproducible measurement: Yes

			Higher levels of pain, anxiety and depression were significantly associated with current needs. Pain was the only factor significantly associated with any future needs, although people with metastatic disease and those with anxiety had substantially higher odds of have future needs. Depression and pain were significantly associated with current physical needs. Pain and locally advanced disease were the main factors associated with future physical needs. Anxiety, depression and pain were associated with current psychological needs. Patients with metastatic disease had higher odds of future psychological needs.	Basic data adequately described: Yes Results presented clearly: Yes Internally consistent: Yes Data suitable for analysis: Yes Clear description of the methods of analysis: Yes Appropriate methods: Yes Correctly performed/interpreted: Yes Method for calculating response rate: No Method for handling missing data: Yes, intermittent missing data imputed and weighted GEEs used to allow data to be missing at random Information on how non-respondents differ from respondents: No Results discussed in relation to existing knowledge: Yes Limitations of the study reported: Yes Can the results be generalised: Unclear

				Attempts to establish reliability of validity: Yes Authors Conclusions: Justified
Boyd A et al. (2012) Screening for depression, sleep related disturbances and anxiety in patients with adenocarcinoma of the pancreas: a preliminary study Aim: to evaluate the symptoms of depression, sleep and anxiety disorders in pancreatic cancer patients. Setting: Single centre, secondary care (patients presenting to a pancreatic cancer clinic) Country: USA	N=27 Exclusions: Inability to communicate in English or to understand verbal or written English. N=24 patients provided consent and at least one assessment N=22 patients with confirmed pancreatic cancer were included	Personal Health Questionnaire 9 (PHQ9) to screen for depression and to monitor symptoms during treatment Penn State Worry Questionnaire (PSWQ) for generalised anxiety University of Michigan Sleep Assessment Questionnaire to monitor sleep symptoms	Screening for depressive symptoms Discrepant results – text and table don't match. Results from the table are reported here. A total of 60% of participants reported mild (32%), moderate (23%) or moderately severe depressive symptoms (5%). 41% of participants reported no symptoms of depression No participants reported severe depressive symptoms Numbers add up to 101 likely due to rounding. Screening for general anxiety 55% of participants screened reported subclinical levels of anxiety (score of 0-40) 36% of participants reported a moderate level of anxiety of possible clinical significance (score of 40-60) 5% (N=1) participant reported and anxiety score indicative of a likely anxiety disorder (score >60). Screening for sleep disturbance 45% of participants reported no sleep disturbances 41% of participants recorded scores indicative of a potential sleep problem 10% (n=2) recorded scores indicative of a sleep problem. Interrelationship between the measures	Clear Aims: Yes Clear & appropriate design: Yes Clear description of context: Yes Existing tools used: Yes (PHQ9, PSWQ, SAQ) Clear Description of survey population and time frame: Yes Representative population: Yes (spread across stage) Full spectrum of the population of interest: Unclear, single centre in the USA, possible selection bias Study large enough: Unclear, no sample size calculations All subjects accounted for: Yes All appropriate outcomes considered: Yes Ethical Approval: Yes Response Rate: 89% Clear what is being measured: Yes

			There was no correlation between the scores from the PHQ or SAQ and PSWQ. There was a correlation between the PHQ and SAQ indicating a possible link between depressive symptoms and sleep disturbances thought this correlation was not significant (p=0.009). It was estimated that 16% of the depressive score is explained by the SQ scores. There was a possible correlation between SAQ and cancer stage (p=0.08) and between PHQ and stage (p=0.11).though again this was not significant. Encouraging the use of tablets by patients Only 10% of the patients entered their own data into the system 90% of participants filled out the paper forms and the data were entered by research staff.	Valid Measurement: Yes Reliable Measurement: Yes Reproducible measurement: Yes Basic data adequately described: Yes Results presented clearly: Partly – some discrepancy between text and tables Internally consistent: Partly – some discrepancy between text and tables Data suitable for analysis: Yes Clear description of the methods of analysis: Yes Appropriate methods: Yes Correctly performed/interpreted: Yes Method for calculating response rate: No Method for handling missing data: Partly, some discussion around imputing missing data Information on how non-respondents differ from respondents: No

				Results discussed in relation to existing knowledge: Yes Limitations of the study reported: Yes Can the results be generalised: Unclear Attempts to establish reliability of validity: Yes Authors Conclusions: Justified
Chapple A et al. (2012) An alarming prognosis: How people affected by pancreatic cancer use (and avoid) internet information Policy and Internet 4;2:3 Aim: to explore the role of the internet for patients with pancreatic cancer by collecting accounts how patients and relatives used the internet and their perceptions of what they had found. To help to understand the potential negative effects of the internet for people	N=40 respondents recruited through two surgeons, two oncologists, a doctor who specialised in palliative care and a cancer nurse specialist all working in different parts of the UK. Recruitment was also carried out by advertising in a London newspaper, via personal contact and via snowball method. N=8 participants who responded to the advertisement and to the TV and radio programs were relatives of	Interview at a place of participants choosing (mostly home)	80% of participants interviewed had used the internet at least once to find out something in relation to their pancreatic cancer or had children, partners or friends who had done so on their behalf. Those using the internet had many reasons for doing so: Finding information about signs and symptoms, treatments, medical terms, clinical trials and side-effects of treatment Finding information about how to prepare children for a parent's life threatening or terminal illness Raise awareness of pancreatic cancer Language used by participants implied that the internet was an unremarkable and routine part of everyday life using terms like 'obviously', 'of course' and 'we all looked it up' "Well, obviously on the internet" "of course" he looked it up on the internet "Yes I did the internet trawl" Some people used the internet at different stages of their illness. One participant did not look at the internet when she was first	Clear Aims: Yes Clear & appropriate design: Yes Clear description of context: Yes Existing tools used: Unclear, no details of the interview questions/format were provided. Clear Description of survey population and time frame: Yes Representative population: Partly, a broad and diverse sample was included (patients, relatives) but numbers were small. Full spectrum of the population of interest: Yes

with a life threatening illness. Settings: Tertiary care/Follow-up Country: UK	people who had died of pancreatic cancer.		diagnosed as she was in too much pain but later used it “extensively” to find out more about the treatment she had been prescribed. Making sense of what the clinician says Some people used the internet to try to understand what they had been told during consultation but in some cases, this led to false hope. “At that time I had absolutely no exposure to cancer. Knew nothing about the implications of cancer (…) so it’s a shock when you’re sort of faced with it, had no information. Went on the internet to find out exactly what metastases were. I just saw the word ‘primary’ and just automatically assumed well maybe these are the early stages of cancer, because you sort of zone in on certain words (..) I felt quite positive (>>) But when I looked at it on the internet [again] I just saw ‘metastases’ and realised that actually we’re talking about final stages of cancer” Responses from one participant who was herself a GP showed that the need to make sense of what the health professionals say was not limited to those without medical training. “They did ultrasound and the radiographer who was doing it kept going backwards and forwards over the top part of my abdomen. And so I said ‘is there a problem?’ And she said, actually the bile duct and the pancreatic duct are dilate. And I don’t know why (…) I looked it up on the internet ‘dilated pancreatic duct’ and ‘dilated bile duct’ and they were saying ‘It’s pancreatic cancer until proved otherwise’ and I was	Study large enough: Unclear, no sample size All subjects accounted for: Unclear, responses quoted appear to be from the same small number of participants All appropriate outcomes considered: Yes Ethical Approval: Yes Response Rate: No details Clear what is being measured: Yes Valid Measurement: Yes Reliable Measurement: Yes Reproducible measurement: Yes Basic data adequately described: Yes Results presented clearly: Yes Internally consistent: Yes Data suitable for analysis: No Clear description of the methods of analysis: Not applicable Appropriate methods: Yes

			thinking ‘could it be a stone?’ and obviously I think a stone would have shown up. Health information found on websites can have the capacity to affect the relationship between professionals and patients. One participant diagnosed with advanced pancreatic cancer, looking for information on the internet while waiting for the confirmation of his diagnosis helped him to understand and accept that surgery was not a treatment option for him although he acknowledged the need to be careful about what one reads on the internet. “I think he said ‘well we can’t operate, you know, because of the difficulty of reaching a diagnosis of pancreatic cancer, by that time it would be far too advanced, too big to cut out without doing damage to other organs or other surrounding blood vessels.’ And I didn’t really have any difficulty in accepting this because I’d done my own research on the internet and I know none has to be careful about getting information from the internet because, you know, if you’re not careful you can end up thinking you know more than the doctors and nurses because you’ve read it all on the internet. So I was aware of the dangers of taking it sort of not too literally, but I did find it very useful to get some background information about the various forms of pancreatic cancer, the various forms of treatment and all the associated facts. And I had them at my fingertips before I saw this guy.” “So it was useful in helping me to accept, come to terms with the verdict, because I’d done my own research” Finding out more about treatments and what they involved	Correctly performed/interpreted: Yes Method for calculating response rate: No Method for handling missing data: not applicable Information on how non-respondents differ from respondents: No Results discussed in relation to existing knowledge: Yes Limitations of the study reported: Yes Can the results be generalised: Yes Attempts to establish reliability of validity: No Authors Conclusions: Justified

			Some people used the internet to find out more about the treatments they had been offered. Surgeons tried to explain to their patients what they were going to do but naturally patients wanted to find out more information for themselves. The “information” and “support” roles of the internet are not easily separated. Some participants appear to find both support and information by going online. “And looking at the internet, was that useful or not?” “Oh, very useful. I don’t’ think I could have through it as well as I did without the information that I got off the internet and the people that I spoke to on the internet as well, people that I spoke to on the internet as well, people who had been through it. There was one lady in particular; her sister had just had the Whipple’s [operation] while I was waiting to have mine. And her sister was absolutely wonderful, gave me in great detail…what her sister had gone through with her operation, so I knew what to expect which was what I wanted…” “How did you find those people on the Internet to ask questions?” “I just did, I just kept searching in the search engines really under pancreatic cancer headings, usually, or Whipple’s, which was the operation. And that would bring up a wealth of sites to look at. And it was just a case of going through the sites one by one, trawling through them and seeing what they were and how they worked, and just negotiating my way through them really”	

			Checking the advice given and finding potential treatments and trials Some participants used the internet to look for new treatments or to check that they were getting 'true' information from their doctor or to confirm what they were being told by their doctor. "Have you looked at the internet considerably for information or not?" "A fair amount. In general I found that the information which I got from the hospital has been sufficient really for most of my needs. [Um], and I suppose I've used the internet a little bit to just confirm what I've been told is true. I think that obviously in the early stages, there was a little bit of just generally trying to understand more about what pancreatic cancer means, and the treatments available and so on." One respondent noted that he was surprised to have had to search the internet to find his own solution to symptoms he was suffering as a result of chemotherapy. "And do you have to take any other medication? Or medicines like Creon because of the pancreatic cancer?" "I have to take Creon. It was me, I looked up Creon on the internet, you know because I was getting, feeling so sick with everything I ate (…) and I spoke to the oncologist, I said, 'Is there an enzyme I can take?" And he said 'Yes there is' and I thought 'Oh it's funny that I have to ask for it, why didn't they say there is an enzyme you can take.' I looked it up on the internet and it said you know, you often will be prescribed an enzyme, to help with the digestion of these foods etcetera. Because	

			you won't be able to digest it. So I actually asked for that." One participant reported that her relative has been 'a very informed consumer' and wanted to be 'in control' of treatment decisions. "She was very in control. She was a very controlled person and she was very in control. So she did a lot of research on the internet. She looked at a lot of stuff. She read a lot of literature. She explored American hospitals, English hospitals. What the best research was, what the intervention should be etc. And so she would, she was a very informed consumer and engaged in a lot of dialogue with her own consultant about, "What about this drug? I've heard there's a trial at this hospital. Why can't I be on that trial? I want to go on that trial.' And so she pushed. She tried different experimental drugs, and she pushed to be on trials, within the conventional world (...) She did a lot of internet research and we did as well." Some respondents reported that they spent much time searching for information about clinical trials and asking the oncologist for a second opinion about the trials. "So when you were referred to an oncologist?" "Yes" "Could you say what happened then?" Luckily, a friend's son had been on the internet, looking to see what pancreatic cancer was all about. And he'd found that Liverpool University were doing a clinical trial which he thought was useful. And he told me about this and he gave me the	

			computer printout. And it did look interesting to me. So luckily, I was able to go along to this meeting armed with these two A4 sheets of computer printout about this clinical trial. And I'm so pleased I did, because the oncologist was depressing. And it would have upset me an awful lot had I not had the, if you like, this back-up of this information off the internet. And so I asked then if I could go on this trial, if I could be put forward to it. And he said he would consider it, which he did. And I was accepted on this clinical trial, and moved away from that oncology department. Supporting Children One respondent reported that a MacMillan Nurse helped to prepare her to explain her diagnosis to her 12 year old daughter and suggested a website intended for children whose parents have cancer (http://riprap.org.uk/) "Did the MacMillan nurse tell you where you get any support for the children?" "Well they gave me lots of leaflets and information on how to tell people, especially children. There's even websites that children can go on, it's called Riprap or something. They can go on there and put on their thoughts and how they are feeling. Things like that. And, so I though right, well I'll get her to look at that and things (...) "And has she used the website?" "Yeah, yeah she's been on it a couple of times" The website, Winston's Wish (http://www.wnstonswish.org.uk) specialises in helping children after bereavement and helped one respondent talk to their	

			daughter about her mother's terminal diagnosis: "My daughter was three. And we told her that it was called cancer. We told her that there was a lump in Mummy's tummy. And that she was going to hospital to have medicine to try and take the lump away I think. You know we didn't want to give it any funny names. This is where resources such as a website, Winston's Wish, was useful. And also the hospital were good at giving literature as to you know some of the basics, and where to find information. Handling unwelcome internet information Some patients looked at the internet but then decided not to look at it again because what they found made them anxious or frightened. "Did you look for information on the internet at that stage?" "I didn't no, I suppose I'm a bit of a coward there. When I was first diagnosed or the first possibility of pancreatic cancer was mentioned, I went on the internet. And I remember I was on the internet on a computer in the library and the first thing that came up was a banner across the monitor screen saying, 'survival rate 9 to 12 months.' And I thought, 'oh right.' And I didn't want to read any more. I remember I just sort of turned the computer off in a panic and got out and walked out of the library rather shocked. And really I've been like that ever since." The same respondent was later glad to get information about a clinical trial which a friend's son found on the internet but he	

			was too frightened to go searching the internet himself. One respondent reported that his wife had been “shocked” by what she found on the internet and so decided not to look at it again. “She’d looked up on the website about pancreatic cancer just the once and was quite shocked by all she read and the statistics etc. (…) And she’d picked up enough from the website to know that in fact they couldn’t tell for sure on any of this [the prognosis], and it would only be guesswork. So far better to stay with what was real, and what she was involved with. What she could do now.” One respondent had hoped for potentially curative surgery and after her diagnosis she looked for information on the internet but what she saw deterred her from searching further. This respondent’s husband filtered what he found on the internet. “You said to me off camera earlier that you didn’t’ want to seek out any other information for yourself. Can you say a bit about that?” “Right. I think when I was first diagnosed my husband went onto the website, I have got a sheaf of papers this thick that he printed off. I did look at some of the websites. I did find there was just an incredible amount of information. A lot of the information I was seeing about the pancreatic cancer was very, very, negative, very negative (...) So, I decided I didn’t really want to look a t that. My husband kept telling me about all the stories of the, the people that, you know, had made good progress etc., which was	

			fine but actually I didn't really want to go there at all." In terms of understanding information on the internet and determining which information is useful, one respondent reported that his academic background meant that he could filter unreliable information: "Did you find some internet sites more useful than others?" "Yeah (...) I mean I'm lucky that I teach psychology and therefore I've got a background in you know, I know how to recognise a more academic paper. So I was able to filter things out. (…) And you know it is a quagmire. I mean I spent hours and hours and hours and hours…trawling through, and I think I'm lucky that because of my background I knew how to recognise serious papers. And I had the time and the know how to sort of explore them. So if I saw a paper then I would go into, then I'd be looking into their names and finding out who these people were before I even started reading a paper, so I knew I had to trust it you know. So I did find some very good information like the Telovac trial, you know I learned all about telomerase and the Telovac trial itself. I looked up reviews of the trial itself, academic papers. So you know I was just lucky really that I could do all that." The respondent's wife reported not looking at the internet because she only wanted to hear about positive results which for her, were impossible to find, so she was seeing her spiritual healer.	

			“And I mean I had to, I was driven, you know. Kate didn’t want to know because she was, she’d be seeing her spiritual healer, while I’d be looking at academic papers. She didn’t want to know, she didn’t want to know facts and figures. She wanted to know of any research with was positive. Of course there wasn’t any. That was the hard thing, increasingly we were diverging in terms of what I was understanding and where she was you know, so it was difficult in that sense.” One respondent reported that although he supported his wife in many ways, the way he and his wife looked for information sometimes made life difficult rather than harmonious. He reported that he was cynical of some therapists making a living by selling alternative treatments to people who are dying, however he did ‘stray from the academic papers in looking for more anecdotal evidence of things that can work’ He was desperate to learn of treatment that ‘were said’ to work even if the scientific evidence was lacking. A total of 8 respondents reported that they did not use the internet to look for health information. Reasons included a lack of easy access to a computer, too busy caring for partner or plenty of information from health professionals so felt they didn’t want or need anymore. “Had you looked for information about pancreatic cancer before the operation? Had you looked anywhere else?” “No I hadn’t. Id only relied on information they’d given me through the ward staff and I chose that because I always feel that if try	

			to go into territory you are not familiar with then you can only confuse yourself. "Can you tell me when you got the diagnosis, were you given very much information? Did you want much information? Did you seek it out? You know, what happened? In finding out about what this thing was that you'd got?" "Yes the consultant drew a diagram explaining what I'd got. Initially the information was a bit patchy but certainly as I had more tests it became clearer that there was more information there. What I didn't do, I didn't go on the internet of ring up any support groups, because I think I was probably frightened of what they would say, you know, they might say, 'Oh it's pretty dodgy' And I think we just, my wife and I decided we wanted to sort of handle it ourselves."	
Coleman J et al. (2005) The effect of a frequently asked questions module on a pancreatic cancer web site/family chat room Cancer Nursing 28;6:460-468 Aims: To determine whether the FAQ module met the information needs of website users and to refine the existing FAQ	N=600 postings from the Johns Hopkins Pancreatic Cancer website Patient/Family Chat room N=300 consecutive postings generated between April 13-April 30 1998 prior to the addition of the FAQ module. N=300 consecutive	Addition of an FAQ module to a pancreatic cancer website Examine qualitative and quantitative changes in chat room conversations pre and post addition of an FAQ module to the pancreatic website.	An 8 month gap after the FAQ module was allowed for a new group of chat room users. It was considered that due to the rapid progressive nature of pancreatic cancer, the 8 month gap would be long enough would allow for different users in the chat room. The first 50 postings were analysed by each member of the team for agreement on common categories. Readily apparent categories included: Treatments Symptoms Social support Spiritual support Seeking support or giving support or both	Clear Aims: Yes Clear & appropriate design: Yes – descriptive-comparative mixed methods design Clear description of context: Yes Existing tools used: No, no interaction with patients/caregivers/family members Clear Description of survey population and time frame: Yes Representative population: Unclear –

module information based of findings. Setting: Country: USA	postings collected from December 1 through December 29, 1999 after the addition of the FAQ module to the website.		The second 50 postings were analysed and discussed to gain consensus on the identified themes and categories. Following this, pairs of investigators analysed 50 postings each and shared results with the team. IF a new category was identified, investigators re-analysed previous postings to search for the new category. For posts reporting the current status or death of a family member or significant other. 'Reporting' was identified for postings that neither sought nor gave support. Quantitative Analysis 3/600 (0.8%) postings were blank or a duplicate message leaving 597 posts to be analysed. There was a significant difference in the proportion of people 'giving information', 'seeking information', or 'both' in the pre FAQ period compared with the post FAQ period. A greater proportion sought information after the FAQ module was added to the site. There was no significant difference among the proportion of postings 'seeking support'. 'giving support' or 'both' in the pre and post FAQ periods. A significantly greater proportion of postings reported current status of the individual with cancer in the pre-FAQ period, whereas a greater proportion of post-FAQ periods posts reported deaths. The sample of postings indicated that family members were more likely to access the chat room with only 7% of postings coming from the patients themselves.	it study examined a convenience sample so not clear whether it was representative Full spectrum of the population of interest: Unclear – it study examined a convenience sample so not clear whether it was representative Study large enough: Unclear, large number of postings but not way to tell how many unique posters existed. All subjects accounted for: Not applicable All appropriate outcomes considered: Yes Ethical Approval: Yes Response Rate: Not applicable Clear what is being measured: Yes Valid Measurement: Unclear Reliable Measurement: Unclear Reproducible measurement: Unclear Basic data adequately described: Yes

			Postings were almost 3 times more commonly composed of women (particularly daughters). Pain was the most commonly reported symptoms both before and after the addition of the FAQ module suggesting more attention to this symptom is needed regarding the importance of reporting pain, recognition that experiencing pain is no “an exception” and that pain can be managed. Questions about fatigue decreased by 3 fold after the addition of an FAQ module, suggesting the information provided was sufficient to address many queries. A number of postings described end of life symptoms without an awareness that death was near suggesting that more work needs to be done to prepare and support loved ones to recognise and accept that death was imminent. Qualitative Analysis Theme 1: Information: seeking, giving or both Information was defined as any posting that gave or sought details about treatment, nutrition, prognosis, end of life care, disease progression, cost of care or symptoms. Treatment: The most common treatment strategy reported was medical treatment. The 2 important areas “best approaches” to cure and reduction of tumour burden. Inquiry into the treatment of common symptoms, including pain, anorexia and indigestion. Other information sought included efficacy of surgical interventions, chemotherapy and	Results presented clearly: Yes Internally consistent: Yes Data suitable for analysis: Partly – unclear on the number of unique posters Clear description of the methods of analysis: Yes Appropriate methods: Yes Correctly performed/interpreted: Yes Method for calculating response rate: No Method for handling missing data Information on how non-respondents differ from respondents: No Results discussed in relation to existing knowledge: Yes Limitations of the study reported: Yes Can the results be generalised: No Attempts to establish reliability of validity: No Authors Conclusions: Yes

			radiation therapy protocols and alternative or complementary therapies such as Milk thistle/traditional chines medicine). People posting shared information concerning other relevant websites, books or personal experiences with various treatment options. Symptoms Posts around symptoms included inquiries about what a symptom 'means', how it relates to prognosis, and how it is treated. Inquiries about symptoms such as pain, nausea, anorexia and jaundice generally occurred at the time of initial diagnosis while symptoms such as anasarca, ascites, or thromboembolic events were consistent with evidence of disease progression. The most commonly reported symptom was pain. Other Limited or unclear understanding of the disease, the staging process and implications of prognosis was evident from a number of postings. Some postings commented on recent changes in symptoms such as lower extremity swelling, ascites or increased or unrelenting pain and asked related questions about survival or a loved one's proximity to death. Information about palliative care, hospice and end of life symptoms were commonly reported. Similarly information about specific symptoms such as weight loss, edema, ascites and pain were commonly reported.	

			A worsening of symptoms prompted requests for information or support about what and how to provide relief and to improve the patient's quality of life. Many postings demonstrated a lack of information or knowledge about common symptoms associated with disease progression and the physical appearance of a loved at the end of life. Theme 2: Support: Seeking, giving or both Support was defined as any posting that gave and/or sought social, emotional, spiritual or physical assistance Social and spiritual Many postings offered or requested emotional or spiritual support for dealing with the shock of the diagnosis Feelings of confusion, anger, sadness and hopelessness related to a loved one's diagnosis of terminal cancer were expressed and some posters requested advice on how others were coping with similar situations. Some posters looked for advice on how to communicate with a loved one with cancer so as not to diminish their hope and will to survive. Physical Requests were made for information around monetary issues related to specific treatment regimens particularly pharmacotherapeutics. Theme 3: Reporting Reporting was defined as a posting that provided details about the status of the person with pancreatic cancer including	

			postings announcing the death of a friend or loved one. Status Participants in the chat rooms updated each other about a loved one's current status including disease progress or changes in condition. There were some inquiries requesting feedback from people with similar experiences. Death Postings about the death of a loved one generally followed a break In chat room participation. Participants would report and summarise the final days/hours, reflect on the entire process, and offer encouragement and support to those still battling cancer.	
D'Angelica M. (1998) Surgeon-patient communication in the treatment of pancreatic cancer Arch Surg 133;962-966 Aims: To assess the quality of long and short term surgeon-patient communication and to assess the role of the surgeon in the emotional support of patients with pancreatic cancer	N=48 patients who underwent pancreatic resection between January 1994 and September 1996	A questionnaire consisting of 4 sections (1. demographics, pain and mood assessment; 2. preparation for surgery, 3. operation and 4. emotional support) Mailed to patients and followed up by telephone where the survey was reviewed and answers recorded.	Study Period = 34 months N=134 patients undergoing pancreatic resection N=35 died before the survey N=21 too ill to be surveyed N=2 from foreign countries N=76 surveys mailed out N=7 (9%) further deaths or too ill to participate N=69 remaining eligible surveys N=17 (24%) refused to participate N=4 (6%) did not respond Response Rate=70% Mean time from operation to survey was approximately 13 months (range 3-13 months). Preparation for surgery	Clear Aims: Yes Clear & appropriate design: Yes Clear description of context: Yes Existing tools used: No, a questionnaire was developed for the purposes of the study Clear Description of survey population and time frame: Yes Representative population: Unclear, 134 patients were eligible however only patients well enough and giving consent, were interviewed.

Setting: Urban tertiary cancer referral centre Country: USA			Most patients were informed of their diagnosis prior to meeting their surgeon. 73% (n=35) from their primary care physician 10% (n=5) from their surgeon Approximately 50% of patients recalled having the risks and benefits of an operation explained to them before meeting their surgeon. 94% of patients did not require more time with their surgeon following their initial meeting. This response was not significantly associated with sex, pain, current mood or time from operation to survey. Most patients recall spending more than 10 minutes with their surgeon. 8% (n=4) thought their initial meeting was less than 10 minutes. 69% (n=33) patients thought their initial meeting was longer than 20 minutes. 96% (n=46) used positive words such as patient, warm, understanding or supportive to describe the demeanour of their surgeon at the initial meeting. 38% (n=18) of patients were seen by a resident or fellow prior to meeting their attending surgeon and 67% found this to be a benefit. 92% (n=44) of patients recalled having no questions left unanswered following their initial meeting and the response was not significantly associated with sex, pain, current mood or time from operation to survey. 3 patients recalled having unanswered questions, though 2 of these could not specify the unanswered question.	Full spectrum of the population of interest: Unclear, 24% of patients refused consent, no details given as to why. Study large enough: Unclear, no sample size calculation All subjects accounted for: Yes All appropriate outcomes considered: Yes Ethical Approval: Yes Response Rate: 70% Clear what is being measured: Yes Valid Measurement: Yes Reliable Measurement: Yes Reproducible measurement: Yes Basic data adequately described: Yes Results presented clearly: Yes Internally consistent: Yes Data suitable for analysis: Yes Clear description of the methods of analysis: Yes Appropriate methods: Yes

			52% (n=25) of patients recalled wanting to know the chance for cure and 38% (n=18) asked their surgeon how long they were likely to survive. 83% of patients asking about survival were generally satisfied with the answer received. 60% (n=29) patients reported that they did not ask their surgeon about the likelihood of survival but 3 reported being told. 54% of patients though that, in retrospect, it is beneficial to know their prognosis. Information regarding the operation 85% (n=41) of respondents remembered their surgeon discussing the necessity and explanation of the surgical procedure. 69% (n=33) of respondents reported that the risks or the operation were explained to them and 25% (n=12) reported that other options were discussed. On a scale of 1-5 with 5 bing complete understanding, the mean understanding reported by patients was 4.7 regarding the explanation of their surgery. 83% (n=44) of patients had no unanswered questions regarding their operation before surgery and there was no significant associations with sex, pain, current mood or time from operation to survey. 54% (n=26) of patients reported wanting to have a detailed description of their operation and 71% (n=34) recalled having it explained to them. 38% (n=18) recalled having a videotape describing the disease and operation shown to them. Following surgery, 63% (n=30) of patients recalled having more than 5 discussions	Correctly performed/interpreted: Yes Method for calculating response rate: No Method for handling missing data: No Information on how non-respondents differ from respondents: No Results discussed in relation to existing knowledge: Yes Limitations of the study reported: Yes Can the results be generalised: No Attempts to establish reliability of validity: No Authors Conclusions: Justified

			with their attending surgeon while in hospital (on average patients recalled having approximately 5 discussions). 88% (n=42) patients had the results of their surgery discussed at least once while family or friends were present and all found this helpful and supportive. On discharge, 94% (n=45) of patients reported being satisfied that all their questions about their disease and operation had been answered satisfactorily. 21% (n=10) of patients reported an unexpected outcome of their surgery which had not been discussed prior to operation and of these 60% (n=6) involved long term medical problems such as diabetes or gastrointestinal complaints. 27% (n=13) of patients reported still having unanswered questions about their diagnosis and treatment and the time of survey and this response was significantly associated with being in pain ($p<0.05$). Of these patients, 69 % (n=9) had questions relating to medical follow up and/or treatment and 23% (n=3) had questions about prognosis. Provision of Emotional Support Approximately 50% of patients recalled their surgeon discussing their feelings both before and after operation. Recollection was not associated with sex, pain, current mood or time from operation to survey. 96% (n=46) of patients reported the surgeon looking them in the eye during discussions and finding this comforting. 81% reported the surgeon sitting while speaking to them and again fond this comforting.	

			69% recalled their surgeon using some form of physical contact (hand holding/hugs) and all found this a comfort. 75% (n=36) believed that the discussions were not emotionally difficult for the surgeon. In relation to how well emotional issues were addressed, on a scale of 1-10 (0 being the worst and 10 being the best) patients reported a mean score of 8±2.3 during hospitalisation and 8.2±3.2 after hospitalisation. 50% of patients reported needing no additional emotional support during hospitalisation and of the remaining respondents 33% reported their surgeon to be the person they would have liked to have received more emotional support from. Other choices included resident, psychologist, family, nurses and clergy. 67% (n=32) of patients reported no need for further emotional support after hospitalisation. Of the remainder, 38% (n=6) would have preferred more emotional support from their surgeon. Other sources of support mentioned included mental health professional, family, nurses and clergy.	
Grant M et al. (2015) Asking questions of a palliative care nurse practitioner on a pancreatic cancer website Palliative and Supportive Care 13:787-793	A convenience sample of particpants made up of anyone who used the website. Participants were recruited or direct to the website from notices on the JHKCC	Mixed methods descriptive design Eight domains from the National consensus project were used as a framework for the analysis including: Structure and process Physical Psychological Social Spiritual	The palliative care nurse practitioner (PCNP) site was interactive from Augusts 2011 until May 2012 (35 week study period). There were 2174 visits to the webpage (average was 62 visits per week). Approximately 25% (n=543) were repeat visits.	Clear Aims: Yes Clear & appropriate design: Yes Clear description of context: Yes Existing tools used: Partly – questionnaire and webpage developed as part of a pilot study.

Aims: to investigate how many people would visit a website when they could interact with a palliative care nurse practitioner, see how many would ask questions and the type of questions and obtain feedback on the usefulness of the webpage Setting: Tertiary care Country: USA	website, links from other JHKCC and Johns Hopkins pancreatic cancer websites or through internet searches.	Cultural Imminently dying Ethical and legal aspects of care 23 question survey was developed for the study and included 6 questions modified for pancreatic cancer form the Computer-mediated social network scale (CMSNS). Helpfulness questions used a four point Likert-type scale (1=not helpful, 4=very helpful)	Average time spent on the site was 5.03 minutes 83% of visits came from outside Maryland (location of the centre) and 23% originated from outside the USA. Questions to PCNP 84 participants sent questions to the PCNP. 43% were female relatives of those with pancreatic cancer 32% were people asking about their own health but who did not report a diagnosis of pancreatic cancer. 11% were patients with pancreatic cancer. 24 % sent multiple questions to the PCNP or posted/sent multiple comments 3% (n=2) posted a similar question both to the public PCNP webpage and in an e-mail. 110 question were sent to the PCNP with 59% sent via e-mail and 41% posted onto the public PCNP webpage. The rate of questions averaged 3.14 per week and only 2 (2%) were not approved (spam or inappropriate). 52.7% of questions related to palliative care issues with 23.2% relating to psychological issues specifically. Most involved anxiety about illness (14.3% of total) or concern for a familial risk of pancreatic cancer (7.1%). 18.8% of the total posted questions relating to physical aspects including issues like pain, gastrointestinal symptoms, postoperative complications and nutrition. 20.5% of questions/messages did not fall into any specific category. Some were expressions of thanks to the PCNP (8%) and updates on previously queried situation (7.1%).	Questionnaire contained elements of validated tools Clear Description of survey population and time frame: Yes Representative population: Unclear – convenience sample with few details though would appear to be mostly relatives rather than patients. Full spectrum of the population of interest: No Study large enough: Unclear All subjects accounted for: No All appropriate outcomes considered: Yes Ethical Approval: Yes Response Rate: Not applicable Clear what is being measured: Yes Valid Measurement: Yes Reliable Measurement: Yes Reproducible measurement: Yes Basic data adequately described: Yes

			6.3% of questions related to wanting a second opinion at Johns Hopkins and 5.3% of questions were enquiring about the availability of a vaccine for pancreatic cancer. Online Survey 39 participants completed the survey (57% completion rate) and respondents were predominantly female (87%), white (85%), older (59%) and highly educated (79%). 89.7% were living in the USA and 97.4% were living in English speaking countries. 44% were patients or individuals concerned about the own health and 52% were relatives of people with pancreatic cancer. 92.9% of respondents had come the PCNP webpage for the first time Only 22 people had had the chance to read the posts on the PCNP webpage before filling in the survey therefor they likely had limited knowledge of what was contained on the webpage. 13% (n=9) had asked the PCNP a question and 7 participants had received a response. 6/7 participants considered the response to be 'helpful' or 'very helpful' Among the 22 who had read the webpage, it was rated at: 3.3/4 for helping participants learn about physical symptoms/treatments of pancreatic cancer 3.1/4 for learning about emotional issues 3/4 for learning about palliative care 2.8/4 for learning about hospice 3.3/4 for reading other people's questions Responses to the modified CMSNS showed that use of social networks varied:	Results presented clearly: Yes Internally consistent: Unclear Data suitable for analysis: No – descriptive results only Clear description of the methods of analysis: Not applicable Appropriate methods: Not applicable Correctly performed/interpreted: Not applicable Method for calculating response rate: Not applicable Method for handling missing data: Not applicable Information on how non-respondents differ from respondents: Not applicable Results discussed in relation to existing knowledge: Yes Limitations of the study reported: Yes Can the results be generalised: Unclear Attempts to establish reliability of validity: No

			35.9% did not use them for gaining information on pancreatic cancer 25.7% used them daily 76.9% of participants did not contact people through online social media to ask for help or use internet chatrooms or discussion boards to get information on pancreatic cancer	Authors Conclusions: Justified
Petrin K et al. (2009) Adjusting to pancreatic cancer: perspectives from first-degree relatives Palliative and Supportive Care 7;281-288 Aims: To describe the experience of family members in communicating about and adjusting to a first degree relatives diagnosis of pancreatic cancer Setting: Tertiary Country: USA	The study classifies participants as cases, spouses/partners and first degree relatives. Inclusions: ≥18 years of age Never been diagnosed with cancer Sample included: 7 offspring 4 parents 11 siblings Nine interviewees had relatives deceased from pancreatic cancer and 11 had diagnosed relatives who were still living at the time of the interview.	Participants were recruited to the Cancer Genetics Network (CGN) from four population based centres. Cancer centres with registries used them to contact and enrol patients and their family members. In clinic based centres, physicians and other health care professionals directly referred patients.	Transcripts were reviewed and compared to capture larger themes emerging which was then arranged to form a coherent narrative. Feelings surrounding News of the Diagnosis Many participants reported initial shock and disbelief upon learning the news. This was often followed by a period of denial and devastation. This was followed by a sense of fear of the disease and what the future might bring “I think right after the diagnosis it was very difficult. It was a shock.” “My father and I had a close relationship and [the news] was devastating” “It was definitely emotional and very hard to take…[I was] feeling scared and upset and…I guess sad too.” Participants ascribed these feelings to other family members and all participants described pancreatic cancer as having a significant impact on their lives. Coping in the aftermath of the diagnosis Seeking information was one of the most commonly reported coping strategies. “I needed to get more information I think was the big thing. I needed to find out…so exactly what does this mean? How big is the tumour? What’s going on? You know,	Clear Aims: Yes Clear & appropriate design: Yes Clear description of context: Yes Existing tools used: Unclear, questionnaires used but no details on whether they were standard questionnaires with validated elements. Clear Description of survey population and time frame: Partly, the population are described but no details on the time frame for the study. Representative population: Yes Full spectrum of the population of interest: Yes – range of close family members included

			how did he know he was even sick? I mean, what was he feeling? You know, I just needed to know everything." Others were concerned about getting to grips with their family members prognosis and what could be expected in the months ahead. Participants described looking for information about survival, symptoms and treatments "I was in school and had access to PubMed…I [read] a lot of journal articles myself so I had kind of a good idea of what the research said about life expectancies and different treatments." Participants also reported focusing on the process of handling the illness, particularly with there was a feeling that things were happening quickly. "It was so far along when he was diagnosed. It was really hard. And it just kind of went – it was like a steam engine. You know, everything just went fast, fast, fast. You know, he was in the hospital and he had his treatments and he had his surgery and everything just went – seemed to go so fast." Family members felt responsible for helping the patient by taking care of scheduling and attending doctor's appointments and treatments. This seemed to help take one's mind off the emotional handling of the illness Other participants were concerned with managing their family member's illness. By focusing on everyday activities participants were able to manage the day to day aspects of the illness without confronting the larger issues.	Study large enough: Unclear, no sample size calculation All subjects accounted for: Unclear, no details provided All appropriate outcomes considered: Yes Ethical Approval: Yes Response Rate: Not reported Clear what is being measured: Yes Valid Measurement: Yes Reliable Measurement: Yes Reproducible measurement: Yes Basic data adequately described: YEs Results presented clearly: Yes Internally consistent: Unclear, no details provided Data suitable for analysis: No – narrative results presented Clear description of the methods of analysis: Not applicable Appropriate methods: Not applicable

			"No one really had time to stop and to pause to do any, you know, reflection…We'd have to keep going with all the medical appointments and surgery and treatment." Another theme which emerged was participants making more time for the ill relative (physical time or phone calls) "Just being with him was the big thing…just our normal stuff, had Saturday dinners and played games and watched movies and stuff. Just tried to make it as normal as possible. I tried to go see him more." "I try to get over there as much as possible to see [my father] so [we're] probably closer. Visit...a little more often. Make sure he's okay. And do a couple of things with the rest of the family that he used to do." Not being able to visit more often was a source of stress for some participants with one participant attributing her weight gain to the frustration of not being able to spend time with her ill sibling. "I attribute it to...I guess having a lot, you know, like being so far away and not being able to just drop in and see him whenever I want to and still going to work every day and coming home and being stressed out and eating and I also attribute it to the antidepressants." Participants often reported better relationships with their relative as a result of spending more time with them since their diagnosis. "We'll talk three or four times a months. Where 10 years ago it might be 6 months or 10 months you know between phone calls."	Correctly performed/interpreted: Not applicable Method for calculating response rate: No details Method for handling missing data: partly, some information reported in the methods section but nothing clear Information on how non-respondents differ from respondents: No Results discussed in relation to existing knowledge: Yes Limitations of the study reported: No Can the results be generalised: Unclear Attempts to establish reliability of validity: No Authors Conclusions: Possibly justified

			Coping with the diagnosis appeared to present challenges for participants and this was a time of significant strain in their lives. Stress stemmed from both the emotional and physical aspects of managing the illness. Addressing one's own feelings Participants confessed to having hidden their feelings during the time of crisis. This seemed to be a natural reaction to handling the situation rather than it being a conscious decision. Participants felt strongly that it was important to focus their energies on the relative with pancreatic cancer. "My life was rather hectic at the time. And I just – I just had too much to do and too much to think about to be – let myself be overwhelmed by grief or anything like that." "Sometimes you have to put aside you own feelings and emotions and…concentrate on the one that's sick and just be there for him." Support System There was variation in the degree to which participants felt they received information and support. Some participants reported communicating with family members including the ill relative "Kind of the nature of our family to – you can argue on the outside but when something's important you just kind of hang together and take care of it." Other participants sought to communicate with friends, particularly if they had similar experiences. Some participants also sough support through the church. "I have a strong faith and…I have a lot of good friends and…I have a lot of people	

			that stand behind me…I think I did okay, you know." A small number of participants sought professional therapy including counselling and, in one instance, a course of antidepressant therapy. "The counsellor just helped me kind of deal with the fact that, um, it's not something that's catchy, you know, that I don't have to sit around and keep myself from my children in bubbles in hopes that we don't get it." Some participants reported a lack of family communication or more formal support. "I felt like I couldn't open up and talk to [my husband] about it because…I don't think it was because he didn't want to hear it. I think he just didn't want to see me so upset." "There was no support system. A support group or any group or resources out there that would assist the family that can, you know, go through the process. Same way you feel like the only one going through it and have no provider that we can ask clear questions." Family Dynamics Participants described few changes in family dynamics post diagnosis. "How families deal with things is how they're going to deal with this. Kind of almost predetermined in their relationship [than it is something that's pancreatic specific, I guess." Close families tended to remain close, families with more distant relationships remained distant. Some participants coming from families that distant harboured some resentment as a	

			result of feeling burdened with caring for the ill family member. “I feel like, you know, there should be more of the share of the responsibility instead of myself running the whole show and dealing with it, emotionally and financially. So I feel there is a great sense of resentment.” The Future Many participants, particularly siblings and offspring, expressed concern about their own future health and that of their other family members. “I wonder what is the probability of me having cancer and going through this and fear of pain. And fear of, you know, if I, if this is genetic that it would pass down to my son.” “I spend more time taking care of myself, you know, having yearly check-ups and worrying about, you know, am I going to be the next one? Am I going to be able to finish raising my kids? Or am I going to see them reach adulthood? Am I going to be the one that gets and doesn’t live.” Participants reported making resolutions to positively change their behaviour such as quitting smoking, getting more exercise or eating a healthy diet. “My sister’s diagnosis made me take notice and do something I hadn’t been able to do in a long time. I smoked cigarettes for 40 years and I quit.” “I must say that maybe 2 years ago I was probably in the poorest physical condition that I’ve been in my life and I don’t think that’s necessarily true now. So I’ve been working hard on improving my own physical fitness and, again, who’s to say if, you	

			know, I didn't say, 'gee, my sisters got cancer. I've got to start looking after myself' but maybe it had something to do with it." Once participant however expressed the completed opposite as her brother had always been extremely health conscious. "It doesn't matter how you take care of your body." Some participants reported and new awareness of their own mortality and an appreciation for the value of their own lives. "I just don't put up with as much, you know. Life's too short. If I don't want to do something, I'm not going to do it. If I don't want to go somewhere, I'm not going to go." "Your family and friends and not going to be around forever so you better, you know, take what you got and enjoy it while you can." Almost all participants expressed concerns regarding the impact of a pancreatic cancer diagnosis would affect their futures. Some participants found it difficult to get over the death of family member. Family members of individuals who survived were concerned for the patient's health and their ability to cope with future events. "I know when the time comes, it's going to be bad for me."	
Schildmann J et al. (2013) 'One also needs and bit of trust in the doctor.' a qualitative interview study with pancreatic cancer patients about their perceptions and	Inclusions Diagnosis of pancreatic cancer At least one regimen of chemotherapy Sampling strategy	Semi structured face to face interviews A selection of transcripts were analysed by 3 or more researchers to gain a common understanding of the themes and enhance validity of results. Enrolment of participants and further data analysis was stopped following 'theoretical saturation'.	N=12 patients were interviewed Two stages of information and treatment decision making were identified relating to the perceptions and preferences of patients at earlier and later stages of their disease. Information and treatment decision making Stage 1: no choice and trust in the physician	Clear Aims: Yes Clear & appropriate design: Yes Clear description of context: Yes Existing tools used: Unclear, questionnaires used

views on information and treatment decision-making. Annals of Oncology 24:2444-2449 Aims: To explore pancreatic cancer patients perceptions and preferences on information and treatment decision making Setting: Single centre, Tertiary care/follow-up Country: Germany	Recruitment of consecutive patients treated in the in or out patients setting. The interviewer could designate characteristics which were deemed relevant for this research (purposive sampling)		All patients provided information on their preferences and perceptions. Regarding the early stage diagnosis and initial treatment decisions patients emphasised that the perceived no choice and having limited interest in the details of treatment related information but that trust in the physician was paramount: "I was told that this would be the only way to treat me, in this way. It does not work differently for me. […]Yes, and he said, 'You must do this' otherwise you won't live to see the next half year.'" "Did you want to know something specific about the operation?" "No, I placed my llife and my illness in the hands of the specialist and said you will do this right […]." "One also needs a bit of trust in the doctor or total trust in such a thing. I think if I trust a doctor then I would do what the doctor tells me. One must really have trust." Regarding place of treatment, patients mostly took the recommendations given by the physician or healthcare team who diagnosed the disease. Patients often consulted other people such as healthcare professionals in their own private circle or family physicians to discuss the recommendations. Patients expressed some specific criteria for their choices such as it being a 'cancer centre' or having a high volume of patients being treated for the same disease. "Yes, there where they do most of the operations. That was the most important thing. […] X actually had a very good reputation. And as the head physician told	but no details on whether they were standard questionnaires with validated elements. Clear Description of survey population and time frame: Partly, the population are described but no details on the time frame for the study. Representative population: Unclear Full spectrum of the population of interest: Unclear Study large enough: Yes – data are rich and theoretical saturation was achieved All subjects accounted for: Unclear, no details provided All appropriate outcomes considered: Yes Ethical Approval: Yes Response Rate: Not reported Clear what is being measured: Yes Valid Measurement: Yes Reliable Measurement: Yes

			me: Go to X, to Prof Y. You are in good hands there." Stage II: Information seeking in light of experiences with disease and treatment Patients emphasised the physical and psychosocial burdens they experienced during the course of their illness and how treatment affected their wellbeing. "Since we changed the therapy, I feel much better. The last therapy was unbearable. Mainly, I couldn't go out, I was freezing and trembling and saw so little of the outside." Some patients indicated taking on a more proactive role in the treatment decision making over the course of their illness including asking more questions or negotiating about treatment in light of priorities that were not health related. "But now I am going forward. Today I am asking until I know what I want to know. I am also now a bit further ahead." "During the operation, one abandons oneself, all parallel planning were put aside with the recovery, the desire to go into private planning again returns. And the schedule of the chemo, it competed with the holiday […]." Supportive measures were an area of interest for patients including information around complementary or alternative treatments. Patients sought information not only from physicians but also from family members, friends and other patients. "For example, Mr X […] who has the same story as I, we're talking intensively with each other about nutrition […]. I'm not so keen on	Reproducible measurement: Yes Basic data adequately described: Yes Results presented clearly: Yes Internally consistent: Unclear, no details provided Data suitable for analysis: Qualitative analysis – narrative results of the themes identified Clear description of the methods of analysis: Yes Appropriate methods: Yes Correctly performed/interpreted: Yes Method for calculating response rate: No details Method for handling missing data: No Information on how non-respondents differ from respondents: No Results discussed in relation to existing knowledge: Yes Limitations of the study reported: Yes Can the results be generalised: Unclear

			natural healing. It was never my cup of tea. But now I have a very different situation." Treatment at the end of life: Hope and challenges of anticipatory decision making All patients discussed the poor prognosis of pancreatic cancer and the threat to life. Spontaneous examples of family members or friends who had died in circumstances perceived to be overtreatment were provided. Patients identified that hope was an important driver in the decision to undergo further treatment and highlighted the difficulty in deciding when to stop cancer treatment. "Well I think one gets used to reality, but, as Schiller said: 'still on the grave, he plants on hope'." "[…] but I really couldn't say that's the limit now, at this point I don't want to go on anymore. Perhaps, only sometimes when I will get to the point where they say there is nothing more that can be done […]." When asked who should decide the limitation of cancer treatment in advanced disease, some patients referred to the physicians expertise and recommendations indicating they considered it to be a task of the physician like any other treatment decision "So, as it is at the moment, I plan to do everything that Dr X. says and I'm really doing it. Do I know what is good for me and how far do I have to go." Other patients however emphasised their right to make decisions about the limitation of treatment in advanced cancer. These patients based their views on the argument	Attempts to establish reliability of validity: Yes Authors Conclusions: justified

			that personal experiences with treatment and personal values relevant to treatment are outside the professional domain. "[…] well, so a chemo-patients who just went from chemotherapy to chemotherapy also becomes a specialist. […] And he drifts more and more into a life decision, a life situation, where he knows that he has to now take decisions and responsibility for himself and this can't be done by a doctor […]. That is another basis for decision-making."	
Sun V et al. (2016) Pilot study of an interdisciplinary supportive care planning intervention in pancreatic cancer Support Care Cancer 24:3417-3424 Aims: Pilot study to determine the feasibility of an interdisciplinary supportive care planning intervention in patients with pancreatic cancer Settings: Ambulatory clinics of one NCI designated comprehensive cancer centre Country: USA	N=10 patients Confirmed diagnosis of pancreatic cancer Enrolled within 6 months of diagnosis All stages/ resectability	Nurse completed comprehensive QoL assessments organised in physical, psychological, social and spiritual wellbeing domains. A care plan was completed by the nurse Nurse presented each patient at meetings attended by oncologists, representatives from supportive care services (pain specialists, palliative medicine, social work, chaplaincy, rehabilitation and nutrition) and the research team. The interdisciplinary team made care coordination and recommendations tailored to each patient's needs. Referrals to supportive care services were made as required. A second component involved educating patients on QoL concerns. Content for patient education sessions consisted of common disease and treatment related concerns for pancreatic cancer patients Baseline evaluation using self-reported outcome measures.	Over a four month period, 19 patients were invited to take part and 11 agreed to participate for a response rate of 58%. Reasons for declining included: Being too ill (78%) Too overwhelmed (22%) One patient discontinued study participation due to disease progression Overall patients reported high levels of social support but all patients reported at least one functional impairment in relation to activities of daily living at all three time points. Physical and psychosocial concerns were common. Pain, fatigue and overall treatment side effects were the most frequently discussed at interdisciplinary meetings. Common psychosocial concerns included anxiety, changes in appearance, feeling sad and the ability to work or undertake normal activities. Mean length of time for the physical/psychological patient education session was 44.2 mins. Most commonly	Clear Aims: Yes Clear & appropriate design: Yes Clear description of context: Yes Existing tools used: Yes Clear description of survey population and time frame: Yes Representative population: Unclear Full spectrum of the population of interest: Unclear Study large enough: Unclear, no sample size calculation All subjects accounted for: Yes All appropriate outcomes considered: Yes Ethical Approval: Yes Response Rate: 58%

		Patient reported outcome measures FACT-Hep was used to assess QoL and symptoms (45 items rated on a 5 point Likert scale with higher scores reflecting better QoL). Items are divided into physical, social/family, emotional and functional wellbeing domains. Healthcare utilisation was assessed through patient self-reporting use of cancer related services, hospital admissions and outpatient visits outside of the cancer centre setting. Financial burden and out of pocket medical costs were self-reported Patients completed a survey on satisfaction with the intervention on study completion.	discussed topics included pain/neuropathy (40%), constipation (20%) and lack of appetite/weight loss (20%). For the social/spiritual wellbeing session mean length of time was 32.6mins and the most commonly discussed topics included social support (40%), advance care planning (40%) and family needs (20%). Changes in QoL were detected across the 2 month study timeframe but they were not statistically significant. In relation to healthcare utilisation, referrals to social work, pain/palliative care team and nutrition were the most common. Unscheduled outpatient encounters for symptom management were at 30%. 70% of patients reported a decrease in household income since diagnosis. Out of pocket expenses included doctors' bills, medical supplies, prescription and over the counter medications. 70% of patients rated the overall intervention as 'excellent' and 30% rated it 'very good' indicating high satisfaction. 80% of patients though the time spent in the education sessions was the right amount however 70% of patients thought there was too much information in the written manuals.	Clear what is being measured: Yes Valid Measurement: Yes Reliable Measurement: Yes Reproducible measurement: Yes Basic data adequately described: Yes Results presented clearly: Yes Internally consistent: Yes Data suitable for analysis: Yes Clear description of the methods of analysis: Yes Appropriate methods: Yes Correctly performed/interpreted: Yes Method for calculating response rate: No details Method for handling missing data: No Information on how non-respondents differ from respondents: No Results discussed in relation to existing knowledge: Yes Limitations of the study reported: Yes

				Can the results be generalised: Unclear Attempts to establish reliability of validity: Unclear Authors Conclusions: justified
Uitdehaag M et al. (2015) Problems and needs in patients with incurable esophageal and pancreaticobiliary cancer Gastroenterology Nursing 38:1:42-54 Aims: to investigate which problems patients experience and how often care is expected for these problems to provide optimal professional care. Settings: Outpatient clinic Country: Netherlands	N=98 eligible patients N=57 agreed to take part Reasons for refusal were: questionnaire would be too burdensome to complete (n=22) Still hope for a cure (n=2) No reason (n=9) Response rate=63% Recruited between September 2005 and June 2006 N=33 pancreaticobilliary patients	Problems and Needs for Palliative Care questionnaire Consists of questions in 9 domains including activities of daily living, role performance, physical problems, loss of autonomy, social issues, healthcare providers and emotional, spiritual and financial issues. EORTC QLQ – PAN26	N=33 pancreatic cancer patients completed the questionnaires a median of 2 months after diagnosis and a median of 4 months before death. Experienced Problems Pancreatic patients rated 30/90 potential problems in the PNPC questionnaire and 'problematic' and these problems were distributed over all nine domains. 2 patients experienced less than 10 items as problematic 3 patients experienced more than 60 items as problematic. Fatigue was the primary problem of 88% of pancreatic patients, followed by fear of physical suffering (79%), metastases (73%), inability to continue usual activities (76%) and difficulties coping with the unpredictability of the future (73%). Disease specific problems Emotional problems were the most common problems for patients with pancreatic cancer including: Fear of future health (96%) Disability to plan the future (83%) Most common physical problems included: Dry mouth (79%) Changed bowel habits (79%) Expectation for professional care	Clear Aims: Yes Clear & appropriate design: Yes Clear description of context: Yes Existing tools used: Yes Clear description of survey population and time frame: Yes Representative population: Unclear Full spectrum of the population of interest: Unclear Study large enough: Unclear, no sample size calculation All subjects accounted for: Yes All appropriate outcomes considered: Yes Ethical Approval: Yes Response Rate: 63% Clear what is being measured: Yes Valid Measurement: Yes

			On average pancreatic cancer patients expected professional care for 22/90 items from the PNPC questionnaire: Pain (56%) Fear of physical suffering (56%) Fatigue (72%) Lack of appetite or change of taste (50%) Unmet needs Pancreatic patients reported inadequate professional care for: Their fear of physical suffering (34%) Lack of written information (28%) Fatigue (22%) No expectation for professional care Problems reported were not always highly in need for professionals care including: Employment/study Inability to continue usual activities Frustration that they can do less Dependency on others Reluctance to give tasks out of hands.	Reliable Measurement: Yes Reproducible measurement: Yes Basic data adequately described: Yes Results presented clearly: Yes Internally consistent: Yes Data suitable for analysis: Yes Clear description of the methods of analysis: Yes Appropriate methods: Yes Correctly performed/interpreted: Yes Method for calculating response rate: No details Method for handling missing data: No Information on how non-respondents differ from respondents: No Results discussed in relation to existing knowledge: Yes Limitations of the study reported: Yes Can the results be generalised: Unclear

				Attempts to establish reliability of validity: Unclear Authors Conclusions: justified

F.81 Pain

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Full citation Amr, Y. M.& Makharita, M. Y. Comparative study between 2 protocols for management of severe pain in patients with unresectable PC: one-year follow-up, The Clinical journal of pain, 29, 807-13, 2013 Ref ID 450153 Country/ies where the study was carried out: Egypt Study type: Randomised controlled trial (RCT) Aim of the study: To investigate the effect of controlling severe pain with medications and then	Sample size N=60 patients randomised in 2 groups Characteristics M/F=19/11 (G1); 20/10 (G2) Mean age (SD): 50(12) years -G1; 51(11) years -G2 Other: Duration of pain: 30± 16 days (group 1); 33± 12 days (group 2) Site of the pancreatic mass: 1) Head of the pancreas=21 (G1), 19 (G2); 2) Body and tail of the pancreas=9 (G1), 11 (G2) Inclusion criteria Patients had to have: nonresectable pancreatic adenocarcinoma that had been histologically proven or	Interventions G1: Early NCPB (NCPB was performed early after the first meeting and then analgesic requirements were managed according to the severity of the pain WHO analgesic ladder. G2: Late NCPB (Medical management (analgesic therapy) was given first according to the WHO analgesic ladder and the NCPB was performed later when they reported a VAS score <40). A pain physician was responsible for performing the NCPB immediately or after medical control of pain to a VAS score <40, who was then not involved in post-procedural follow-ups. NCPB: A single-needle	Details Design: Unblinded RCT Randomization method: not stated Setting: the study was conducted from March 2010 to March 2012 in the outpatient setting in pain relief units in anesthesia departments of 2 university teaching hospitals (Tanta University and Mansoura University Hospitals) in Egypt.	Results Reduction in opioid medication Pain Relief/ improved analgesia (pain scores) Adverse Events (Diarhoea, reduction in Opioid induced side effects)	Random sequence generation: Unclear risk (No details given in the text) Allocation concealment: Low risk Blinding of participants and personnel Assessments: Low risk Blinding of outcome assessment: Low risk Incomplete outcome data: Low risk Selective reporting: Unclear risk (no study protocol to permit judgement on this criterion) Other sources of bias: None

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
performing a celiac block and compared the results with those obtained by performing the celiac block first followed by pharmacotherapy for controlling severe pain Study dates: Data collection: March 2010 to March 2012 Source of funding: No reported	radiologically consistent 9 a VAS score >=70 on 400 mg tramadol and 4000 mg paracetamol daily. Patients with continuous or intermittent visceral pain localized to the upper abdomen, epigastrium, or to the right or left hypocondrium, radiating to the back, and frequently accentuated by palpitation and described as deep not superficial were included in the study Exclusion criteria Patients with coagulopathy, international normalized ratio>1.5, platelet count <50,000, local infection at the area of needle insertion, severe hypotension, or decompensated cardiac disorders. Patients who developed side effects against opioids and	transaortic approach was used (40 mL of 70% alcohol with 5 mL of 1% lidocaine was injected) Duration: One year			

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
	who could not tolerate a dose escalation needed to attain an analgesic effect, those with documented metastatic lesions including para-aortic lymph nodes, and patients who had undergone neurolytic blocks previously that could affect PC–related pain or had psychiatric illness affecting cooperation and assessments were excluded from the study. Patients were excluded from the study at any stage if they developed another characteristic of pain such as somatic pain (localized, superficial sharp pain accentuated by palpitation of intercostal spaces).				
Full citation Arcidiacono Paolo, G., Calori, G., Carrara, S., McNicol Ewan, D. & Testoni	Sample size This review includes 6 RCTs: Lillemoe et al. 1993	Interventions Where possible data was extracted from the Cochrane SR. The full copy of the study was	Details Details Where possible data was extracted from the Cochrane SR. The full	Results Where possible data was extracted from the Cochrane SR. The full copy of the study was	Lillemoe et al. 1993 Random sequence generation: Unclear risk (No details given in the text)

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Pier, A. Coeliac plexus block for PC pain in adults, Cochrane Database of Systematic Reviews, 2011 Ref ID 450164 Country/ies where the study was carried out: Italy, USA, Japan and China Study type: Systematic review with meta-analysis (Cochrane review) Aim of the study: To determine the efficacy and safety of CPB in reducing PC pain, and to identify adverse effects and differences in efficacy between the various techniques employed. Additionally, to compare the minimally invasive techniques for CPB (EUS-, CT-, fluoroscopy-guided) with conventional medical therapy.	Mercadante et al. 1993 Polati et al. 1998 Kawamata et al. 1996 Wong et al. 2004 Zhang et al. 2008 Characteristics Where possible data was extracted from the Cochrane SR. The full copy of the study was checked for accuracy and completeness. Lillemoe et al. 1993 N=137; M/F = 76/54; Mean age: 59 Inclusion criteria: unresectable, histologically proven PC Exclusion criteria: periampullary tumour; benign inflammation Mercadante et al. 1993 N=20; M/F = 11/9; Mean age: 62.3 Inclusion criteria: severe pain; palliative care unit Exclusion criteria: not stated Polati et al. 1998	checked for accuracy and completeness. Lillemoe et al. 1993 G1-Intervention Vs G2-comparison: NCPB (chemical splanchnicectomy - Intraoperative bilateral 20 mL 50% ethanol) versus analgesic therapy (NSAID, morphine). All patients underwent surgical exploration with biopsy of the tumour and palliative biliary or gastrointestinal bypass. Chemical splanchnicectomy was performed by the operating surgeon by the injection of 20 ml of either 50% alcohol or saline solution each side of the aorta at the level of the celiac axis using a 20 or 22 G spinal needle. Duration: Till death Mercadante et al. 1993 G1-Intervention Vs G2-comparison: NCPB (X-ray posterior bilateral 25 ml 75% alcohol) versus analgesic therapy	copy of the study was checked for accuracy and completeness. Lillemoe et al. 1993 Design: Double blinded RCT Randomization method: not stated Setting: Mercadante et al. 1993 Design: Unblinded RCT Randomization method: not stated Setting: Polati et al. 1998 Design: Double blinded RCT Randomization method: not stated Setting: Kawamata et al. 1996 Design: Unblinded RCT Randomization method: not stated Setting: Wong et al. 2004 Design: Double blinded RCT Randomization method: Central telephone number Blocks of 4 Setting: Zhang et al. 2008	checked for accuracy and completeness.* Lillemoe et al. 1993 Pain Relief (VAS pain scores Overall survival*: NO HR Mercadante et al. 1993 Pain Relief (VAS pain scores) Polati et al. 1998 Reduction in opioid medication* Pain Relief (VAS pain scores) Adverse Events (Diarhoea, reduction in Opioid induced side effects) Overall survival* Kawamata et al. 1996 Reduction in opioid medication* Pain Relief (VAS pain scores) Duration of effect/ duration of relief Adverse Events (Diarhoea, reduction in Opioid induced side effects)* HRQoL (functional domains) Wong et al. 2004	Allocation concealment: Unclear risk (No details given in the text) Blinding of participants and personnel Assessments: Low risk Blinding of outcome assessment: Low risk Incomplete outcome data: Low risk Selective reporting: high risk (some outcomes of interest [e.g. Overall survival rate] are reported incompletely) Other sources of bias: None detected Mercadante et al. 1993 Random sequence generation: Unclear risk (No details given in the text) Allocation concealment: Unclear risk (No details given in the text) Blinding of participants and personnel Assessments: Low risk (No blinding, but the outcome and the outcome measurement are not likely to be influenced) Blinding of outcome assessment: high risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Study dates: Searches up to December 2010. Source of funding: No reported	N=24; M/F = 17/7; Mean age: 58.5 Inclusion criteria: unresectable, histologically proven cancer. Outpatient pain centre Exclusion criteria: not stated Kawamata et al. 1996 N=21; M/F=9/12; Mean age age: 62.3 Inclusion criteria: severe pain; palliative care unit Exclusion criteria: not stated. Wong et al. 2004 N=100; M/F = 53/47; Mean age: 63 Inclusion criteria: histologically proven or radiologically consistent unresectable cancer; Mayo Pain Clinic; palliative surgery allowed; VAS > 3 or opioids required and VAS < 6	(NSAID, morphine - saline). Duration: Till death Polati et al. 1998 G1-Intervention Vs G2-comparison: (Fluoroscopy posterior bilateral 7 mL 100% ethanol) versus analgesic therapy (NSAID, morphine). Duration: Till death Kawamata et al. 1996 G1-Intervention Vs G2-comparison: NCPB (X-ray posterior bilateral 15 to 20 ml 80% ethanol) versus analgesic therapy (NSAID, morphine) Duration: Ten weeks Wong et al. 2004 G1-Intervention Vs G2-comparison: NCPB (Fluoroscopy posterior bilateral 10 mL 100% ethanol) versus analgesic therapy (NSAID, morphine). Duration: 24 weeks Zhang et al. 2008 G1-Intervention Vs G2-comparison: NCPB (CT-guided posterior bilateral block with 20 ml	Design: Outcome assessors blinded RCT Randomization method: not stated Setting:	Reduction in opioid medication* Pain Relief (VAS pain scores) Adverse Events (Diarhoea, reduction in Opioid induced side effects)* HRQoL (functional domains)* Overall survival* Zhang et al. 2008 Reduction in opioid medication* Pain Relief (VAS pain scores) HRQoL (functional domains)	(outcome assessors were no blinded) Incomplete outcome data: Low risk Selective reporting: Unclear risk (no study protocol to permit judgement on this criterion) Other sources of bias: None detected Polati et al. 1998 Random sequence generation: Unclear risk (No details given in the text) Allocation concealment: Unclear risk (No details given in the text) Blinding of participants and personnel Assessments: Low risk (No blinding, but the outcome and the outcome measurement are not likely to be influenced) Blinding of outcome assessment: Low risk Incomplete outcome data: Low risk Selective reporting: Unclear risk (no study protocol to permit

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
	Exclusion criteria: epidural or intrathecal analgesia Zhang et al. 2008 N=56; M/F = 35/31; Mean age: 58 Inclusion criteria: unresectable, histologically proven cancer Exclusion criteria: previous neurolytic celiac plexus block; psychiatric disease that could have affected the study assessments Inclusion criteria Exclusion criteria	100% ethanol) versus analgesic therapy (MS Contin - oral controlled-release morphine) Duration: 3 months			judgement on this criterion) Other sources of bias: None detected Kawamata et al. 1996 Random sequence generation: Unclear risk (No details given in the text) Allocation concealment: Unclear risk (No details given in the text) Blinding of participants and personnel Assessments: Low risk (No blinding, but the outcome and the outcome measurement are not likely to be influenced) Blinding of outcome assessment: High risk (outcome assessors were no blinded) Incomplete outcome data: unclear risk (insufficient reporting of attritions/exclusions) Selective reporting: high risk (some outcomes of interest [QOL, Pain scores, analgesic use are reported incompletely)

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
					Other sources of bias: None detected Wong et al. 2004 Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel Assessments: Low risk (No blinding, but the outcome and the outcome measurement are not likely to be influenced) Blinding of outcome assessment: Low risk Incomplete outcome data: low risk (no missing data) Selective reporting: Unclear risk (no study protocol to permit judgement on this criterion) Other sources of bias: None detected Zhang et al. 2008 Random sequence generation: Unclear risk (No details given in the text) Allocation concealment: Unclear risk (No details given in the text)

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
					Blinding of participants and personnel Assessments: Low risk (No blinding, but the outcome and the outcome measurement are not likely to be influenced) Blinding of outcome assessment: Low risk Incomplete outcome data: high risk (reason for missing data [n=10 of 46] likely to be related to the true outcome, to affect the balance across intervention groups) Selective reporting: Unclear risk (no study protocol to permit judgement on this criterion) Other sources of bias: None detected
Full citation Suleyman Ozyalcin, N., Talu, G. K, Camlica, H., Erdine, S. Efficacy of coeliac plexus and splanchnic nerve blockades in body and tail located PC pain, European	Sample size N=39 patients randomised randomised in 2 groups (G1 - G2) Characteristics M/F= 14/5 (G1); 12/8 (G2)	Interventions G1: NCPB (performed by transaortic techniques by injecting 40 mL of ethanol approx. 75% -30 ml of ethanol 96%+10 ml of lidocaine 10 mg/ml) G2: SNB (Splanchnic nerves neurolytic blockade – 6 ml of	Details Design: Outcomes' assessor blinded RCT Randomization method: Random numbers Setting:	Results Reduction in opioid medication Pain Relief/ improved analgesia (pain scores) Overall survival	Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel Assessments: Low risk (No blinding, but the outcome and the outcome measurement

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Journal of PainEur J Pain, 8, 539-45, 2004 Ref ID 450271 Country/ies where the study was carried out: Turkey Study type: Randomised controlled trial (RCT) Aim of the study: To compare the efficacy, side effects and QOL-effects of NCPB and splanchnic neurolytic blockade (SNB) in pain due to body and tail located PC Study dates: Data collection: September 1999 and May 2001 Source of funding: No reported	Mean age: 57 +-7 years (G1); 61 +-8 years (G2) Other: Accompanying symptoms= Jaundice;, weight loss, Nausea–vomiting (in both groups) Inclusion criteria Patients diagnosed as adenocarcinoma of pancreas, located on tail and/or body admitted to the Algology Department of Medical Faculty of Istanbul between dates September 1999 and May 2001, with no accompanying chronic pain condition. Exclusion criteria Not stated	ethanol approx. 75% solution -4.5 ml ethanol 96% + 1.5 ml of lidocaine 10 mg/ml -was administered bilaterally - a total of 12 ml) Duration: 18 weeks			are not likely to be influenced) Blinding of outcome assessment: Low risk Incomplete outcome data: unclear risk (insufficient reporting of attritions/exclusions) Selective reporting: high risk (some outcomes of interest [Pain score and analgesic use overtime] are reported incompletely) Other sources of bias: None
Full citation LeBlanc, J. K., Al-Haddad, M., McHenry, L., Sherman, S., Juan, M., McGreevy, K., Johnson, C., Howard, T. J.,	Sample size N=50 patients randomised in 2 groups (G1-G2) Characteristics M/F=24/26 (G1-G2) Mean age: 63 years (G1-G2); 63.2 +-11.9	Interventions G1: EUS-NCPB (1 injections) G2: EUS-NCPB (2 injections) All patients received the same amount of medication (20 mL	Details Design: Single (patients) blinded RCT Randomization method: Random table without stratification or blocking. Setting:	Results Reduction in pain medication Pain Relief/ improved analgesia (pain scores)	Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel Assessments: Low risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Lillemoe, K. D., DeWitt, J. A prospective, randomised study of EUS-guided celiac plexus neurolysis for PC: one injection or two?, Gastrointestinal endoscopy, 74, 1300-7, 2011 Ref ID 450365 Country/ies where the study was carried out: USA Study type: Randomised controlled trial (RCT) Aim of the study: To compare pain relief and safety of alcohol given as 1 versus 2 injections during EUS-guided CPN (EUS-CPN) in patients with PC–related pain. Study dates: Data collection: December 2002 to September 2008 Source of funding: None	years (G1); 62.4+-11.1 years (G2) Other: Location of tumor in pancreas: Head, N=20; Body, N=19; Tail, N=2; Uncinate, N= 3 Neck, N=1; Multiple (neck/body/tail), N=5. Inclusion criteria Patients with known or suspected PC–related pain secondary to PC Exclusion criteria Patients were excluded if they had an implanted pain-relieving device or an arterial aneurysm of the upper abdomen.	0.75% bupivacaine and 10 mL 98% alcohol). In the G1, the medication was injected into the base of the celiac trunk at its origin from the aorta. In the G2, half of the medication was injected into both sides of the celiac trunk Duration: not clear			Blinding of outcome assessment: unclear risk (no information reported on blinding of outcome assessors) Incomplete outcome data: unclear risk (insufficient reporting of attritions/exclusions) Selective reporting: high risk (All outcomes of interest [Pain score and analgesic use overtime] are reported completely, but no details about the time frame of the outcome measurement) Other sources of bias: None

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Full citation Wyse, J. M., Carone, M., Paquin, S. C., Usatii, M., Sahai, A. V. Randomised, double-blind, controlled trial of early endoscopic ultrasound-guided celiac plexus neurolysis to prevent pain progression in patients with newly diagnosed, painful, inoperable PC, Journal of Clinical OncologyJ Clin Oncol, 29, 3541-6, 2011 Ref ID 450479 Country/ies where the study was carried out: Canada Study type: Randomised controlled trial (RCT) Aim of the study: To test the hypothesis that, as compared with conventional pain management with narcotics alone, early	Sample size N=96 patients randomised in 2 groups (G1-G2) Characteristics M/F=21/28 (G1), 26/23 (G2) Mean age (SD): 66.5 (10.0)–G1; 66.6(9.3)–G2; Other: Pain history weeks=9.6-G1; 8.6-G2 Inclusion criteria 18 years or older referred for EUS for diagnosis and staging of suspected PC. Suspected PC and any new-onset pain considered to be cancer-related (centrally located, constant, with no other obvious cause) Exclusion criteria Exclusion criteria were an allergy to bupivacaine, possible future surgical management of the tumour, expected survival less than 3 months (suspected or proven carcinomatosis and/or liver	Interventions G1: conventional pain management G2: EUS guided-NCPB In patients assigned to G2, the technique was performed immediately using a 19-gauge needle (Echotip 19, Cook Medical, Winston-Salem, NC) with bilateral injection around the celiac axis with a total of 10 mL of 0.5% bupivacaine and 20 mL of 100% alcohol. Beyond 1 month after randomization, patients were permitted to undergo open-label EUS-CPN at the discretion of their referring physician Duration: 3 months	Details Design: Double blinded RCT Randomization method: Computer-generated number sequence Setting:	Results Reduction in opioid medication Pain Relief/ improved analgesia (pain scores)	Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel Assessments: Low risk Blinding of outcome assessment: Low risk Incomplete outcome data: Low risk Selective reporting: Unclear risk (no study protocol to permit judgement on this criterion) Other sources of bias: Contamination bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
EUS-CPN would prevent progression of pain and narcotic use in patients with painful, inoperable PC. Study dates: Data collection: April 2006 to December 2008 Source of funding: Centre hospitalier de l'Université de Montréal (CHUM)	metastases), and inability or unwillingness to provide informed consent.				
Full citation Johnson, C. D., Berry, D. P., Harris, S., Pickering, R. M., Davis, C., George, S., Imrie, C. W., Neoptolemos, J. P., Sutton, R. An open randomised comparison of clinical effectiveness of protocol-driven opioid analgesia, celiac plexus block or thoracoscopic splanchnicectomy for pain management in patients with pancreatic and other abdominal malignancies, Pancreatology	Sample size N=65 patients (58 with PC) were randomised (18 withdrew) in 3 groups: G1: MM, n=24 G2: MM + NCPB n=20 G3: MM +TS, n=21 Characteristics M/F: G1=16/8; G2=10/10; G3=6/15; Mean age (SD): G1=65.5(9.1); G2=60.5(9.2); G3=60.2(9.3); Site of primary cancer: 1) Pancreas=21(G1), 19(G2), 18(G3); 2) Other=3(G1), 1(G2), 3(G3)	Interventions G1: MM – medical management (oral morphine-or other opioid- was prescribed according to standard practice at each centre) G2: MM + NCPB (injection of a neurolytic agent -usually alcohol- in two sites adjacent to the celiac trunk, aorta and vertebral bodies to achieve bilateral destruction of the celiac plexus and/or splanchnic nerves) G3: MM + thoracoscopic splanchnicectomy-TS (patient positioned prone under general anaesthesia with a	Details Design: Open RCT Randomization method: By blocks of 3 stratified by treatment centre, tumour type and by current opioid status Setting:	Results Pain Relief/ improved analgesia (pain scores)	Random sequence generation: Low risk Allocation concealment: Unclear risk (No details given in the text) Blinding of participants and personnel Assessments: Low risk (No blinding, but the outcome and the outcome measurement are not likely to be influenced) Blinding of outcome assessment: High risk (no blinding of outcome assessors) Incomplete outcome data: unclear risk (the proportion of missing outcomes compared

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Pancreatology, 9, 755-63, 2009 Ref ID 450718 Country/ies where the study was carried out: UK Study type: Randomised controlled trial (RCT) - Multicentre study Aim of the study: To assess celiac plexus block (CPB) and thoracoscopic splanchnicectomy (TS) in patients receiving appropriate medical management (MM) Study dates: Data collection: 2005 Source of funding: Health Technology Assessment Programme reference 97/09/53.	Inclusion criteria clinical, radiological or histological evidence of irresectable primary or secondary malignancy in the upper abdominal viscera (pancreas, stomach, oesophagus, duodenum, bile duct or gallbladder, or hepatic metastases of any origin), including recurrence after resection of a primary tumour, and if they had pain requiring any opioid medication at least once per day. irresectable pancreatic and gastric cancer before the onset of abdominal pain (which usually develops in this group) Exclusion criteria Patients were excluded if they had any previous thoracic surgery or history of pulmonary tuberculosis or other intrathoracic inflammatory conditions likely to cause extensive	single lumen endotracheal tube, and partial lung collapse induced by pneumothorax) Duration: 2 months			with observed event risk/effect size might induce relevant bias in intervention effects estimates) Selective reporting: Low risk Other sources of bias: None detected

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
	adhesions, if they were unfit for general anaesthesia or if they had advanced disease with anticipated life expectancy less than 1 month				
Full citation Gao, L., Yang, Y. J., Xu, H. Y., Zhou, J., Hong, H., Wang, Y. L., Li, D. C. A randomised clinical trial of nerve block to manage end-stage PCous pain, Tumour BiologyTumour Biol, 35, 2297-301, 2014 Ref ID 450873 Country/ies where the study was carried out: China Study type: Randomised controlled trial (RCT) Aim of the study: To evaluate the effectiveness of standard pain medication with or without celiac plexus nerve block Study dates:	Sample size N=100 patients randomised in 2 groups: G1: NCPB + pain medication, n=68 G2: Sham procedure (pain medication alone), n=32 Characteristics M/F= not stated Mean age: 65.5 (10.2)-G1; 66.6(9.9)-G2 Other: Mean pain score at baseline: 7.5 (0.4)-G1, 7.4(0.5)-G2; Pain duration a day (hr): 14.6 (0.3)-G1; 14.3(0.5)–G2. Inclusion criteria patients of 18 and older; male or female; with unresectable or inoperable carcinoma of the pancreas as determined by CT or	Interventions G1: NCPB + pain medication (EUS-NCPB was carried out using a 19-gauge needle injecting 10 mL 100% alcohol + 5 mL 0.5% bupivacaine on each side of the celiac takeoff) G2: Sham procedure (pain medication alone: same medication [analgesic therapy] injected into gastric lumen) Duration:	Details Design: Blinded RCT Randomization method: not stated Setting:	Reduction in opioid medication Pain Relief/ improved analgesia (pain scores) HRQoL (functional domains) PROMS	Random sequence generation: Unclear risk (No details given in the text) Allocation concealment: Unclear risk (No details given in the text) Blinding of participants and personnel Assessments: Low risk (No blinding, but the outcome and the outcome measurement are not likely to be influenced) Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: unclear risk (insufficient reporting of attritions/exclusions) Selective reporting: Unclear risk (no study protocol to permit judgement on this criterion)

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Data collection: not reported Source of funding: The present study was supported by the Post-Graduate Scientific Research Innovation Project of Education Department of Jiangsu Province (CXZZ12_0842), China	endoscopic ultrasound (EUS); staging as determined per 2010 AJCC staging manual [18]; presence of mid-abdominal pain (3 on VAS scale) at least 2 days per week [19], lasting at least 1 h per day; no known coagulopathy as measured by prothrombin time (INR) 1.5; platelets are ≥50,000; and with life expectancy at >3 months Exclusion criteria Exclusion criteria were unable to sign the informed consent, patients with previous blocks, and patients with chronic pancreatitis.				Other sources of bias: None

1

F.92 Nutritional Interventions

Study details	Participants	Interventions	Methods	Outcomes	Comments
Full citation	Sample size	Interventions	Design: Un-blinded RCT	Overall Survival at median follow up of 18 months	Limitations

Study details	Participants	Interventions	Methods	Outcomes	Comments
Brennan, M. F., Pisters, P. W., Posner, M., Quesada, O., Shike, M. A prospective randomized trial of Parenteral nutrition after major pancreatic resection for malignancy, Annals of Surgery, 220, 436-41; discussion 441-4, 1994 Ref ID 452934 Country/ies where the study was carried out: USA Study type: RCT Aim of the study: To analyse the impact of adjuvant Parenteral nutrition (PN) after major resection for pancreatic cancer Study dates: Publication date: 1994 Data collection/patients enrolment: 1988-1993	N=117 patients with PC after surgery* Characteristics M/F (n): 34/26 (G1); 27/29 (G2) Median age (range): 65 (34-86) years (G1); 63 (30-86) years (G2) *Surgical procedure: Pancreaticoduodenectomy: n=110 Distal pancreatectomy: n=3 Total pancreatectomy: n=4 Inclusion criteria No details reported Exclusion criteria Patients with: No details reported	G1: Parenteral nutrition (n=60) - The PN formula employed was designed to deliver 1 g of protein/kg/day modified as required for renal or hepatic dysfunction G2: no intervention (n=57) - standard dextrose-containing salt solutions were administered until postoperative intake exceeded 1000 kcal/day. The PN treatment began on the first postoperative day, and continued until oral intake exceeded 1000 kcal/day and was administered by a dedicated nutrition service	Randomization method: not stated Duration: not stated	Treatment related morbidity Major complications Minor complications Overall complications	Random sequence generation: Unclear risk (No details given in the text) Allocation concealment: Unclear risk (No details given in the text) Blinding of participants and personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: Unclear risk (No details given in the text) Selective reporting: Unclear risk (no study protocol to permit judgement on this criterion) Other sources of bias: high risk of contamination bias (“ten control patients that crossed over to PN... [G1]” from the control group [G1]) Other information

Study details	Participants	Interventions	Methods	Outcomes	Comments
Source of funding: This study was supported by the Lawrence M. Gelb Foundation.					
Full citation Bruno, M. J., Haverkort, E. B., Tijssen, G. P., Tytgat, G. N., van Leeuwen, D. J., Placebo controlled trial of enteric coated pancreatin microsphere treatment in patients with unresectable cancer of the pancreatic head region, Gut, 42, 92-6, 1998 Ref ID 471845 Country/ies where the study was carried out: The Netherlands Study type: RCT Aim of the study: To assess the role of pancreatic enzyme replacement therapy (PERT) in combination with dietary counselling in	Sample size N=24 patients with unresectable PC M/F (n): xx/xx (G1); 4/6 (G2) Mean age (SD): 73 (11) years (G1); 79 (9) years (G2) Type of cancer: Pancreatic cancer: n=19 Distal common bile duct carcinoma: n=1 Ampullary carcinoma: n=1 Inclusion criteria Patients with: clinical presentation (medical history, physical examination, and information from imaging studies) compatible with cancer of the pancreatic head region obstruction of the common bile duct proven by endoscopic retrograde	Interventions G1: Pancreatic enzyme therapy (n=11) - Panzytrat 25 000 (Nordmark GmbH, Uetersen, Germany), an enteric coated pancreatin microsphere preparation containing 25 000 PhEur units of lipase, 1250 PhEur units of proteases, and 22 500 PhEur units of amylase per capsule. G2: Placebo (n=10) - placebo matched the active drug in appearance, taste, and weight and contained pharmacologically inactive substances Patients used two capsules during main meals and one capsule during in between snacks. Capsules were swallowed whole.	Design: Double blinded RCT Randomization method: not stated Duration: 8 weeks	Nutritional status at 8 weeks follow-up Change in body weight (%) Change in body weight (KG) Daily dietary intake of total calories (MJ)	Limitations Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel Assessments: Low risk Blinding of outcome assessment: Low risk Incomplete outcome data: Low risk (3 patients were not available for analysis, but the true outcome and the outcome measurement of the trial are not likely to be influenced) Selective reporting: Unclear risk (no study protocol to permit judgement on this criterion) Other sources of bias: Low risk (None detected) Other information

Study details	Participants	Interventions	Methods	Outcomes	Comments
reducing/preventing weight loss in patients with unresectable PC with occlusion of the pancreatic duct. Study dates: Publication date: 1998 Data collection/patients enrolment: 1993-1994 Source of funding: This study was supported financially by Knoll BV, Amsterdam, The Netherlands.	cholangiopancreaticography; obstruction of the pancreatic duct with less than 2 cm filling of the distal duct, or no filling despite multiple attempts not eligible for resectional surgery because of poor general condition, local unresectability, or advanced disease with metastases a patent biliary endoprosthesis at trial entry as assessed by medical history, physical examination and blood samples and a Karnofsky performance status greater than 60. Exclusion criteria Patients with: history of major gastrointestinal surgery history of chronic gastrointestinal disease (for example, coeliac disease, Crohn's disease) coexistent other primary malignancy				

Study details	Participants	Interventions	Methods	Outcomes	Comments
	radiotherapeutic or cytostatic treatment; and any use of antacids, mucosal protective agents				
Full citation Fearon, K. C., Von Meyenfeldt, M. F., Moses, A. G., Van Geenen, R., Roy, A., Gouma, D. J., Giacosa, A., Van Gossum, A., Bauer, J., Barber, M. D., Aaronson, N. K., Voss, A. C., Tisdale, M. J. Effect of a protein and energy dense N-3 fatty acid enriched oral supplement on loss of weight and lean tissue in cancer cachexia: a randomised double blind trial, Gut, 52, 1479-86, 2003 Ref ID 471921 Country/ies where the study was carried out: International multicentre study involving 12 centres across six Countries: UK, Italy,	Sample size N=200 losing weight patients with unresectable PC Characteristics M/F (n): 54/41 (G1); 56/49 (G2) Mean age (SEM): 67 (1) years (G1); 68 (1) years (G2) Other: % weight loss from usual weight, mean (SEM): 17.9 (0.9) (n = 88 –G1); 17.1 (0.8) (n = 97- G2) Pancreatic enzyme supplementation, mean (SEM): 30 (32%) G1; 29 (28%) G2 Inclusion criteria Patients with: Unresectable PC histologically proven or a firm radiological or operative diagnosis of PC when had lost more than 5% of their pre-illness	Interventions G1: n-3 fatty acid and antioxidant enriched oral supplement (n=95) G2: identical supplement (isocaloric- isonitrogenous control supplement) without n-3 fatty acids and enhanced antioxidants (n=105) Both oral supplements were provided by Ross Products Division, Abbott Laboratories (Columbus, Ohio, USA) and were ready to use, energy dense, high protein, low fat formulations intended to act as a supplement to the patient's usual diet.	Design: Double blind RCT Randomization method: Patients were randomised at enrolment in permutation blocks of two using a sequential series of numbered sealed envelopes containing computer generated random assignments Duration: 8 weeks	Health Related Quality of Life at 8 weeks* Nutritional status at 4/8 weeks Change in Lean body mass (kg/month) Change Weight (kg/month)	Limitations Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel Assessments: Low risk Blinding of outcome assessment: Low risk Incomplete outcome data: High risk (more than 55% of patients were not available for analysis at the last follow-up, and there was not reported enough information to judge whether the true outcome of the trial would have been influenced) Selective reporting: high risk (no study protocol to permit judgement on this criterion for all the outcomes, and for an important outcome - i.e. HRQL* - no information regarding uncertainty of the

Study details	Participants	Interventions	Methods	Outcomes	Comments
Netherlands, Canada, Belgium, Australia Study type: Multicentre RCT Aim of the study: To compare the effect of the n-3 fatty acid and antioxidant enriched supplement with an isocaloric isonitrogenous supplement on weight, body composition, dietary intake, and quality of life in weight losing pancreatic cancer patients. Study dates: Publication date: 2003 Data collection/patients enrolment: 1999-2001 Source of funding: Support was provided by Abbott Laboratories, Chicago, IL, USA.	stable weight over the previous six months had a Karnofsky performance score of 60 or more and had a life expectancy greater than two months Exclusion criteria Patients with: surgery, endoscopic stenting, radiotherapy, or chemotherapy during the previous four weeks; other active medical conditions (major gastrointestinal disease, chronic renal failure, uncontrolled diabetes, and human immunodeficiency virus) a body mass index greater than 30 kg/m2; or received medication which could profoundly modulate metabolism or weight, in particular, the use of fish oil or n-3 fatty acid preparations exceeding 200 mg/day EPA, or one capsule of fish oil/day within the previous 90 days				estimates was reported) Other sources of bias: Low risk (None detected) Other information *no data are reported in the paper. The Authors describe the findings just narratively.

Study details	Participants	Interventions	Methods	Outcomes	Comments
Full citation Satoi, S., Sho, M., Yanagimoto, H., Yamamoto, T., Akahori, T., Kinoshita, S., Nagai, M., Hirooka, S., Yamaki, S., Nishiwada, S., Ryota, H., Ikeda, N., Nakajima, Y., Kon, M. Do pancrelipase delayed-release capsules have a protective role against nonalcoholic fatty liver disease after pancreatoduodenectomy in patients with pancreatic cancer? A randomized controlled trial, Journal of Hepato-Biliary-Pancreatic Sciences, 23, 167-73, 2016 Ref ID 454155 Country/ies where the study was carried out: Japan Study type RCT Aim of the study:	Sample size N=57 patients with PC after surgery Characteristics M/F (n): 19/10 (G1); 12/16 (G2) Median age (range): 67 (52-81) years (G1); 69 (47-84) years (G2) Other - Body mass index, median (range): G1=21.2 (14.9-25.8) G2=19.5 (13.3-29.2) Inclusion criteria No details given Exclusion criteria Patients with: alcohol addiction (>150 g/week), obesity (body mass index (BMI) > 30), or using routinely of steroid pathological diagnosis of fatty liver disease as assessed by liver biopsy during surgery no initiation of PERT over the 2 months after PD, allergy to porcine protein or digestive enzymes, severe co-morbid disease, past drug dependence	Interventions G1: pancrelipase replacement therapy (n = 29) - 12 pancrelipase delayed-release capsules (1800 mg, LipaCreon, Eisai Pharmaceutical Co. Ltd, Tokyo, Japan) daily. G2: conventional PERT (n = 28) - ncreatic enzyme formulations such as Politose 1200 mg/day (Takeda Pharmaceutical Co. Ltd, Osaka Japan) or Toughmac-E 3 g/day (Ono Pharmaceutical Co. Ltd, Osaka, Japan) In the G2 group, crossover to pancrelipase replacement therapy was allowed if NAFLD, malabsorption or malnutrition developed.	Design: Un-blind RCT Randomization method: no stated Duration: 12 months	Treatment related morbidity NAFLD at 1 year follow-up Nutritional status BMI at 6 and 12 months follow-up	Limitations Random sequence generation: Unclear risk (No details given in the text) Allocation concealment: Unclear risk (No details given in the text) Blinding of participants and personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: Low risk (no missing data) Selective reporting: Low risk Other sources of bias: Low risk (None detected) Other information

Study details	Participants	Interventions	Methods	Outcomes	Comments
To evaluate the role of pancrelipase replacement therapy on non-alcoholic fatty liver disease (NAFLD) after surgery in patients with pancreatic cancer in comparison with conventional pancreatic enzyme supplementation. Study dates: Publication date: 2016 Data collection/patients enrolment: 2011-2013 Source of funding: No details given	Pregnancy or insufficient contraception, acute pancreatitis or ileus, chronic pancreatitis, and other serious concomitant systemic disorders incompatible with the trial in the investigators' judgment.				
Full citation Gade, J., Levring, T., Hillingso, J., Hansen, C. P., Andersen, J. R. The Effect of Preoperative Oral Immunonutrition on Complications and Length of Hospital Stay After Elective Surgery for Pancreatic Cancer-A Randomized Controlled Trial, Nutrition &	Sample size N=35 patients with PC after surgery* Characteristics M/F (n): 12/7 (G1); 6/10 (G2) Median age (range): 68 (50-81) years (G1); 69 (53-79) years (G2) Other - Surgical procedure, G1/G2-n: PD=89/69 DP=5/0	Interventions G1: Supplementary per oral immunonutrition –IN (n=19): Oral Impact Powder® (Nestlé, Vevey, Switzerland) as a supplement to their normal diet to reach a total goal of 1.5 g protein/kg body weight (BW) by adding IN to their habitual protein intake. G2: no intervention – habitual diet (n=16): This	Design: One-blind RCT Randomization method: unclear Duration: 1 month	Nutritional status (weight loss) Treatment related morbidity* Patients with infectious complications Patients with non-infectious complications Total patients with complications (infectious+ non-infectious) Postoperative mortality PROMS: Satisfaction	Limitations Random sequence generation: Unclear risk (No details given in the text) Allocation concealment: Unclear risk (No details given in the text) Blinding of participants and personnel Assessments: Low risk*

Study details	Participants	Interventions	Methods	Outcomes	Comments
CancerNutr Cancer, 68, 225-33, 2016 Ref ID 472040 Country/ies where the study was carried out: Denmark Study type: RCT Aim of the study To examine the effect of supplementary per oral immunonutrition (IN) seven days before surgery for PC on postoperative complications, length of hospital stay, functional capability and body weight. Study dates: Publication date: 2016 Data collection/patients enrolment: March - October 2012 Source of funding: University of Copenhagen	TP=5/25 SP=0/6 Other - BMI (kg/m2), median (range): G1=24.3(18.8-28.3) G2=23.8(18.1-30.8) Inclusion criteria Patients: above 18 years of age who were candidates for elective and potentially curative surgery for PC who had a minimum period of 7 days prior to planned surgery Exclusion criteria Patients who: were pregnant or lactating were unable to understand and speak Danish, had renal dysfunction or milk intolerance received a surgery was not performed as planned, regardless of the reason	includes routine nutritional screening for disease-related malnutrition using NRS-2002, individual advice by nurses on intake of nutritional supplements in case of malnutrition and by a dietician prior to discharge The IN comes in packages as a powder to be diluted with 250 ml of water, and each package contains 16.8 g of protein			Blinding of outcome assessment: High risk* Incomplete outcome data: Low risk (11 patients were not available for analysis after the allocation at the second assessment: 10 patients (n=9 G1;n=4 DG2) were excluded because got a metastatic disease and one patient in the control group received a surgery elsewhere. For these reasons, missing data were judged to do not affect the true outcome of the trial) Selective reporting: high risk (even though a study protocol was registered a priori, the primary outcome is reported unclearly) Other sources of bias: Low risk (None detected) Other information *“Surgeons, physicians, and other hospital staff were unaware of the patients' treatment allocation, but the

Study details	Participants	Interventions	Methods	Outcomes	Comments
					investigators and the patients were unblended”
Full citation Gianotti L, Braga M., Gentilini O., Balzano G., Zerbi A., Di Carlo V. Artificial nutrition after pancreaticoduodenectomy. Pancreas. 2000 Nov;21(4):344-51 Ref ID Ginotti 2000 Country/ies where the study was carried out: Italy Study type: RCT Aim of the study: To evaluate whether early enteral nutrition may be a suitable alternative to Parenteral nutrition for patients with PC undergoing surgery, and whether enteral formulas specialized (enteral immunonutrition) could affect the immunometabolic response and	Sample size N=220 patients with PC after surgery* Characteristics M/F (n): 43/25 (G1); 47/26 (G2); 44/27 (G3) Mean age (SD): 60.2 (10.4) years (G1); 59.8 (12.2) years (G2); 61.1 (11.9) years (G3) Other – tumour type, G1/G2/G3 n: Pancreatic cancer: 39/42/41 Periampullary: 19/20/18 Endocrine tumour: 5/4/6 Pancreatitis: 5/7/6 Inclusion criteria Patients candidates for pancreatoduodenectomy for lesion of either the pancreatic head or the periampullary region Exclusion criteria Patients were not eligible when they had:	Interventions G1: parenteral nutrition (n = 68) G2: standard enteral nutrition (n = 73) G3: enteral immunonutrition (n=71) - enteral diet enriched with arginine, omega-3 fatty acids, and RNA (Impact; Novartis Nutrition, Bern, Switzerland) The three regimens were processed to deliver the same amount of calories and nitrogen over a week of postoperative treatment In all patients assigned to the enteral groups, a catheter-feeding jejunostomy was performed at the end of surgery before closing the wound. A feeding tube was inserted into the peritoneal cavity through a small incision of the skin and of the abdominal wall at the left flank. Then, the third jejunal loop (30 cm aborally from the gastrojejunal anastomosis) was selected.	Design: Assessors-blind RCT Randomization method^: “Once PD was completed, randomization was performed using sealed envelopes” Duration: 8 days post-surgery	Treatment related morbidity* Patients with infectious complications (in detail) Patients with non-infectious complications (in detail) Total patients with complications (infectious+ non-infectious) Postoperative mortality Treatment related morbidity** SEN versus EIN side effects	Limitations Random sequence generation: Unclear risk (No details given in the text) Allocation concealment: Low risk^ Blinding of participants and personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: Low risk (“Members of the surgical staff not involved in the trial recorded postoperative complications” Incomplete outcome data: Unclear risk (insufficient reporting of attritions/exclusions) Selective reporting: Unclear risk (no study protocol to permit judgement on this criterion) Other sources of bias: Low risk (None detected)

Study details	Participants	Interventions	Methods	Outcomes	Comments
improve outcome in these patients. Study dates: Publication date: 2000 Data collection/patients enrolment: no details given Source of funding: This study was partially supported by Novartis Nutrition, Bern, Switzerland.	creatinine level above 3 mg/L ascites/portal hypertension New York Heart Association class >3 ongoing pulmonary or biliary infection patients for arterial PaO2 <70 mm Hg; Preoperative radiochemotherapy excluded for metastatic disease or unresectable primary tumour, and palliative surgery (biliary and/or gastrointestinal bypass) was advised.				Other information *For all interventions groups **data on G2 versus G3
Full citation Liu, C., Du, Z., Lou, C., Wu, C., Yuan, Q., Wang, J., Shu, G., Wang, Y. Enteral nutrition is superior to Parenteral nutrition for pancreatic cancer patients who underwent pancreaticoduodenectomy, Asia Pacific journal of clinical nutrition, 20, 154-60, 2011	Sample size N=58 patients with PC after surgery Characteristics M/F (n): 17/13 (G1); 16/112 (G2) Mean age (SD): 60.5 (11.9) years (G1); 59.7 (11.2) years (G2) Other - Body mass index, mean (SD): G1=22.9 (0.76) G2=22.5 (1.05) Inclusion criteria Patients with:	Interventions G1: Parenteral nutrition – PN (n=30) - Main content of the PN formulas were glucose, alanine, aspartic acid, phenylalanine, glutamic acid, glycine, histidine, isoleucine, lysine, methionine, praline, serine, threonine. G2: standard enteral nutrition –EN (n=28) - EN formulas mainly contained omega-3 fatty acid, saturated fatty acid, protein, lactose, dietary	Design: Un-blind RCT Randomization method: Patients were randomly allocated between groups according to the smallest imbalance index scheme Duration: 14 days post-surgery	Treatment related morbidity Total patients with postoperative complications Postoperative mortality	Limitations Random sequence generation: Low risk Allocation concealment: Unclear risk (No details given in the text) Blinding of participants and personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: Unclear risk (No details given in the text)

Study details	Participants	Interventions	Methods	Outcomes	Comments
Ref ID 453721 Country/ies where the study was carried out: China Study type: RCT Aim of the study: To determine the effects of Parenteral nutrition (PN) and enteral nutrition (EN) on biochemical and clinical outcomes in pancreatic cancer patients who underwent surgery. Study dates: Publication date: 2011 Data collection/patients enrolment: 2006-2008 Source of funding: No details given	Blood loss during operation less than 400 ml. Confirmed diagnosis as pancreatic adenocarcinoma by pathologic procedures postoperatively age from 18 to 80 years BMI from 16 to 30 kg/m2. Exclusion criteria Patients who: suffered from endocrinal disease or abnormal fat metabolism, such as hyperthyroidism, diabetes with pharmaceutical therapy, hypertriglyceridemia, liver dysfunction, such as hepatitis and chronic liver disease, HIV infection, severe respiratory dysfunction, cardiac arrest, severe kidney dysfunction, and instable vital sign Received Cortisol, cytotoxic drugs and immunosuppressive agents during two weeks preoperatively,	fibre, mineral matters, microelements and vitamins Both the PN and EN patients were treated with isonitrogenous and isocaloric nutrients. Intake of calories was 113 KJ (27 kcal)/kg/d, and the intake of nitrogen was 0.2 g/kg/d. The ratio of nitrogen to calories was 1:130. For the EN patients, a tube was employed and placed into the jejunum through a jejunostomy. For PN patients, a transfusion apparatus was applied and nutrients were delivered intravenously through the central venous catheter 18-20 h/d, and the transfusion speed was 1-2 ml/kg/d.			Incomplete outcome data: high risk (2 patients were not available for analysis after the allocation because they discontinued the standard enteral nutrition (for intolerance to the feeding method). Therefore, missing data were judged to potentially affect the true outcome of the trial) Selective reporting: Unclear risk (no study protocol to permit judgement on this criterion) Other sources of bias: Low risk (None detected) Other information

Study details	Participants	Interventions	Methods	Outcomes	Comments
	or allergic to the nutrient supplement were also excluded.				
Full citation Kraft, M., Kraft, K., Gartner, S., Mayerle, J., Simon, P., Weber, E., Schutte, K., Stieler, J., Koula-Jenik, H., Holzhauer, P., Grober, U., Engel, G., Muller, C., Feng, Y. S., Aghdassi, A., Nitsche, C., Malfertheiner, P., Patrzyk, M., Kohlmann, T., Lerch, M. M. L-Carnitine-supplementation in advanced pancreatic cancer (CARPAN)--a randomized multicentre trial, Nutrition Journal, 11, 52, 2012 Ref ID 472127 Country/ies where the study was carried out: Germany Study type: Multicentre RCT Aim of the study	Sample size N=72 patients with unresectable PC Characteristics M/F (n): 20/18 (G1); 23/11 (G2) Mean age (SEM): 64.4 (1.67) years (G1); 64.4 (1.65) years (G2) Other - Karnofsky performance status, mean (SEM): G1= 76.8 (1.87) G2= 80.0 (2.16) Other - weight loss during the last 6 month, present/assent: G1=34/4 G2=31/3 Other - weight loss (kg) during the last 6 month, mean (SEM): G1= 11.4 (1.28) G2= 12.3 (1.56) Inclusion criteria Patients with: histologically proven, advanced and irresectable PC	Interventions G1: oral L-Carnitine (n = 38): al liquid formulation of L-Carnitine (4 g/d, obtained from Lonza, Basel, CH) G2: Placebo (n = 34): identically formulated	Design: Double-blind RCT Randomization method: Patients were randomly allocated between groups using sequential series of 4 per block, sealed envelopes, and computer generated randomization code Duration: 12 weeks	Overall Survival at follow up of 1500 days Health Related Quality of Life EORTC-QLQ-C30/PAN26* Nutritional status % change of BMI at 6/12 weeks body composition (% change of body fat and BCM at 6/12 weeks)	Limitations Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel Assessments: Low risk Blinding of outcome assessment: Low risk Incomplete outcome data: High risk (Even tough in the report was stated that “Dropout rates and reasons were not different between both treatment arms”, the high dropout rate (data missing on 43 of the 72 randomized patients [59%] is still significant) Selective reporting: high risk (study protocol was registered a priori but some important outcomes are reported unclearly) Other sources of bias: Low risk (None detected)

Study details	Participants	Interventions	Methods	Outcomes	Comments
To investigate the role of oral L-Carnitine supplementation on cancer cachexia in pancreatic cancer. Study dates: Publication date: 2012 Data collection/patients enrolment: 2006-2009 Source of funding: This study was supported by the Alfried-Krupp-von-Bohlen-und-Hahlbach-Foundation (Graduate Schools Tumour Biology and Free Radical Biology), the Deutsche Krebshilfe/ Dr. Mildred-Scheel-Stiftung (109102), the Deutsche Forschungsgemeinschaft (DFGgRK840-E3/E4, MA 4115/1-2/3, NI 1297/1-1), the Federal Ministry of Education and Research (BMBFgANI-MED 03152061A and	Karnofsky performance status of >60 Declared written informed consent to participate Exclusion criteria Patients with: liver failure a second malignancy treatment with omega-3-fatty acids and the presence of a mental disorder precluding informed consent				Other information *not enough detail on results data are reported in the paper. The Authors describe the findings just narratively.

Study details	Participants	Interventions	Methods	Outcomes	Comments
BMBF 0314107) and the European Union (EU-FP-7: EPC-TM and EU-FP7-REGPOT-2010-1).					
Full citation Hamza, N., Darwish, A., O'Reilly, D. A., Denton, J., Sheen, A. J., Chang, D., Sherlock, D. J., Ammori, B. J. Perioperative Enteral Immunonutrition Modulates Systemic and Mucosal Immunity and the Inflammatory Response in Patients With Periampullary Cancer Scheduled for Pancreaticoduodenectomy: A Randomized Clinical Trial, Pancreas, 44, 41-52, 2015 Ref ID 453352 Country/ies where the study was carried out: UK Study type: RCT Aim of the study:	Sample size N=37 patients with resectable PC Characteristics M/F (n): 9/8 (G1); 11/9 (G2) Median age (range): 63 (58-69) years (G1); 67 (63-70) years (G2) Type of tumour, G1/G2 (n): Pancreatic: 10/13 Cholangiocarcinoma: 0/3 Ampullary: 4/2 Duodenal: 1/1 Ductal atypia: 2/1 Inclusion criteria Patients with: preoperative diagnosis of PC whether presumed or confirmed by histology scheduled for surgery Exclusion criteria Patients: with chronic pancreatitis with gastric outlet obstruction	Interventions G1: enteral immunonutrition –EIN (n=17): IMPACT [Novartis Medical Nutrition, Horsham, West Sussex, UK]) that contained arginine, omega-3 polyunsaturated fatty acid (PUFA), and mRNA G2: standard enteral nutrition –SEN (n=20): Fresubin [Fresenius Kabi Ltd, Runcorn, UK] Both feeds provided 150 kcal/100 mL, but were not isonitrogenous; the protein content of the IMPACT feed was 8.4 g/100 mL in comparison with 6.0 g/100 mL of the standard feed. Patients were asked to consume 3 cartons (200 mL per carton) of either feed per day for 14 days before surgery. Postoperatively, the corresponding feed (100 kcal/100 mL) was administered via a nasojejunal tube within 24	Design: Un-blind RCT Randomization method: Patients were randomly allocated between groups using sequential series of 4 per block of 10 patients Duration: 3 weeks (2 weeks before and 1 week after surgery)	Treatment related morbidity Complication rate at 1 week after surgery Health Related Quality of Life at 1 week after surgery Karnofsky score Nutritional status at 1 week after surgery BMI strength test/ muscle function – mid-arm circumference (MAC), corrected arm muscle area (CAMA)	Limitations Random sequence generation: Low risk Allocation concealment: Unclear risk (no detail are reported to judge the appropriateness of allocation methods) Blinding of participants and personnel Assessments: High risk (“Neither the investigators nor the patients were blinded to the type of feed”) Blinding of outcome assessment: High risk (“Neither the investigators nor the patients were blinded to the type of feed”) Incomplete outcome data: High risk (Data were missing for 5 of the 42 randomised patients: G1 n=3 DG n=2 were missed because inadequate intake and metastatic disease, respectively. For these reasons,

Study details	Participants	Interventions	Methods	Outcomes	Comments
To compare the effects of perioperative enteral immunonutrition (EIN) versus standard enteral nutrition (SEN) on systemic and mucosal immunity in patients undergoing surgery for periampullary cancer. Study dates: Publication date: 2015 Data collection/patients enrolment: no details given Source of funding: The trial was funded by charitable donations.	with low nutritional risk as assessed by the malnutrition universal screening tool (MUST) with previous gastrointestinal surgery/disease/or resection, or malignancy of the body or tail of the pancreas those who expressed a strong dislike to the immune or standard feed at the time of the prerandomization taste trial patients with hepatic or renal failure those on investigational medicine within the last 6 months; patients on prednisolone or those with immune system disorders and septic patients.	hours of surgery at a rate of 25 mL/h			missing data were judged to affect the true outcome of the trial) Selective reporting: Low risk (study protocol registered a priori) Other sources of bias: Low risk (None detected) Other information
Full citation Moses, A. W., Slater, C., Preston, T., Barber, M. D., Fearon, K. C. Reduced total energy expenditure and physical activity in cachectic patients with pancreatic	Sample size N=24 patients with advanced PC Characteristics M/F (n): 6/3 (G1); 4/11 (G2) Mean age (SEM): 65 (2) years (G1); 70 (3) years (G2)	Interventions G1: n-3 fatty acid enriched oral supplement (n=9) - two cans per day of either an n-3 fatty acid containing oral nutritional supplement G2: identical supplement (isocaloric- isonitrogenous	Design: Double-blind RCT (see other information*) Randomization method: patients were randomly allocated between groups first stratifying for study site and histological	Nutritional status Change in weight (kg) at 8 weeks Change in lean body mass at 8 weeks EE and PAL Change in TEE at 8 weeks Change in REE at 8 weeks Change in PAL at 8 weeks	Limitations Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel Assessments: Low risk

Study details	Participants	Interventions	Methods	Outcomes	Comments
cancer can be modulated by an energy and protein dense oral supplement enriched with n-3 fatty acids, British Journal of Cancer, 90, 996-1002, 2004 Ref ID 472262 Country/ies where the study was carried out: UK Study type: RCT Aim of the study: To determine whether the decreased total energy expenditure (TEE) and physical activity level (PAL) is observed in patients with pancreatic cancer and to test the influence of an energy and protein dense oral supplement either enriched with or without the n-3 fatty acid eicosapentaenoic acid (EPA)	Other - % weight loss in previous 6 months, mean (SEM): G1= 21 (2) G2= 19 (2) Other - Body mass index, mean (SEM): G1= 21 (1) G2= 20 (1) Inclusion criteria Patients who: had lost more than 5% of their preillness stable weight over the previous 6 months Had a Karnofsky performance score of 60 or more and had a life expectancy greater than 2 months Had a clinically confirmed diagnosis of PC Exclusion criteria Patients if they had: undergone major surgery endoscopic stenting radiotherapy or chemotherapy during the previous 4 weeks other active medical conditions	control supplement) without n-3 fatty acids (n=15) The control and experimental (n-3 enriched) oral supplements were isocaloric and isonitrogenous. The increase in the n-3 fatty acid content of the experimental supplement was balanced by an increase in the n-9 (oleic) fatty acid content of the control supplement.	proof of diagnosis to permutation blocks of two, and then by using a sequential series of numbered, sealed, opaque envelopes containing computer-generated random assignments Duration: 8 weeks		Blinding of outcome assessment: Low risk Incomplete outcome data: Low risk Selective reporting: Low risk Other sources of bias: Low risk (None detected) Other information * The study involved patients who had also been included in in a larger Double-blind RCT (Fearon 2003)

Study details	Participants	Interventions	Methods	Outcomes	Comments
Study dates: Publication date: 2004 Data collection/patients enrolment: 1999-2001* See Fearon 2003 Source of funding: No details given	a body mass index (BMI) greater than 30 kg m−2 received medication that could profoundly modulate metabolism or weight, in particular, the use of fish oil or n-3 fatty acid preparations exceeding 200 mg day−1 EPA or one capsule of fish oil/day within the previous 90 days xxx				
Full citation Woo S.M., Joo J., Kim S.Y., Park S.J., Han S.S., Kim T.H., Koh Y.H., Chung S.H., Kim Y.H., Moon H., Hong E.K., Lee W.J. Efficacy of pancreatic exocrine replacement therapy for patients with unresectable pancreatic cancer in a randomized trial. Pancreatology. 2016 Sep 4. pii: S1424-3903(16)31182-6 Ref ID Woo 2016	Sample size N=77 patients with unresectable PC Characteristics M/F (n): 22/12 (G1); 21/12 (G2) Mean age (SD): 63.7 (9.7) years (G1); 64.1 (10.6) years (G2) Other - weight [kg], mean (SD): G1= 58.7 (10.8) G2= 56.1 (8.3) Other - Body mass index, mean (SD): G1= 16.1 (13.5) G2= 13.3 (6.9) Inclusion criteria Patients if they had:	Interventions G1: Pancreatic enzyme therapy (n=34) – Norzyme, a high dose enteric pancreatic enzyme preparation. G2: Placebo (n=33) - placebo matched the active drug in appearance, taste, and weight and contained pharmacologically inactive substances	Design: Double-blind phase II randomized trial Randomization method: patients were randomly allocated between groups first stratifying for the extent of disease (i.e. locally advanced or metastatic), and then by using unique patients number Duration: 8 weeks	Nutritional status at 8 weeks follow-up Change in body weight (%) Change in body weight (KG) Health Related Quality of Life EORTC-QLQ-C30 Overall Survival	Limitations Random sequence generation: low risk Allocation concealment: unclear risk Blinding of participants and personnel Assessments: low risk Blinding of outcome assessment: low risk Incomplete outcome data: low risk Selective reporting: low risk Other sources of bias: Low risk (None detected) Other information

Study details	Participants	Interventions	Methods	Outcomes	Comments
Country/ies where the study was carried out: Republic of Korea Study type: RCT Aim of the study: To assessed whether pancreatic exocrine replacement therapy (PERT) could reduce or prevent weight loss in patients with unresectable PC. Study dates: Publication date: 2016 Data collection/patients enrolment: 2011-2014 Source of funding: Phambio Korea Co., Ltd (1141310-1) National Cancer Center, Korea (1510202-2; 1610040-1)	unresectable PC proven by cytology or histology local unresectability, or advanced disease with metastases aged over 18 years ECOG scale of performance status (0-3) Exclusion criteria Patients if they had: History of major gastrointestinal surgery Chronic gastrointestinal disease Decompensated diabetes ECOG diabetes mellitus with severe gastroparesis				

F.101 Biliary obstruction

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Full Citation Artifon, E. L. A., Aparicio, D., Paione, J. B., Lo, S. K., Bordini, A., Rabello, C., Otoch, J. P., Gupta, K. Biliary Drainage in Patients With Unresectable, Malignant Obstruction Where ERCP Fails Endoscopic Ultrasonography-Guided Choledochoduodenostomy Versus Percutaneous Drainage, Journal of Clinical Gastroenterology, 46, 768-774, 2012 Country/ies where the study was carried out: Brazil Study type: Single-centre RCT Aim of the study: (1) To compare success and efficacy of EUS-CD with PTBD in patients with unresectable malignant biliary obstruction. (2) To compare complications, cost-effectiveness, and quality of life (QOL) of EUS-CD and PTBD	N=25 patients with unresectable malignant biliary obstruction in which ERCP or EUS-guided transpapillary rendezvous has failed Arm 1=13 Arm 2=12 Inclusion Failure of ERCP or EUS-guided transpapilliary rendezvous Unresectable biliary obstruction Informed consent Characteristics (SDs not reported) Age (mean, SD): EUS-CD 63.4 (11.1); PTBD 71 (11.9) Male/f: EUS-CD 9/4; PTBD 8/4	Arm 1: Endoscopic Ultrasonography-guided choledochoduodenostomy (EUS-CD) with pcSEMS Arm 2: Percutaneous Transhepatic Biliary Drainage (PTBD) with pcSEMS	Randomisation The randomization was performed using the simple sealed envelope method. Randomization performed when the patient was sedated at the time of failed standard procedure. In patients randomized to EUS-CD, procedure was done at the same sedation, whereas patient randomized to PTBD, drainage was done within next 1 or 2 days. Treatment All EUS-CD procedures performed by a single endoscopist. All PTBD patients transferred to the radiology suite. All subjects were admitted to the hospital for observation. All the patients received broad-spectrum prophylactic antibiotics in both the groups. Procedures were performed under general anesthesia in both the groups. EUS-CD A therapeutic echoendoscope with a large working channel is used to perform both biliary access and stent placement in 1 step.	Relief of symptoms Treatment-related complications Quality of life Relief of symptoms Laboratory findings (SDs not reported) EUS-CD (n=13) / PTBD (n=12) / p-value: Total bilirubin (mean) 7 days: 3.3 / 3.8 / 0.2 30 days: 2.2 / 1.98 / 0.3 Gamma glutamyl transferase (mean) 7 days: 133 / 174 / 0.0 Alkaline phosphatase (mean) 7 days: 101 / 129 / 0.0 Treatment-related complications Complications: EUS-CS N=13 / PTBD N=12 / p-value Total: 2 / 3 / 0.44 Bleeding: 1 / 0 Biloma: 1 / 0 Bile leak: 0 / 1 Abscess: 0 / 2 Quality of life (SDs not reported) Overall SF-36 score at 7 days: 73.3 vs 74.4, p=0.48 Overall SF-36 score at 30 days: 73 vs 74.2, P=0.4	Overall high risk of bias Note: unclear number of PC patients • Random sequence generation: High risk (Simple sealed envelope method used, no other details provided) •Allocation concealment: unclear risk (no other details provided) •Blinding of participants and personnel assessments: low risk (No blinding but outcome not likely to be influenced); high risk for QoL outcome (subjective self-report measure used) •Blinding of outcome assessment: low

Study details	Participants		Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Study dates: May 2007 to July 2011 Source of funding: None reported	female (n) QoL (mean) Total serum bilirubin(mean) Gamma glutamyl transferase (mean) Alkaline phos	58.3 16.4 554.3 539	57.8 17.2 743.5 518	General anesthesia or MAC is used for prolonged sedation and to prevent aspiration due to gastric outlet obstruction. A dose of prophylactic broad-spectrum antibiotic is given to the patient before the procedure. The echoendoscope is advanced to the duodenal bulb. After a counter-clockwise rotation within the duodenal bulb, the dilated common bile duct or the common hepatic duct is usually visualized. Fluoroscopy is used to ensure that the echoendoscope is directed in the cephalad direction so that the needle is directed toward the hepatic hilum. Usually a 19-G needle, which is preloaded with contrast and a guidewire is used to access the bile duct. After needle puncture, bile is aspirated and then contrast is injected. Once the intraductal location of the needle is confirmed the guidewire is advanced, making certain that it is advanced toward the intrahepaitc ducts. Once the guidewire is in place the needle is carefully removed. A self-expanding metal stent with or without dilation of the fistula tract, depending on how		risk (outcome not likely to be influenced by lack of blinding) •Incomplete outcome data: low risk (no missing outcome data) •Selective reporting: High risk (Incomplete reporting of outcomes) •Other sources of bias: High risk (no power calculation; small sample size)

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
	ph ata se (m ea n)		easy it is to push the stenting catheter into the bile duct is then passed over the guidewire and deployed (Figs. 6–9). Needle knife or dilating catheter can be used for enlargement of the duodenal fistula. Patients are kept NPO and admitted for overnight observation after their EUS-CD procedures. PTBD Under sonographic and fluoroscopic guidance the dilated right hepatic biliary tree is accessed using a 22-G CHIBA needle. Initially a 0.018-inch guidewire was passed but was subsequently replaced by a 0.035-inch guidewire. Over the guidewire a partially covered self expanding metal stents (SEMS) is advanced and deployed in the standard fashion Quality of life Assessed using SF-36 Follow up Follow up at 7 and 30 days after procedure Sample size calculation Not reported.		
Full Citation	N=32 patients with unresectable	Arm 1: EUS-guided	Randomisation	Relief of symptoms	Overall high risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Artifon, E. L. A., Loureiro, J. F., Baron, T. H., Fernandes, K., Kahaleh, M., Marson, F. P. Surgery or EUS-guided choledochoduodenostomy for malignant distal biliary obstruction after ERCP failure, Endoscopic Ultrasound, 4, 235-43, 2015 Country/ies where the study was carried out: Brazil Study type: Single-centre RCT Aim of the study: To determine outcome differences between two biliary drainage techniques in patients with distal malignant biliary obstruction and failed ERCP. Study dates: March 2011 to September 2013 Source of funding: None reported	distal malignant biliary obstruction where ERCP has failed EUS-CD=16 Surgical bypass=16 Inclusion Age ≥18 years Unresectable distal malignant obstruction of distal bile duct Failed standard ERCP Exclusion Informed consent not provided Patients with severe coagulopathy	Choledochoduodenostomy (EUS-CD) Arm 2: Surgical bypass (Surgical hepaticojejunostomy)	Block randomization was performed using Microsoft Excel 2007 software to randomly allocate patients. Sealed, numbered envelopes were prepared in advance that contained the allocation of each patient. The patient allocations were revealed from the envelopes immediately after ERCP failure. Treatment EUS-CD General anesthesia with tracheal intubation was used to prevent bronchoaspiration. Before the procedure, a single dose of antibiotics was administered. The dilated common bile duct was identified from the transduodenal route, with the linear echo-endoscope positioned in the duodenal bulb. Color Doppler was used to identify any vascular structures in the path of the needle. Transduodenal puncture of the dilated common bile duct with a 19-gauge needle was performed, and the intraductal position confirmed by aspiration of bile and subsequent cholangiography, delineating biliary anatomy and the	# reduction bilirubin>50% from baseline Overall Survival Treatment-related complications Quality of Life Relief of symptoms (clinical success) Reduction of total serum bilirubin >=50% from baseline after 7 days EUS-CD 10/14 Surgical bypass 14/15, p=0.169 EUS-CD / Surgical Bypass Outcome | N | Mean | SD | N | Mean | S Total serum bilirubin 0 days | 14 | 12.79 | 5.68 | 15 | 15.3 | 5 2 7 days | 14 | 5.14 | 3.58 | 15 | 3.43 | 1 5 30 days | 14 | 2.43 | 1.02 | 15 | 2.17 | 0 7 60 days | 11 | 1.86 | 0.23 | 14 | 1.8 | 0 5 90 days | 7 | 1.84 | 0.26 | 6 | 1.83 | 0 Gamma glutamyl transferase 0 days | 14 | 777 | 353.02 | 15 | 951.96 | 4 5 5 7 days | 14 | 253.93 | 151.91 | 15 | 137.47 | 3 7	Note: unclear how many PC patients • Random sequence generation: Low risk (computer-generated block randomization) •Allocation concealment: Low risk (sealed, numbered envelope prepared in advance) •Blinding of participants and personnel assessments: Low risk (No blinding but outcomes unlikely to influenced by lack of blinding); high risk for QoL outcomes •Blinding of outcome assessment: low risk (unclear but not likely to affect measurement); high risk for QoL (self-report)

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
			stenotic lesion. A 0.035-inch hydrophilic guide wire was passed through the needle. The needle was then withdrawn, leaving the guide wire in the intraductal position. Dilation of the choledochoduodenal fistula was done using a needle-knife with electrocautery. A self-expandable metallic biliary stent (partially covered) with the distal end positioned in the biliary and proximal end in the duodenal bulb was then placed under endoscopic and fluoroscopic guidance. All patients remained in fasting and were hospitalized for 1 night for observation. Surgical bypass All procedures were performed under general anesthesia. Intravenous cefazolin (1 gm) was administered prophylactically 1 h before the procedure. A cross section of jejunal loop was taken and a termino-lateral jejuno-jejunal anastomosis (3-4 cm opening) was constructed between the proximal and distal jejunal pouches using 3-0 nylon monofilament suture on a single plane. Construction of termino-lateral hepaticojejunal	30 days 14 156.5 14 0.53. 15 102.67 1 2 60 days 12 96.08 25.41 14 95.86 1 6 90 days 7 94.43 18.73 6 80 1 6 Alkaline phosphatase 0 days 14 484.07 13 5.94 15 554.73 2 5 9 7 days 14 168.21 87.5 15 103.67 2 4 30 days 14 98.86 63.35 15 87.47 9 3 60 days 12 94.5 16.75 14 89.71 1 6 90 days 7 95.57 11.72 6 90.17 6 5 Complications EUS-CD= 3/14 (bleeding duodenal wall; early biliary fistula; early stent migration into abdominal cavity) Surgical bypass= 2/15 (1 bacteremia, 1 gastric bleeding due to gastroenterostomy) No significant difference between arms, p=0.651 Overall survival Median OS=82.36 vs 82.27 days % died 90 days after surgery: (6/14) 42.9% vs 60% (9/15) (p=0.389)	•Incomplete outcome data: Low risk (3 patients excluded due to technical failure, unlikely to be related to true outcome) •Selective reporting: high risk (one or more primary outcomes not reported; HRs for overall survival not reported; diff bt treatment not reported for QoL outcomes) •Other sources of bias: high risk (No power calculation)

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
			anastomosis with total separate stitches using mononylon 5-0 surgical wire was performed. Then construction of latero-lateral gastrojejuno anastomosis with distal segment of the proximal jejunal loop was performed. The anastomosis was located at the greater gastric curvature with a 6-cm aperture using 3.0 catgut wire on two levels: The first being with continuous seromuscular stitches and the second, total, also with continuous stitches. Construction of latero-lateral jejuno-jejunal anastomosis between the proximal jejunal and jejunal loop that makes up the Roux-en-Y was performed. Temporary drainage of the abdominal cavity was achieved by placing a 20-Fr Penrose drain. Follow up After the procedure, patients were followed up for 90 days for clinical complications, laboratory, quality of life, and survival. Sample size calculation None reported	HR=0.64 (95%CI, 0.23-1.78) [calculated from # deaths and p-value using method 7 Tierney et al 2007] SF-36 Quality of life Sig improvement (p<0.5) in all subscales for each treatment except for general health and vitality subscales EUS-CD / Surgical Bypass SF-36 subscale / N / Mean / SD / N / Mean / S Functional Capacity 0 days / 14 / 27.9 / 7.8 / 15 / 26.3 / 9 7 days / 14 / 40 / 16.2 / 15 / 33.7 / 1 30 days / 14 / 51.4 / 11.5 / 15 / 40.7 / 2 60 days / 12 / 54.2 / 12.9 / 14 / 44.3 / 9 90 days / 7 / 55.7 / 5.3 / 6 / 57.5 / 8 Physical health 0 days / 14 / 3.6 / 9.1 / 15 / 5 / 4 7 days / 14 / 23.2 / 15.4 / 15 / 21.7 / 2 8 30 days / 14 / 26.8 / 11.9 / 15 / 31.7 / 2	

Study details	Participants	Interventions	Methods	Outcomes and Results						Limitation (risk of bias)
				60 days	12	35.4	12.9	14	28.6	
				90 days	7	35.7	24.4	6	45.8	
				Pain						
				0 days	14	41.3	26.3	15	60.2	
				7 days	14	74.3	13.9	15	78	
				30 days	14	79.4	13.2	15	76.7	
				60 days	12	66	15.6	14	70.4	
				90 days	7	73.4	6.4	6	88.7	
				General Health perceptions						
				0 days	14	40.4	14.3	15	41	
				7 days	14	38.7	11.3	15	42.1	
				30 days	14	36.6	10.2	15	40.7	
				60 days	12	35.1	11.9	14	38.4	
				90 days	7	39.3	11	6	34.8	
				Vitality						
				0 days	14	38.2	8	15	38.7	
				7 days	14	40.7	11.6	15	38	

Study details	Participants	Interventions	Methods	Outcomes and Results						Limitation (risk of bias)
				30 days	14	47.9	14.2	15	40.3	
				60 days	12	45	13.8	14	42.9	
				90 days	7	47.1	19.8	6	32.5	
				Social role functioning						
				0 days	14	25	13	15	30	
				7 days	14	45.5	13.5	15	45.8	
				30 days	14	54.5	9.3	15	54.2	
				60 days	12	42.7	14.6	14	43.8	
				90 days	7	53.6	11.9	6	52.1	
				Emotional role functioning						
				0 days	14	11.9	16.6	15	8.9	
				7 days	14	38.1	17.8	15	35.6	
				30 days	14	47.6	17.1	15	46.7	
				60 days	12	50	26.6	14	40.5	
				90 days	7	47.6	17.8	6	38.9	
				Mental health						
				0 days	14	48.6	6.6	15	45.9	

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
				7 days 14 53.1 10.5 15 44 30 days 14 52.6 11.3 15 39.7 60 days 12 54 13.4 14 45.1 90 days 7 44.6 12.3 6 42.7	
Full Citation Artifon, E. L., Sakai, P., Cunha, J. E., Dupont, A., Filho, F. M., Hondo, F. Y., Ishioka, S., Raju, G. S. Surgery or endoscopy for palliation of biliary obstruction due to metastatic pancreatic cancer, The American journal of gastroenterology, 101, 2031-7, 2006 Country/ies where the study was carried out: Brazil Study type: Single-centre RCT Aim of the study: To evaluate the costs and quality of life associated with endoscopic metal stent placement compared to surgical drainage for	N = 30 unresectable PC patients n = 15 ES->SEMS n = 15 surgery Inclusion unresectable pancreatic cancer (stage IV, with documented liver metastasis on CT/MRI/endoscopic ultrasound) medically stable for general anaesthesia and surgery Exclusion Advanced ampullary tumour prior history of gastrectomy and Roux-en-Y surgery	Arm 1: Endoscopic sphincterotomy with covered SEMS Arm 2: Surgery	Randomisation Random assignments were made using a list of computer-generated random numbers. The gastroenterologist, surgeon and hospital administrators were not blinded to the results of randomisation. Written, informed consent was obtained from all participants. Treatment ES with cSEMS Participants underwent ERCP (under conscious sedation) by an experienced endoscopist. A covered, self-expandable metal stent (Shim-Hanarostent, Model MItech, Seoul Korea) was inserted. Surgery Participants underwent bilioenteric anastamosis by an experienced pancreatico-biliary surgeon, which consisted of a Roux end-to-side hepatojejunostomy. In	Relief of obstruction Relief of symptoms Overall Survival* Treatment-related mortality Treatment-related morbidity Treatment-related (early/late) complications Quality of life Relief of biliary obstruction: Surgery group: 15/15 (n = 13 choledocojejunostomy, n = 2 cholecystojejunostomy) ES->Stent group: 15/15 Bilirubin decrease to <2.5mg/dL on day 30 Surgery group: 8/15 ES->Stent group: 8/15 Serum bilirubin level at 30 days Surgery: 2.2 (0.94) ES->Stent: 1.9 (1.16)	Overall high/unclear risk of bias • Random sequence generation: Low risk (computer-generated random numbers) •Allocation concealment: Unclear risk (insufficient information) •Blinding of participants and personnel assessments: Low risk (Although neither participants nor individuals administering care blinded, outcome unlikely to be affected);

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Limitation (risk of bias)</th></tr>
<tr>
<td>palliation of biliary obstruction.
Study dates:
July 2001 and October 2004.
Source of funding:
None reported</td>
<td>duodenal obstruction
resectable cancer
<table>
<tr><td>Characteristics</td><td>ERCP</td><td>Surgery</td></tr>
<tr><td>Mean age, years</td><td>64.2</td><td>61.4</td></tr>
<tr><td>Male sex, %</td><td>40</td><td>53</td></tr>
<tr><td>Jaundice, %</td><td>100</td><td>100</td></tr>
<tr><td>Pruritis, %</td><td>53</td><td>40</td></tr>
<tr><td>Abdominal pain, %</td><td>66.6</td><td>46.6</td></tr>
<tr><td>Vomiting, %</td><td>10</td><td>20</td></tr>
</table>
</td>
<td></td>
<td>addition, a gastrojejunostomy was created in all the patients. The abdominal cavity was drained with a laminar drain tube.
Quality of Life
Assessed with SF-36 by non-blinded gastroenterologist
Follow up
Participants were reviewed during the course of their hospital admission (following the procedure) and at 30, 60, 120 days afterwards, or until death. Information recorded at each visit included symptoms of biliary obstruction and gastric outlet obstruction, quality of life measures and complications
Sample size calculation
Not reported.</td>
<td>Overall survival
Surgery group, mean ± SD: 202 ± 71 days/median=90 days
ES->Stent group, mean ± SD: 162 ± 57 days/median 13 days
p = 0.06

Procedure-related mortality
Surgery group: 0/15
ES->Stent group: 0/15

Procedure related morbidity
Surgery group: 4/15 (26%)
ES->Stent group: 3/15 (20%)
p = 0.71

Postoperative complications
Surgery group: 7/15 (47%)
ES->Stent group: 5/15 (33%)
Early onset complications
Surgery group: 5/15 (33%)
ES->Stent group: 3/15 (20%)
p = 0.09

Late onset complications
Surgery group: 4/15 (26%)
ES->Stent group: 3/15 (20%)
p = 0.12

Severe Complications
ES->Stent (n=15) Stent (n=</td>
<td>High risk for QoL outcomes
•Blinding of outcome assessment: Low risk (investigators not blind to group allocation but unlikely to affect outcome)
•Incomplete outcome data: Low risk (All participants completed study)
•Selective reporting: high risk (survival/quality of life outcomes not fully reported)
•Other sources of bias: high risk (No power calculation for sample size)</td>
</tr>
</table>

Study details	Participants			Interventions	Methods	Outcomes and Results			Limitation (risk of bias)
	History of diabetes mellitus, %	40	20			Post-ERCP Pancreatitis	1	0	
	History of hypertension, %	33.3	53			Stent-related complications	4	0	
	History of renal failure, %	6.6	0			Bleeding	1	0	
	History of hepatic disease, %	13.3	6.6			Pneumonia	0	2	
						Readmission for complications Surgery: 9/15 ES->Stent: 6/15 Quality of life – SF-36 scale Authors report that the improvement in quality of life scores was superior in the endoscopy group compared to the surgical group at 30 days (p = 0.042) and 60 days (p = 0.05) post procedure. At 120 days quality of life measurements decreased to values before the procedure. No other data are reported.			

Study details	Participants			Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
	History of heart disease, %	20	6.6				
	Mild Malnutrition %	60	73				
	Moderate malnutrition %	40	27				
Full Citation Artifon, E. L., Sakai, P., Ishioka, S., Marques, S. B., Lino, A. S., Cunha, J. E., Jukemura, J., Cecconello, I., Carrilho, F. J., Opitz, E., Kumar, A. Endoscopic sphincterotomy before deployment of covered metal stent is associated with greater complication rate: a prospective randomized control trial,	N=74 patients with unresectable distal bile duct obstruction Arm 1=37 (inc. 30 PC patients) Arm 2=37 (inc. 30 PC patients) Inclusion diagnosis of unresectable malignant distal bile duct obstruction			Arm 1: Endoscopic sphicterotomy followed by covered SEMS Arm 2: Covered SEMS	Randomisation Patients were randomized after successful cannulation of the bile duct according to a computer-generated randomization list. Note: article reports that “Patients were randomized (without blocking or stratification) in a double blind fashion using random numbers” to groups. However, article also states “A block randomization list with alternating block sizes was	Survival* Treatment-related complications Mean Survival (days) ES->SEMS: 132 (range 37-156) SEMS: 159 (range 45-182) P=0.72 Treatment-related complications ES->SEMS (n=37) / SEMS (n=37) / p-valu Total 19 / 8 / 0.006 Bleeding 5 / 0 / 0.037	Overall high/unclear risk of bias • Random sequence generation: low risk (computer-generated list) •Allocation concealment: unclear (insufficient information)

Study details	Participants	Interventions	Methods	Outcomes and Results			Limitation (risk of bias)
Journal of Clinical Gastroenterology, 42, 815-9, 2008 Country/ies where the study was carried out: Brazil Study type: Single-centre RCT Aim of the study: To evaluate whether ES before SEMS placement was associated with a greater likelihood of stent migration and other complications in patients with malignant obstruction of the distal common bile duct Study dates: April 2002 to October 2006 Source of funding: None reported	Exclusion refusal to provide consent prior Billroth surgery severe coagulation abnormalities		generated using SAS (SAS Version 8.2, SAS Institute, Inc, Cary).” The randomization code was not accessible to the clinical investigators. The allocation sequence was concealed in envelopes and if cannulation was unsuccessful, the sealed envelope was used for the next patient. Treatment Wallstent SEM (n=37, 19 in ES->SEMS group, 18 in SEMS only) and Shim-Hanaro SEM (n=37, 18 in ES->SEMS, 19 in SEMS only) used in study. The covering of the distal 0.5 cm at each end was carefully removed using a sharp blade to render the Shim-Hanaro stent identical to the Wallstent. All procedures were performed by 3 experienced biliary endoscopists using a therapeutic side-viewing endoscope (Olympus, model TJF-140). Patients were sedated using midazolam and fentanyl and monitored during the procedure using pulse oximetry and continuous cardiac monitoring. Prophylactic antibiotics were	Retroduodenal perforation Contralateral wall ulcer Stent malfunction Due to Stent occlusion Due to Stent migration	4 3 9 3 6	0 0 4 3 1	0.07 0.135 0.163 1 0.075	•Blinding of participants and personnel assessments: low risk (double blind and unlikely that outcomes affected even if broken) •Blinding of outcome assessment: low risk (assessor blinded and unlikely that outcomes affected by blinding) •Incomplete outcome data: low risk (no missing data) •Selective reporting: high risk (one more outcomes reported incompletely) •Other sources of bias: low risk (appears free of other bias)

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
			administered to all patients before ERCP. ES was performed using an Ultratome (Boston Scientific, Natick) with pure cut current using an ERBE electrosurgical generator (ERBE, Inc, Marietta, GA). After the diagnostic ERCP, a visually adequate sphincterotomy, which extended from the ampullary opening to the transverse duodenal fold above the ampulla was performed among patients in ES group. The stent was inserted over a guidewire and positioned across the narrowing with 3 to 4mm (4 to 5 diamonds of the wire mesh) of the distal end of the stent protruding into the duodenum. Patients were admitted to observation for 12 hours after the procedure. Follow up Patients were followed until death. A gastroenterologist blinded to study randomization examined the patients on days 30, 60, and 90 after the procedure and upon development of adverse symptoms. Family members were instructed to inform the study coordinators upon death		

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
			of the patient. No autopsies were performed. Patients with bleeding, perforation, and oxygen desaturation were treated as clinically appropriate. Complications Immediate complications were defined as those occurring during the first 30 days after the procedure. Late complications were those occurring from day 31 until the end of the study or death. Sample size calculation A sample size analysis to detect superiority at 5% significance level (1-tail test) and a power of 80%, assuming a complication rate of 35% in ES group and 10% in SEM only group showed that 34 patients had to be enrolled in each group.		
Full Citation Gardner, T. B., Spangler, C. C., Byanova, K. L., Ripple, G. H., Rockacy, M. J., Levenick, J. M., Smith, K. D., Colacchio, T. A., Barth, R. J., Zaki, B. I., Tsapakos, M. J., Gordon, S. R. Cost-effectiveness and clinical	N= 63 PC patients with malignant biliary obstruction receiving neoadjuvant chemoradiotherapy (9 patients excluded from primary analysis	Arm 1: Plastic stent Arm 2: Covered SEMS Arm 3: Uncovered SEMS	Randomisation Randomisation was performed using a web-based random number generator. This was conducted during the ERCP after biliary access had been obtained. No blinding took place. Informed consent was obtained from all participants. Treatment	# Stent occlusion/Time to stent occlusion* # Surgical resection/Time to attempted surgical resection* Mortality after initiation of neoadjuvant therapy*/time to death after initiation of neoadjuvant therapy* # post-ERCP pancreatitis (stent-related complication) Hospitalization*	Overall high risk of bias • Random sequence generation: low risk (web-based random number generator) •Allocation concealment:

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
efficacy of biliary stents in patients undergoing neoadjuvant therapy for pancreatic adenocarcinoma in a randomized controlled trial, Gastrointestinal Endoscopy, 10, 10, 2016 Country/ies where the study was carried out: USA Study type: Single centre RCT Aim of the study: To determine which type of stent (plastic, fully covered self-expandable metal [SEMS] or uncovered SEMS) would optimise cost-effectiveness and important clinical outcomes for patients undergoing neoadjuvant chemotherapy. Study dates: February 2010 to April 2013 Source of funding: NIH grant to one investigator. No other funding reported.	due to placement in hospice, neuroendocrine tumour, death from post-ERCP pancreatitis, autoimmune pancreatitis, and loss to follow up.) n = 26 plastic stent n = 17 fully covered SEMS n = 20 uncovered SEMS Inclusion adults able to provide written informed consent referred for ERCP for palliation of extrahepatic malignant biliary obstruction due to pancreatic adenocarcinoma clinical, radiographic and cross-sectional imaging findings consistent with extra-hepatic biliary obstruction requiring stent placement		Procedures were performed by one of two experienced endoscopists. After successful bile duct cannulation and guide wire placement, participants were randomised to one of the three groups. Occurrence of any of the outcomes (Time to stent occlusion, Time to attempted surgical resection, Death after the initiation of neoadjuvant therapy) resulted in follow-up for the trial ceasing. After stent placement, patients were referred to the Dartmouth Multidisciplinary Pancreas Tumor Clinic, where a neoadjuvant treatment protocol was initiated. All patients underwent neoadjuvant chemoradiotherapy using 1 of 3 chemoradiotherapy regimens. Patients eligible for an ongoing clinical trial received cetuximab 400 mg/m2 intravenously (IV) once followed by 250 mg/m2 IV weekly and gemcitabine 50 mg/m2 IV biweekly over 6 weeks with concurrent radiotherapy 5400 cGy over 28 fractions (regimen 1). Other patients received 1 of 2 preoperative regimens based on previous Dartmouth	Stent occlusion (rise in the total bilirubin level and/or concomitant cholangitis associated with the need for stent replacement via ERCP at the discretion of the clinical treatment team) fully covered SEMS: 4/16 (25%) uncovered SEMS: 6/17 (35%) plastic stent: 11/21 (52%) p = 0.22 Time to stent occlusion, days, mean (range) (rise in the total bilirubin level and/or concomitant cholangitis associated with the need for stent replacement) fully covered SEMS: 220 (range 21-341) uncovered SEMS: 74 (range 45-90) plastic stent: 76 (range 7-161) p<0.1 Attempted surgical resection after neoadjuvant therapy fully covered SEMS: 8/16 (50%) uncovered SEMS: 6/17 (35%) plastic stent: 4/21 (19%) p = 0.14 Time to attempted surgical resection, days, mean (range) fully covered SEMS: 165 (127-193) uncovered SEMS: 165 (133-193)	unclear risk (insufficient information) •Blinding of participants and personnel assessments: low risk (not blinded but unlikely to affect outcomes) •Blinding of outcome assessment: unclear risk (insufficient information) •Incomplete outcome data: low risk (reason for missing data unlikely to be related to true outcome) •Selective reporting: high risk (complications not reported) •Other sources of bias: high risk (participants in groups receiving different forms of neoadjuvant chemoradiotherapy)

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
	planned follow up at the same hospital deemed to have disease potentially suitable for neoadjuvant therapy. Exclusion unable to insert stent potentially resectable tumour Resectability status PS / uSEMS / cSEMS Resectable 3 2 5 Borderline 4 4 6		protocols. One regimen consisted of docetaxel 65 mg/m2 IV and gemcitabine 4000 mg/m2 IV given on days 1, 15, and 29, followed on day 43 by radiotherapy at 50.4 Gy with gemcitabine 50 mg/m2 IV twice weekly for 12 doses (regimen 2). The other regimen consisted of radiotherapy of 50.4 Gy in 28 fractions, concurrent with gemcitabine 50 mg/m2 biweekly for 6 weeks (regimen 3).10-12 The regimen that each patient received was not randomized at the time of stent placement and was instead determined by the subsequent treating oncologist. At the completion of neoadjuvant chemo-radiotherapy, all patients underwent attempted operative pancreatic resection unless restaging crosssectional imaging or diagnostic laparoscopy demonstrated evidence of unresectability. Plastic stent: A 10F Cotton-Leung stent was used (7, 9 and 12cm)(Cook Endoscopy, Winston-Salem, NC). SEMS: Both covered and uncovered stents were 10mm WallFlex stents (Boston	plastic stent: 151 (101-184) p = 0.63 Mortality after initiation of neoadjuvant therapy fully covered SEMS: 4/16 (25%) uncovered SEMS: 5/17 (29%) plastic stent: 6/21 (29%) p=0.96 Time to death, days, mean (range) fully covered SEMS: 71 (7-196) uncovered SEMS: 242 (122-453) plastic stent: 187 (96-312) p=0.11 Post ERCP pancreatitis fully covered SEMS: 3/16 (19%) uncovered SEMS: 3/17 (18%) plastic stent: 0/21 (0%) p=0.12 Hospitalization (days) from adverse event Fully covered SEMS: 15 Uncovered SEMS: 14 Plastic: 0 Hospitalization (days) from stent occlusion Fully covered SEMS: 0 Uncovered SEMS: 5 Plastic: 32 Days neoadjuvant therapy delayed	

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
	Loc Ad 14 11 5		Scientific, Marlborough, Mass) or varying lengths (6, 8 and 10cm). The nature of the covering for the fully covered stent is not described. Sample size calculation None reported.	Fully covered SEMS: 3 Uncovered SEMS: 50 Plastic: 73 P<0.01	
Full Citation Giorgio, P. D.& Luca, L. D.,Comparison of treatment outcomes between biliary plastic stent placements with and without endoscopic sphincterotomy for inoperable malignant common bile duct obstruction, World journal of gastroenterology, 10, 1212-4, 2004 Country/ies where the study was carried out: Italy Study type: Single-centre RCT Aim of the study: To assess the possible advantages of ES before PS placement compared toPS placement alone Study dates: March 1996 to June 2001 Source of funding:	N= 172 patients with unresectable bile duct obstruction Arm 1=96 (inc. 64 PC patients) Arm 2=96 (inc. 67 PC patients) Inclusion Unresectable malignant common bile duct stricture Written informed consent Exclusion had previous endoscopic sphincterotomy previous precut papillotomy or stent placements previous Billroth II resection suffering from coagulopathy	Arm 1: Endoscopic sphincterotomy followed by plastic stent Arm 2: Plastic Stent	Randomisation Patients were randomised by using sealed opaque envelopes. Randomization was done only after diagnostic cholangiography had been performed. Treatment All patients underwent operative ERCP with a duodenoscope (JF 140 Olympus) performed by 2 experienced endoscopists. A standard 0.035 –inch guidewire to perform deep cannulation of the biliary tree and to pass through the strictures. Occasionally a hydrophilic guidewire was used. In every patient we also aimed to visualize the pancreatic duct. Plastic stent used was 10F polyethylene stent (Cotton Leung) Complications Early complications (occurring within 30 d) and late effects	Complications Stent malfunction No procedure-related deaths in study. Technical success ES->PS: 92/96 PS: 90/96 Early complications ES->PS (n=92) / PS (n=90) / p-valu Total 6 / 4 / 0.772 Pancreatitis 2 / 2 / 0.629 Bleeding 3 / 0 / 0.252 Clogging 1 / 2 / 0.985 Late complications Acute cholangitis due to stent occlusion ES->PS: 16/92 PS: 15/90 P=0.946 Stent Migration ES->PS: 3/92 PS: 3/90 P=0.698	Overall unclear risk of bias • Random sequence generation: unclear (no details of method used) •Allocation concealment: unclear (insufficient information) •Blinding of participants and personnel assessments: unclear (no details provided) •Blinding of outcome assessment: low risk (no details provided but unlikely that blinding would affect outcome)

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
None reported	ampullary tumours		(from 30 d to stent replacement or death) were assessed. Complications of papillotomy were considered according to the criteria of Cotton Stents were not replaced routinely and patients were treated if occlusion of the stent or cholangitis developed. Occlusion considered in patients with jaundice. Sample size calculation None reported.	Reintervention (needing stent replacement) ES->PS: 41/96 (successful 39/41) PS: 46/96 (successful 45/46) No diff in success, P=0.919 Patency (median) ES->PS: 109 (SD=15) PS: 110 (SD=18) P=0.765	•Incomplete outcome data: low risk (missing data unlikely related to true outcome) •Selective reporting: low risk (no protocol but includes all expected outcomes) •Other sources of bias: low risk (appears free from other sources of bias)
Full Citation Hayashi, T., Kawakami, H., Osanai, M., Ishiwatari, H., Naruse, H., Hisai, H., Yanagawa, N., Kaneto, H., Koizumi, K., Sakurai, T., Sonoda, T. No benefit of endoscopic sphincterotomy before biliary placement of self-expandable metal stents for unresectable pancreatic cancer, Clinical Gastroenterology & Hepatology, 13, 1151-8.e2, 2015	N=200 unresectable PC patients with malignant distal biliary stricture 2 and 4 patients in SEMS and ES->SEMS groups, respectively, did not undergo SEMS placement due to biliary cannulation failure. N=100 ES->SEMS N=100 SEMS Inclusion	Arm 1: Partially-covered SEMS Arm 2: Endoscopic sphicterotomy followed by partially-covered SEMS	Randomisation Participants assigned randomly to groups upon enrolment by a 1:1 centralized allocation using the minimization method. The allocation and data collection were performed using a web-based system that was unavailable to the investigators. Randomization was concealed from patients, endoscopists, and physicians. However, patients, endoscopists, and physicians were unmasked to the treatment allocation. Treatment	Stent malfunction (occlusion/migration) Treatment-related complications Overall Survival* Deaths due to pancreatic cancer progression Serum amylase level Stent occlusion ES->SEMS: 6/100 SEMS: 9/100 Stent migration ES->SEMS: 4/100 SEMS: 3/100 Early-treatment-related complications SEMS (n=98) ES->SEMS (n=96) Difference	Overall low risk of bias • Random sequence generation: low risk (Minimization used) •Allocation concealment: low risk (central allocation used) •Blinding of participants and personnel assessments: low risk (no blinding but outcome not likely to be

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Country/ies where the study was carried out: Japan Study type: Multi-centre RCT Aim of the study: To conduct a non-inferiority trial to examine the necessity of ES before SEMS compared to SEMS alone. Study dates: August 2010 to November 2012 Source of funding: One author supported in part by a grant from The Japanese Foundation for Research and Promotion of Endoscopy.	Distal biliary stricture resulting from unresectable pancreatic cancer diagnosed based on contrast-enhanced computed tomography and/or magnetic resonance imaging findings Histologically or cytologically confirmed pancreatic cancer Age ≥20 years-old Ability to understand and willingness to sign a written statement of informed consent Exclusion Moderate or severe cholangitis according to the Tokyo guidelines of cholangitis Involvement of the ampulla of Vater confirmed by endoscopy		SEMS placement was performed as an inpatient procedure in the participating hospitals, each of which had at least 1 experienced endoscopist (defined as ≥10 years of postresidency experience, ≥2000 ERCP or an annual ERCP caseload >200). All units permitted trainees to perform SEMS placement under the supervision of an experienced endoscopist. All patients underwent SEMS placement under sedation using a combination of diazepam, midazolam, and/or pethidine hydrochloride. Various types of ERCP catheters compatible with the 0.035-inch hydrophilic guidewire were used. The rendezvous method of biliary cannulation was permitted in patients who underwent percutaneous biliary drainage; however, precut sphincterotomy was absolutely prohibited, even for difficult biliary cannulations, in both the non-ES and ES groups. Pancreatic sphincterotomy and prophylactic pancreatic stent placement also were prohibited. In the ES group, after successful	Total, n (%) 9 (9.2) 10 (10.4) -1.2% 9.6 to 7.1) Pancreatitis, n 8 9 Mild Pancreatitis, n 3 6 Moderate Pancreatitis, n 3 3 Severe Pancreatitis, n 2 0 Moderate bleeding, n 0 1 Mild Perforation, n 1 0 Early complications related to SEMS placement SEMS (n=100) ES->SEM (n=100) Total, n (%) 15 (15) 15 (15) Pancreatitis, n 8 9 Mild Pancreatitis, n 3 6	influenced by lack) •Blinding of outcome assessment: low (not blinded but outcome unlikely to be affected by this) •Incomplete outcome data: low risk (missing data not likely to have clinically-relevant impact on effect estimates) •Selective reporting: low risk (study protocol available and all outcomes reported) •Other sources of bias: low risk (appears free of other sources of bias)

Study details	Participants	Interventions	Methods	Outcomes and Results			Limitation (risk of bias)
	Billroth II or Roux-en-Y reconstruction after gastrectomy Intestinal obstruction toward the anal direction of the ampulla of Vater Pancreaticobiliary malfunction Biliary stricture extending to the hilum History of placement of a transpapillary biliary drainage tube with a bore larger than 8F History of previous endoscopic sphincterotomy or precut sphincterotomy Current use of anticoagulant or antiplatelet drugs Prothrombin time–international normalized ratio ≥1.5 and/or ≤50,000 platelets/mL		guidewire placement and cholangiography, an incision was made using a standard traction-type sphincterotome with a blended current and was continued until visual recognition of bile outflow or before reaching the upper edge of the oral protrusion in cases without outflow. In both groups, a 10-mm diameter WallFlex Biliary RX Partially Covered Stent (Boston Scientific Japan, Tokyo, Japan) was inserted over the guidewire under fluoroscopic guidance. A 40-, 60-, or 80-mm stent was chosen according to the location and length of the biliary stricture as estimated by withdrawing the catheter or guidewire from the proximal end of the stricture to the ampulla of Vater. The SEMS routinely was placed across the papilla with approximately 10 mm of its distal end exposed to the duodenal lumen. Follow up After the procedure, all patients fasted until the attending physician confirmed that no AEs had occurred. A blood examination routinely	Moderate Pancreatitis, n	3	3	
				Severe Pancreatitis, n	2	0	
				Moderate bleeding, n	0	1	
				Mild Perforation, n	1	0	
				Moderate liver abscess	3	1	
				Epigastric pain	3	2	
				Vomiting	0	2	
				Late complications related to SEMS placement			
					SEMS (n=100)	ES->SEM (n=100)	
				Total, n (%)	5 (5)	6 (6)	
				Severe Pancreatitis, n	0	1	
				Bleeding, n	1	1	
				Mild bleeding	0	0	
				Moderate bleeding	1	0	
				Severe bleeding	0	1	

Study details	Participants	Interventions	Methods	Outcomes and Results			Limitation (risk of bias)
	ECOG performance status of 4 Severe heart or pulmonary disease Any disorder that compromised the patient's ability to provide written informed consent and/or comply with the study procedure.		was performed 24 hours after the procedure. Patients who experienced AEs were treated in the hospital as necessary. After discharge, blood parameters, clinical signs, and symptoms of the patients were monitored by a physician at an outpatient clinic at least monthly until patient death or the end of the study period, and all AEs, cholangitis incidence, and patient survival were recorded by the participating hospitals. All clinical information was collected consistently, even for patients who visited or were transferred to affiliated hospitals. Patients who developed recurrent cholangitis were re-admitted to the participating hospital, and endoscopy was performed to investigate the cause and for palliative treatment. The follow-up period ended 6 months after enrolment of the last patient. Complications Early and late AEs were defined as any SEMS placement–related AE occurring within 30 days or more than 31 days after	Moderate liver abscess	1	0	
				Duodenal ulcer	1	0	
				Early-onset cholecystitis			
					SEMS (n=93)	ES->SEM (n=91)	
				Total	4	1	
				Mild	0	0	
				Moderate	3	1	
				Severe	1	0	
				Late-onset cholecystitis			
					SEMS (n=93)	ES->SEM (n=91)	
				Total	4	1	
				Mild	0	0	
				Moderate	4	1	
				Severe	0	0	
				Cholangitis 25/100 for each group Overall Survival Median OS 202 (170.5-233.5) vs 255 (187.9-322.1), p=0.2 Deaths from PC progression: ES->SEMS 67/100, SEMS 78/100 Serum amylase level 24 hrs after SEMS placement ES->SEMS: 125.76 IU/L (95%CI, 93.53-161.56)			

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
			SEMS placement, respectively. Sample size calculation Assuming an AE rate of 6% in both the non-ES and ES groups, we calculated that 86 patients per group were required to establish noninferiority with a noninferiority margin of 10%, 80% power, and a 2-sided significance level of 5%. Anticipating potential study drop-outs, we enrolled 100 patients per group (200 patients total).	SEMS: 116.97 IU/L (95%CI, 92.84-147.38) P=0.38 (2-way ANOVA)	
Full Citation Isayama, H., Yasuda, I., Ryozawa, S., Maguchi, H., Igarashi, Y., Matsuyama, Y., Katanuma, A., Hasebe, O., Irisawa, A., Itoi, T., Mukai, H., Arisaka, Y., Okushima, K., Uno, K., Kida, M., Tamada, K. Results of a Japanese multicenter, randomized trial of endoscopic stenting for non-resectable pancreatic head cancer (JM-test): Covered Wallstent versus DoubleLayer stent, Digestive	N= 120 patients with unresectable pancreatic head cancer [7 patients excluded due to death, inability to reach papilla, or duodenal obstruction) N=58 Double-layer Plastic stent N=55 Covered SEMS Inclusion Initial diagnosis of non-resectable pancreatic head	Arm 1: Double-layer plastic stent Arm 2: Covered SEMS	Randomisation Patients were registered on the study website and subsequently assigned to one of the two groups by computer-generated randomization using the minimization method stratified on tumour stage and institution. Treatment Each of the participating endoscopists in this study had performed more than 200 ERCP examinations per year for more than 5 years. All stents were 10mm in diameter. All endoprostheses were usually preceded by insertion of a 6-, 7-, or 8.5-Fr	Overall Survival Stent malfunction (occlusion, migration)/time to dysfunction Stent-related complications Median overall survival (days) Plastic stent: 231 (range 31-586) SEMS: 248 (range 8-761) p-value reported as ns HR=1.28 , 95%CI (0.83-1.99) (calculated from number at risk, survival probability, and method 11 Tierney et al 2007) Stent patency Sig higher in SEMS, p=0.0072 Kaplan-Meier curve provided Stent dysfunction Plastic stent: 32/58 SEMS: 18/55	Overall high risk of bias • Random sequence generation: low risk (computer-generated random numbers using minimization) •Allocation concealment: low risk (study website used) •Blinding of participants and personnel assessments: low risk (blinding

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Endoscopy, 23, 310-5, 2011 Country/ies where the study was carried out: Japan Study type: Multicentre, open-label RCT Aim of the study: To assess the efficacy of the DoubleLayer stent (DLS) and Covered Wallstent (CWS) in patients with pancreatic head cancer Study dates: October 2005 to December 2007 Source of funding: None reported	cancer with distal biliary obstruction International Union Against Cancer classification stage 2b, 3 and 4 Written informed consent Exclusion intraductal papillary mucinous neoplasm (IPMN) endoscopic approach impossible performance status 4 American Society of Anesthesiologists Physical Status Classification System grade of 3 and over. Reasons for unresectability Plastic / SEMS Metastasis 23 / 27 Locally 26 / 20		plastic tube stent or a nasobiliary drainage tube at the initial ERCP. After deciding that the tumor was unresectable, the drainage tube was replaced with a 10-Fr plastic stent or SEMS under fluoroscopic guidance using a therapeutic duodenal endoscope (JF-260V, TJF-200; Olympus, Tokyo, Japan). In patients who were deemed unresectable before the initial ERCP, either a plastic stent or SEMS was inserted at the initial ERCP. An endoscopic sphincterotomy was performed and antibiotics given to all patients before stent insertion. The length of the plastic stent was decided according to the stricture location from the papilla. The plastic stent tends to cause bile duct kinking because of its stiffness. Therefore, we carefully selected the stent size to avoid bile duct kinking at the proximal stent end. We selected the length of the SEMS to be as long as possible to avoid stent occlusion by the tumour overgrowing beyond the stent end and to avoid bile duct kinking due to the strong axial force. We placed the center of	Median time to dysfunction (days) Plastic stent: 133 (range 1-429) SEMS: 285 (range 2-536) Log rank p=0.0209 favouring SEMS HR=1.92 (95%CI, 1.11-3.32) [calculated from 50 cases of stent dysfunction and p-value using Tierney et al 2007 method 7) Stent occlusion (patients presenting with jaundice, cholangitis or cholestasis) Plastic stent: 31/58 SEMS: 13/55 Complications DL plastic stent (n-=58) / SEMS (n=55) / p-value Total 4 / 11 / 0.052 Cholecystitis 0 / 4 / 0.053 Pancreatitis 0 / 1 / 0.491 Migration 1 / 5 / 0.110 Liver abscess 2 / 0 / 0.495 Other 1 / 2 / 0.611	unlikely to affect outcome) •Blinding of outcome assessment: low risk (blinding unlikely to affect outcome assessment) •Incomplete outcome data: low risk (missing data not likely to be related to true outcome) •Selective reporting: low risk (all primary and secondary outcomes relevant to review are reported) •Other sources of bias: high risk (all patients received endoscopic sphincterotomy before stent insertion)

Study details	Participants		Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
	advanced			the CWS at the stricture to avoid stent mis-placement due to a large shortening ratio. Double-layer Plastic stent: The plastic stent used in this study was a 10-Fr DLS duodenum bending type. This stent is a Tannenbaum-type plastic stent constructed in three layers – the perfluoroalkoxy,wire mesh, and polyamide elastomer layers in order from the inner lumen – and has four distal and proximal flaps to prevent stent migration. Three lengths of 50mm, 70mm, and 90mm were used. Covered SEMS: a partial silicone (Permalum) cover was used. Both ends of this stent were uncovered for 5 mm. Three lengths of 40, 60, and 80 mm were used. Follow up Blood biochemistry, clinical signs, and symptoms were monitored on an outpatient basis. Stent occlusion was diagnosed when patients presented with jaundice, cholangitis, or cholestasis. Palliative intervention involving either endoscopic or percutaneous drainage was		
	Advanced age	6	5			
	Concomitant disease	1	2			
	Patient request	1	1			

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
			performed as soon as possible, and the causes of stent obstruction were investigated endoscopically or cholangiographically. Most stents involving complications were removed, and the cause of occlusion was determined by examining the removed stents. Complications Definitions not provided. Sample size calculation For a 5%type I error with 80% statistical power, the required number of patients in each group was estimated to be 60.		
Full Citation Kaassis, M., Boyer, J., Dumas, R., Ponchon, T., Coumaros, D., Delcenserie, R., Canard, J. M., Fritsch, J., Rey, J. F., Burtin, P. Plastic or metal stents for malignant stricture of the common bile duct? Results of a randomized prospective study, Gastrointestinal Endoscopy, 57, 178-182, 2003 Country/ies where the study was carried out: France	N = 118 patients with unresectable malignant common bile duct strictures (75% PC patients) n = 59 plastic stent (43 PC patients) n = 59 SEMS (45 PC patients) Inclusion Jaundice, secondary to a malignant common bile duct stricture	Arm 1: Plastic stent Arm 2: SEMS	Randomisation Participants were randomised by means of sealed envelopes (method not stated). Randomisation was balanced with every four patients enrolled, and stratified by centre. Blinding is not reported. Written, informed consent was provided by all participants. Treatment ERCP was performed by experienced endoscopists. Sphincterotomy was performed at the discretion of the endoscopist, as was dilation prior to stent	Stent-related complications Stent malfunction (occlusion/1-year) Time to non-obstruction* Hospitalization Complications at stent placement Plastic (n=59) / SEMS (n=59) Total 4 / 1 Pancreatitis 3 / 0 post-sphincterotomy haemorrhage 1 / 0 cholangitis 0 / 1 First episode of stent occlusion	Overall high risk of bias • Random sequence generation: unclear risk (method not specified) •Allocation concealment: unclear risk (insufficient information) •Blinding of participants and personnel assessments: low risk (not blinded

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Study type: Multicentre RCT Aim of the study To compare the cost effectiveness of a Tannenbaum-type plastic stent and a metal stent in the palliative treatment of patients with unresectable malignant bile duct strictures. Study dates: March 1997 to December 1999 Source of funding: Grant from the Société Francaise d'Endoscopie Digestive.	Contraindication to surgical resection (metastases, advanced age or poor general health) Exclusion ASA grade of 4 or 5 Hilar obstruction Duodenal obstruction caused by tumour potential for benign cause carcinoma of the major papilla prior endoscopic or percutaneous placement of a stent inability to comply with follow up age <18 years		placement. In case of occlusion of a metal stent, a plastic stent was placed inside the original metal stent. If a plastic stent occluded, it was removed and replaced with a second plastic stent. At the discretion of the attending physician, occluded stents could be treated with antibiotics, without changing the stent (if the episode responded to antibiotics, or in patients with a marked deterioration in health status). Plastic stent: A 10F, 90mm long Tannenbaum-type stent (Soehendra ST-2, Wilson Cook, Clarenton, France) was used. SEMS: An 82mm long, 10mm diameter metal stent (Wallstent, Boston Scientifiic Corp, St. Quentin en Yvelines, France) was used. Follow up Immediate follow up included evaluation for complications related to stent placement (within 7 days). Participants were followed for one year (at 2,4,6,9 and 12 months), or until death. Particular note was taken of signs of stent occlusion (jaundice associated with biochemical evidence of	SEMS: 11/59 (18.6%) plastic stent: 22/59 (37.3%) Occulsion rate at 1-year SEMS: 46% Plastic: 70% Time to non-obstruction Only provides Kaplan-Meier curve Median survival SEMS: 5.1 months plastic stent: 3.3 months non-significant Hospitalization (days) Plastic=246 SEMS=80 P<0.05	but unlikely to affect outcomes) •Blinding of outcome assessment: low risk (unclear whether blinded but outcome measurement unlikely to be affected by blinding) •Incomplete outcome data: low risk (no missing data) •Selective reporting: high risk (incomplete reporting of outcomes of interest) •Other sources of bias: high risk (% of weight loss at baseline; some patients received sphincterotomy)

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
			cholestasis, typical cholangitis, episodes of fever with recurrence or worsening of cholestasis and/or hypertransaminasaemia). Adverse events Sample size calculation Not reported.		

Full Citation
Kitano, M., Yamashita, Y., Tanaka, K., Konishi, H., Yazumi, S., Nakai, Y., Takaoka, M. et al. (2013). Covered self-expandable metal stents with an anti-migration system improve patency duration without increased complications compared to uncovered stents for distal biliary obstruction caused by pancreatic carcinoma: a randomized multicenter trial. The American journal of gastroenterology, 108(11), 1713-1722.
Country/ies where the study was carried out:
Japan
Study type:
Multicentre open-label RCT
Aim of the study:
	N = 120 patients with PC and malignant distal biliary obstruction
	cSEMS=60
	ucSEMS=60
	Inclusion
	Malignant biliary obstruction
	Pathologically diagnosed unresectable pancreatic carcinoma
	Clinical stage >IIb
	Exclusion
	Inability to obtain informed consent
	ECOG performance status of 4
	Severe dysfunction in other organs (ASA physical
		Arm 1: Covered SEMS
		Arm 2: Uncovered SEMS
			Randomisation
			If the eligibility criteria were met following these pathological and radiological examinations, patients were registered on the Web. Immediately after Web registration, they were randomly assigned in a 1:1 ratio to either the covered or the uncovered SEMS group without stratification using a random number generator. The results of randomization were open labelled.
			Treatment
			A covered or uncovered SEMS (Wallflex biliary RX stent) was deployed at the biliary stricture after sphincterotomy during ERCP. Both SEMSs are braided by a wire composed of platinum-cored nitinol with 5-mm uncovered flared portions at both ends. Their axial force at a 20-mm distance from the bending point (0.65 N) is
				Survival
				Stent patency
				Time to stent dysfunction or death
				Adverse events
				Overall survival (median)
				At final evaluation 56 patients in each group had died.
				cSEMS=285
				ucSEMS=222
				log rank p=0.68
				Stent patency (median/mean)
				cSEMS=583/mean 219.3 (159.1) days
				ucSEMS=314/mean 166.9 (124.9) days
				log rank p=0.019
				84 of 120 patients censored due to death without stent dysfunction (n=83) or being alive without dysfunction (n=1)
				Time to stent dysfunction or death (median)
				cSEMS=187
				ucSEMS=132
				log rank p=0.043
				# patients with stent dysfunction
				cSEMS=14/60
					Overall high risk of bias
					• Random sequence generation: low risk (random number generator without stratification)
					•Allocation concealment: low risk (central allocation/web-based centre)
					•Blinding of participants and personnel assessments: low risk (Open label trial but unlikely to affect outcomes)
					•Blinding of outcome assessment: low risk (Open label trial but unlikely

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
To assess the advantages of covered vs. uncovered SEMSs in terms of stent patency and safety Study dates: April 2009 to December 2010 Source of funding: None reported	status classification grade III or IV) Life expectancy ≤3 months Hilar biliary obstruction due to lymph node metastases Prior biliary surgery Intraductal papillary mucinous carcinomas Failure of previous drainage by nasobiliary tube or plastic stent Characteristics cSEMS (n=60) / ucSEMS (n=60) Mean age: 70.6 (10.7) / 68.7 (8.9) Male/female: 25/35 / 29/31 Clinical stage, n		relatively low compared to the other SEMSs such as Wallstent. Covered SEMSs are covered by a silicone membrane. The diameter of the stent was 10 mm in all patients whereas its length (40, 60, or 80 mm) was determined according to the location and length of the biliary stricture; the stent extended at least 1 cm above the top of the stricture and approximately 5 mm into the duodenum. Follow up Patients underwent periodic follow-up at the hospital where the stent was deployed and at the branch hospital until the patients' death. Improvement of jaundice was confirmed with serum total bilirubin at 2 and 4 weeks after the deployment of the SEMS. Stent dysfunction and adverse events were also monitored at 4-week intervals after the stent deployment. Sample size calculation The required sample size to achieve statistical relevance was determined based on a previous study of covered and uncovered SEMSs, in which the stent patency rates for covered and uncovered	ucSEMS=22/60 p=0.08 Causes of dysfunction cSEMS / ucSEMS / p-va Tumour ingrowth: 0 / 15 / <0 Tumour overgrowth: 3 / 2 / 0.6 Occlusion/Sludge formation: 11 / 6 / 0.1 Stent migration: 0 / 0 / - Adverse events cSEMS (n=60) / ucSEMS (n=60) Acute pancreatitis: 1 / 0 Acute cholecystitis: 1 / 2	to affect outcomes) •Incomplete outcome data: Low risk (Reasons for missing outcome data not likely to be related to true outcome) •Selective reporting: High risk (outcome of interest reported incompletely) •Other sources of bias: high risk (difference in length of stents; majority of sample had prior drainage)

Study details	Participants		Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
	II 7 14 III 5 1 IV 48 45 Prior drainage 51 50 Total bilirubin (mg/dl) Before stent 5.07 (4.84) 5.29 (6.02) 2 weeks after stent 1.62 (1.37) 1.84 (3.02) 4 weeks after stent 1.22 (0.98) 1.37 (2.67) Chemotherapy 47 47			SEMSs were 86 % and 62 %, respectively. To demonstrate a 24 % difference (86 % vs. 62 %) in the stent patency rate, using a statistical power of 80 % and with the assumption of a two-sided error rate of 0.05, the protocol required at least 112 randomly assigned patients. Therefore, by taking loss to follow-up into consideration, we determined that a sample size of 120 patients was adequate.		
Full Citation Krokidis, M., Fanelli, F., Orgera, G., Tsetis, D., Mouzas, I., Bezzi, M., Hatzidakis, A. et al. (2011). Percutaneous palliation of pancreatic head cancer:	N = 80 patients with unresectable PC and obstructive jaundice cSEMS=40 ucSEMS=40 Inclusion		Arm 1: Covered SEMS Arm 2: Uncovered SEMS	Randomisation Randomization was performed using a randomization envelope containing 40 bare-stent and 40 covered-stent cards. The cards were randomly divided in the two centres	Survival Stent patency Adverse events All patients had died by end of study. Follow up (median) after stent placement: 192 days (range 104-603).	Overall high/unclear risk of bias • Random sequence generation: unclear risk (insufficient

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
randomized comparison of ePTFE/FEP–covered versus uncovered nitinol biliary stents. Cardiovascular and interventional radiology, 34(2), 352-361. Country/ies where the study was carried out: Unclear (two of UK, Italy or Greece) Study type: Multicentre RCT Aim of the study: To compare the clinical effectiveness of expanded polytetrafluoroethylene/ fluorinated-ethylene-propylene (ePTFE/FEP)–covered stents with that of uncovered nitinol stents for the palliation of malignant jaundice caused by inoperable pancreatic head cancer Study dates: January 2005 to December 2008 Source of funding: None reported	obstructive jaundice caused by unresectable pancreatic head adenocarcinoma, which in turn caused occlusion of the biliary tree at the lower half of the common bile duct Informed consent Exclusion Aged > 80 years-old ECOG score <3 Presence of distal metastases other than to adjacent lymph nodes Cirrhosis with portal hypertension Previous surgical or radiotherapeutic palliative treatment Gastric outlet obstruction At least three of the following:		involved in the study, and one card was drawn out after diagnostic percutaneous transhepatic cholangiography (PTC) proved that the patient fulfilled the study's inclusion criteria. Treatment Covered SEMS The Viabil biliary stent (Gore) is a self-expanding covered stent with an expanded polytetrafluoroethylene/fluorinated-ethylene-propylene (ePTFE/FEP) tubular lining that is externally supported by a helical nitinol stent with radiopaque markers at both ends. Uncovered SEMS Bard Luminexx nitinol - a biocompatible nickel–titanium alloy that permits expansion to a preset diameter on exposure to body temperature - biliary stent is an electrpolished, self-expanding, flexible, grid-like endoprosthesis. Percutaenous transhepatic cholangiography (PTC) was performed with the patient under local anaesthesia (lidocaine 2%) and conscious sedation using 1–8 mg midazolam and 50–200 lg fentanyl. Antibiotic prophylaxis	30-day mortality rate=0% for both groups Time to death (days) cSEMS=247 (SD 126.7) ucSEMS=203.2 (SD 74.8) log rank p=0.063 Survival at 3, 6, and 12 months cSEMS=97.5%, 55%, 20% ucSEMS=100%, 57.5%, 7.5% Stent patency cSEMS=234 (SD 132) ucSEMS=166 (SD 82.8) log rank p=0.007 Stent patency at 3, 6 and 12 months cSEMS=97.5%, 92.2%, 87.6% ucSEMS=7.5%, 69.8%, 69.8% Causes of dysfunction cSEMS / ucSEMS / p-valu Stent dysfunction, n: 4 / 12 / 0.04 Tumour ingrowth: 0 / 11 / 0.00 Tumour overgrowth: 2 / 0 / Ns Sludge formation: 2 / 0 / Ns Gastric outlet: 0 / 0 / ns	information about randomisation method) •Allocation concealment: unclear risk (insufficient information) •Blinding of participants and personnel assessments: low risk (Blinding unlikely to affect outcomes) •Blinding of outcome assessment: low risk (Blinding unlikely to affect outcomes) •Incomplete outcome data: Low risk (reasons for missing data unlikely to be related to true outcome) •Selective reporting: high risk (outcomes of interest reported incompletely) •Other sources of bias: low risk (study appears

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
	total serum bilirubin level≥15 mg/dl leucocytosis l≥ 11 x 109/l gamma glutamil transferase > 165 IU/l prothrombin ratio ≥ 1.4 C-reactive protein ≥5 mg/dl Serum carbohydrate antigen 19-9 level ≥ 10.000 IU/ml cSEMS (n= 40) ucSEMS (n= 40) Male /female 17/ 23 36/ 4 Median age 63.5 (9.8) 65 (8.8) Histologic diagnosis 35 32		(750 mg cefuroxime) was administered before the procedure in all patients and was continued for up to 5 days after the drainage and stenting procedure. Right-side access was chosen in most patients, reserving left-side access for patients in whom there was a significant amount of ascites, thus precluding right-side puncture. Stent placement for both stents types was performed either as a one-step (primary stenting technique) or two-step (secondary stenting technique) procedure. The decision for primary or secondary stenting was physician related and was based on morphologic evaluation of the lesion at the moment of initial PTC. Both covered and uncovered stents were advanced approximately 1 cm below the papilla to avoid occlusion caused by distal overgrowth. If the lesion protruded into the duodenum and infiltrated the enteric lumen, a duodenal stent (Wallstent; Boston Scientific) was placed after deployment of the biliary endoprosthesis. The duodenal endoprosthesis was usually	syndrome Adverse events cSEMS ucSEMS Early complications 5 4 Peritoneal irritation (Class B SIR) 3 2 Self-limited biliary haemorrhage (Class A SIR) 2 2	free of other sources of bias)

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
	Average tumour size (cm) 1.9 1.6 Pre-stent median total bilirubin level 6.1 (1.3) 9.3 (1.1)		placed in another session by way of transoesophageal access. Local anaesthesia (spray) and conscious sedation were administered. Follow up Follow-up parameters consisted of blood laboratory examinations, clinical findings, and outpatient imaging results. When the patient presented with jaundice or cholangitis, stent occlusion was suspected. Imaging (US or CT) and clinical evaluation confirmed stent occlusion, and reintervention was followed by ERCP or PTC. ERCP was the initial approach, and PTC was performed when ERCP was not feasible. Sample size calculation None reported`		
Full Citation Kullman, E., Frozanpor, F., Söderlund, C., Linder, S., Sandström, P., Lindhoff-Larsson, A., Ljungman, M. et al. (2010). Covered versus uncovered self-expandable nitinol stents in the palliative treatment of malignant distal biliary obstruction: results from a randomized,	N = 400 patients with malignant bile duct obstruction (77% PC) cSEMS=200 ucSEMS=200 Inclusion ≥20 years-old Informed consent Ultrasound and/or CT	Arm 1: Covered SEMS Arm 2: Uncovered SEMS	Randomisation Used opaque sealed envelopes with computer-generated random numbers in blocks of 20 (10:10) were used, and was performed by the endoscopist when the patient was in the ERCP suite and after the guidewire had passed the stenosis. Stratification of disease groups was not done Treatment	Survival Mortality Stent patency/failure Adverse events Survival (median) cSEMS=116 days (IQR 242) ucSEMS=174 days (IQR 284) Log rank p=-0.32 Stent patency in first quartile (day when 25% occluded) cSEMS=154 days	Overall high risk of bias • Random sequence generation: low risk (computer-generated random numbers in blocks of 20) •Allocation concealment: unclear risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
multicenter study. Gastrointestinal endoscopy, 72(5), 915-923. Country/ies where the study was carried out: Sweden Study type: Multicentre prospective RCT Aim of the study: To compare differences in stent patency, patient survival, and complication rates between covered and uncovered nitinol stents in patients with malignant biliary obstruction. Study dates: January 2006 to October 2008 Source of funding: One author received financial support from Medical Research Council of Southeast Sweden.	performed before inclusion, with findings consistent with malignant bile duct obstruction Clinical data consistent with malignant bile duct obstruction Typical radiological appearance of malignant common bile duct stenosis at ERCP Proximal margin ≥2cm from hepatic confluence Not suitable for radical surgery (if in doubt, temporary plastic stenting permissible if patient randomised and replaced with metal stent within 4 weeks) Exclusion Eligible for curative surgical resection		The endoscopist decided which SEMS length to use, either 52 or 72 mm, depending on the anatomic circumstances and the length of the stenosis. Fully expanded, the stents reached an inner diameter of 10mm. When in an adequate position, the stents should be visible from the duodenal lumen. The membrane of the covered stent was placed inside of the metal mesh, and only the distal 5 mm of the covered stent was uncovered. The delivery systems for the cSEMSs and uSEMSs were 8F and 7F, respectively. Follow up All procedure-related complications according to current routine and consensus recorded. To confirm successful drainage procedure, liver function tests were performed before and 2 to 5 days after stent insertion. Clinical follow-up was performed once per month, starting at 1 month, and the endpoint was 12 months after randomization. Liver function tests were repeated at the 1-month follow-up. At the 2- to 12-month follow-ups, liver	ucSEMS=199 days Log rank p=0.326 Stent patency at 1, 3, 6 and 12 months cSEMS=95, 83%, 74%, 50% ucSEMS=97%, 87%, 78%, 56% Pancreatic cancer subgroup only, log rank p=0.348 Mortality without stent failure and observed stent failures during FU Withdrawn: cSEMS 12; ucSEMS 9 Death within 12 mo with patent stent: cSEMS 122; ucSEMS 116 Alive at 12 mo with patent stent: cSEMS 19; ucSEMS 30 Observed stent failure: cSEMS 47; ucSEMS 45 Causes of stent failure Stent migration: cSEMS 6; ucSEMS 0; p-value 0.03 Occlusion/Sludge formation: cSEMS 12; ucSEMS 4; p-value 0.071 Tumour over- or in-growth: cSEMS 27; ucSEMS 31; p-value >0.5	(insufficient information) •Blinding of participants and personnel assessments: low risk (blinding unlikely to affect outcomes) •Blinding of outcome assessment: low risk (blinding unlikely to affect outcomes) •Incomplete outcome data: Low risk (reasons for missing data unlikely to be related to true outcome) •Selective reporting: high risk (outcomes of interest reported incompletely) •Other sources of bias: high risk (sig. difference between groups in: age, and hepatic or other metastasis, and

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
	Active hepatitis or other hepatic diseases that may cause jaundice Multiple hepatic metastases with significant blockage of one or more liver segments Stenosis within 2 cm of hepatic confluence Suspicion on non-malignant bile duct obstruction Severe coagulation disturbance (PK-INR >1.6, normal 0.9-1.2) Previous Bismuth II or Roux-en-Y gastric resection or significant duodenal obstruction making ERCP difficult Previous inclusion in study Characteristics		function tests were only performed if there had been any history or clinical signs of jaundice, cholangitis, or itching during the past month. Patients who were not able to visit the outpatient clinic were contacted (or, when necessary, their caregivers were contacted) by a trained study nurse using a standardized questionnaire with regard to symptoms indicating signs of stent dysfunction. Sample size calculation To demonstrate increase from 50% to 75% probability for uncensored stent s to survive after 12 months using log-rank test with an α of .05 and a power of 0.90, approximately 360 patients (180 in each group) were required. Patient survival was expected to be 10% after 12 months, and the probability for stent failure while the patient was still alive (observed stent failure) was estimated to be 22% and 10%, respectively. The power calculation was based on 10,000 simulations in which stent failure time and patient survival time had independently shifted exponential distributions	Proximal overgrowth 11 3 0.053 Distal overgrowth 3 2 >0.5 Proximal + distal overgrowth 4 5 >0.5 Ingrowth 9 21 0.035 Unknown 2 10 0.036 Adverse events (no significant differences) cSEMS / ucSEMS Total 14 20 Haemorrhage 0 1 Cholecystitis 2 2 Pancreatitis 3 4 Retroperitoneal perforation 1 1 Cholangitis (medical therapy) 8 12	unknown causes of stent failure)

Study details	Participants		Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
		cSEMS (n=200)	ucSEMS (n=200)	starting at day 29, and a general censoring was planned after day 365 (end of follow-up).		
	Male/female	88/112	91/109			
	Age	79 (range 39-100)	76 (range 51-95)			
	Who classification (0/1/2/3/4)	47/47/77/27/2	42/48/74/30/6			
	Previous cholecystectomy	23	22			
	Plastic stent before inclusion	29	30			

Study details	Participants		Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
	Days with plastic stent	14 14				
	Antibiotic treatment or prophylaxis	20 29				
	Sphincterotomy	200 200				
	Precut	58 57				
	Diagnosis					
	Pancreatic cancer	152 155				
	Cholangiocarcinoma	12 10				
	Gallbladder cancer	8 3				
	Ampullary	8 9				

Study details	Participants		Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
	cancer					
	Metastatic nodes	16 18				
	Unknown	4 5				
	Hepatic or other metastasis*	90 66				
	Ingrowth in large vessels	63 57				
	Portal vein thrombosis	11 10				
	*Sig. diff, p=0.018					
Full Citation Moses, P. L., Alnaamani, K. M., Barkun, A. N., Gordon, S. R., Mitty, R. D., Branch, M. S., Kowalski, T. E., Martel, M., Adam, V. Randomized trial in malignant biliary obstruction: plastic vs partially covered metal	N = 85 patients with unresectable malignant biliary obstruction (58 PC patients) n = 43 plastic stent (29 PC patients) n = 42 SEMS (29 PC patients)		Arm 1: Plastic stent Arm 2: Partially covered SEMS	Randomisation Method of randomisation not described. The allocation sequence was performed centrally by a third party, not involved with patient care. Participants were allocated to the different interventions in a 1:1 fashion. Sealed envelopes (containing the group allocation) were opened at the	Reduction in bilirubin levels* Time to stent failure Overall survival Stent-related complications Hospitalization Study terminated early due to slow down of participant accrual. Reduction in bilirubin levels (%) Plastic: 63.7 (95%CI 45.5-81.9)	Overall high/unclear risk of bias • Random sequence generation: unclear (no details of method provided)

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
stents, World journal of gastroenterology, 19, 8638-46, 2013 Country/ies where the study was carried out: USA Study type: Multicentre RCT Aim of the study: To compare efficacy and complications of partially covered self-expandable metal stents (SEMS) with plastic stents in patients with malignant, infrahilar biliary obstruction. Study dates: Not reported. Recruitment occurred over 37 months. Source of funding: Boston Scientific Inc; Cook Endoscopy Pentax Corp.	Inclusion aged ≥18 years written informed consent laboratory/imaging and/or histological evidence of malignant biliary obstruction intrinsic or extrinsic malignancy extending to no more that 1cm below the common hepatic ductal bifurcation anticipated life expectancy that would allow for full follow up Exclusion Jaundice related to intrahepatic cholestasis or obstruction Prior attempt at curative surgical resection for the biliary obstructing lesion		time of intended stent insertion. No blinding was conducted. All participants provided written, informed consent. Treatment ERCP was performed by experienced endoscopists. After confirmation of obstruction meeting trial criteria, sealed envelope randomisation was performed. Stents were placed with or without prior dilatation or sphincterotomy at the discretion of the endoscopist. A cholangiogram was performed to document stent patency and position. Plastic stent: A 10Fr Amsterdam-type polyethylene plastic biliary stent was used. SEMS: Partially covered self-expandable metal stents (Wallstent Endoscopic Biliary Prosthesis with Permalume, Boston Scientific, Natick, MA) were inserted. Follow up Each patient had one and three month follow-up, followed by quarterly scheduled follow-up sessions up to 2 years following stent insertion. Sample size calculation	SEMS: 74 (95%CI 60-87.9) Time to stent failure (cholestatic symptoms plus a 50% increase in bilirubin, and/or cholangitis, or repeat ERCP for stent replacement/suspected obstruction) partially covered SEMS group: 385.3 ± 52.5 days plastic stent group: 153.3 ± 19.8 days log rank p= 0.0061 Adjusted for confounding variables, HR=0.29 (95%CI, 0.12-0.75), p=0.011 Overall survival partially covered SEMS group: 192.3 ± 23.4 days plastic stent group: 211.5 ± 28.0 days log rank p = 0.6977 Stent-related complications Plastic (n=41) / SEMS (n=41) / P-valu Pancreatitis 1 / 1 / 1 Cholangitis 10 / 2 / 0.029 Cholecystitis 0 / 2 / 0.4741 % patients with cholestatic symptoms at FU Plastic: 33.3 (13/39) SEMS 24.3 (10/40) Procedure-related hospitalization (days) Plastic: 4.9 (4.7)	•Allocation concealment: low risk (central allocation used) •Blinding of participants and personnel assessments: low risk (no blinding but unlikely to affect outcomes) •Blinding of outcome assessment: low risk (no assessor blinding but unlikely to affect measurement)/high risk for QoL outcomes (blinding likely to affect outcomes) •Incomplete outcome data: low risk (reasons for missing data unlikely to be related to true outcome) •Selective reporting: high risk (incomplete reporting of outcomes) •Other sources of bias: low risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
			A 60% improvement in stent patency duration with SEMS was assumed, with a type I error of 5% and type II error of 20%. This gave a required sample size of 60 participants in each group.	SEMS: 2.5 (1.6)	(appears free of other sources of bias)
Full Citation Schmidt, A., Riecken, B., Rische, S., Klinger, C., Jakobs, R., Bechtler, M., Kahler, G., Dormann, A., Caca, K. Wing-shaped plastic stents vsself-expandable metal stents for palliative drainage of malignant distal biliary obstruction: A randomized multicenter study, Endoscopy, 56, 2015 Country/ies where the study was carried out: Germany Study type: Multicentre non-inferiority RCT Aim of the study: To compare a newly designed, wing-shaped plastic stent without a central lumen to a self-expanding metal stent (SEMS) for biliary drainage in patients with	N=37 patients with unresectable biliary obstruction (24 PC patients) (3 patients excluded due to hilar stenosis or protocol violation) N=16 winged plastic stent (12 PC patients) N=18 SEMS (12 PC patients) Inclusion unresectable biliary obstruction age >18 years written consent signs of cholestasis (2 of 3: ultrasound showing dilated intra- or extrahepatic bile duct; bilirubin ≥2mg/dL or increase ≥1mg/dL, or	Arm 1: Wing-shaped plastic stent Arm 2: SEMS	Randomisation Randomisation was performed with a computer-generated random number series, with odd numbers encoding SEMs, and even numbers for winged stents. Randomisation was performed centrally, directly after inclusion of each patients. No stratification was performed. Blinding is not reported. Informed consent was obtained from all patients. Treatment All procedures were performed by experienced endoscopists. Sphincterotomy was performed in all cases. Winged plastic stent: The ViaDuct plastic stent (GI Supply, Camp Hill, Pennsylvania, USA) was used for biliary drainage. It includes a winged perimeter, allowing bile to flow through channels along the outside of the stent rather than through a central lumen. Only a very narrow	Stent malfunction (occlusion, migration or stent fracture)/Time to stent failure Stent-related complications Overall survival/mortality Treatment-related mortality # ≥30% decrease bilirubin Note: Original aim of study was to demonstrate non-inferiority of winged plastic stent but after interim analysis (in which this stent was obviously inferior), aim changed to examination of stent failure. Stent failure (2 or more of following): a) ultrasound showing new dilation of intrahepatic or extrahepatic bile ducts; b) bilirubin ≥2mg/dL with increase ≥1mg/dL compared to the value after initial successful drainage, or elevation of alkaline phosphatise and/or gamma glutamyltransferase more than twice the normal value with an increase of at least 30U/L; c) signs of cholangitis (fever and leukocyte count >10×109/L or C-reactive protein >20mg/dL). Stent failure/dysfunction Winged stent group: 10/16 (62.5%) SEMS group: 4/18 (22.2%) Time to stent failure	Overall high risk of bias • Random sequence generation: low risk (computer-generated random numbers) •Allocation concealment: low risk (central allocation used) •Blinding of participants and personnel assessments: low risk (no blinding but outcomes unlikely to be affected) •Blinding of outcome assessment: low risk (outcome measurement unlikely to be affected) •Incomplete outcome data:

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
unresectable biliary obstruction. Study dates: March 2010 to January 2013. Source of funding: None reported	elevated ALP/GGT more than twice the normal value or increase of at least 30U/L; fever or leucocyte count >1000million/L or CRP >20mg/dL) malignant distal bile obstruction histologically or cytologically proven malignancy Exclusion potentially resectable malignancy previous treatment with biliary SEMS Billroth II or Roux en Y postoperative situs Pregnancy Psychiatric disorder, or alcohol/drug abuse and unable to comply with study protocol		central lumen is present, used for guidewire insertion. SEMS: Commercially available metal stents with a diameter of 10mm were used. The endoscopist could choose whether to use covered, partially covered or uncovered stents Follow up All ERCP related complications and technical difficulties were recorded. Liver function tests were performed before and 5 days after intervention to confirm adequate biliary drainage. Successful drainage was assumed when serum bilirubin levels had declined by at least 30%. A trained study nurse performed standardised telephone follow up, focusing on symptoms of stent dysfunction (fever, jaundice, pain) every 6 weeks for a maximum period of 12 months. Sample size calculation The trial was designed as a non-inferiority study. To detect a ratio of SEMS and plastic stent patency of at least 89%, with 80% power and a type 1 error of 0.05, 38 patients would be needed per group.	Log rank p=0.002 HR=6.22 (95%CI, 1.95-19.84) [calculated using # of stent failures and p-value, and Tierney et al 2007 method 7] Stent occlusion Winged stent: 8/16 SEMS: 2/18 Mortality Plastic 6/16 SEMS 13/18 Survival Winged stent group: 74 days (range 1-523); mean=159.6 SEMS group: 141.5 days (range 14-363); mean=164.7 No sig diff between groups, p=0.957 HR=1.03 (95%CI, 0.39-2.7) [calculated using no of deaths, p-value, Tierney et al 2007 method 7] Adverse events All stents placed without adverse events and no procedure-related mortality. Stent migration not observed in either group. No other stent-related AEs. Stent-related complications Winged stent (n=16) SEMS (n=18) Cholangitis 5 2	low risk (missing data unlikely to be related to true outcome) •Selective reporting: high risk (incomplete reporting of outcomes of interest) •Other sources of bias: low risk (study terminated early due to high rate of winged stent failure)

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
	Estimated life expectancy < 3 months Karnofsky index <60%		An interim analysis was performed after recruitment of 50% of patients due to an unexpectedly high frequency of stent failure in the plastic stent group.	Cholecystitis 1 0 # ≥30% decrease in serum bilirubin levels (successful drainage) Winged stent: 15/16 SEMS: 18/18	
Full Citation Söderlund, C. & Linder, S. Covered metal versus plastic stents for malignant common bile duct stenosis: a prospective, randomized, controlled trial, Gastrointestinal Endoscopy, 63, 986-95, 2006 Country/ies where the study was carried out: Sweden Study type: Single centre RCT Aim of the study: To compare the patency of plastic stents with covered self-expanding metal stents in patients with malignant distal bile duct strictures. Study dates: August 2001 to April 2003. Source of funding:	N = 100 non-referred patients with unresectable malignant common bile duct strictures (78 PC patients) N=51 plastic stent (38 PC patients) n = 49 covered SEMS (40 PC patients) Inclusion Clinical data and history suggestive of malignant bile duct obstruction, found not to be amenable to resection. radiological appearance of a common bile duct malignant stricture and bilirubin level >50µmol/L	Arm 1: Plastic stent with ERCP Arm 2: Covered SEMS with ERCP	Randomisation Patients were randomised (without stratification of blocking) to one of the two groups using opaque, sealed envelopes and a random table technique. Randomisation occurred when the patient was in the ERCP suite, once the guidewire was in place. Blinding was not applied. Informed consent was obtained from all participants. Treatment Both stents were from Boston Scientific Nordic AB, Helsingborg, Sweden. If the patient had not been investigated adequately an 8.5F thin polyethylene stent was inserted first. At a second session (as soon as possible, but always within 1 month) randomisation was performed and the stent was switched to the appropriate study stent. Plastic stent: A polyethylene plastic 10F endoprosthesis with distal and proximal side	Treatment-related mortality Overall Survival Stent patency* Stent-related complications Aspartate aminotransferase/serum bilirubin levels Functional success (appropriate decline in bilirubin) plastic stent group: 50/51 covered SEMS group: 47/49 Treatment related mortality plastic stent group: 1/51 covered SEMS group: 0/49 Median survival time (SEMS vs plastic) plastic stent group: 3.9 months covered SEMS group: 5.3 months HR 1.25 (95% CI 0.84-1.87), p=0.2776 Stent failures (clinical (cholangitis) and laboratory (S-bilirubin >50 mmol/L, previously normal) signs of stent occlusion confirmed by ERC (dilation of bile ducts proximal to the stricture, occluded or dislocated stent with little, if any, passage of contrast dye) and requiring insertion of a new stent)	Overall low risk of bias • Random sequence generation: low risk (random number table used) •Allocation concealment: low risk (sealed, opaque envelopes with random number table) •Blinding of participants and personnel assessments: low risk (no blinding but outcome unlikely to be affected) •Blinding of outcome assessment: low risk (no blinding but unlikely to

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Boston Scientific Nordic AB, Helsingborg, Sweden.	(normal <26µmol/L) ultrasound and CT and/or MRI performed informed consent obtained Exclusion Extremely poor medical condition, such that ERC with stent impossible for ethical reasons Candidate for surgical resection Stenosis in, or close to, hilum of the liver Suspected non-malignant obstruction Previous Billroth type II gastric resection, pyloric or duodenal obstruction making ERCP difficult Previous treatment with bile duct stent, except temporary		flaps and adjacent side holes was used. Covered SEMS: A silcone polymer-covered self-expandable steel metal Wallstent was used. Follow up Participants attended outpatient follow-up appointments at one month, four months and 10 months (end point) after stent insertion. Study end points were uneventful follow up at ten months, death and confirmed stent failure (ERC with intervention). Patients and caregivers were given information on the symptoms of cholangitis and asked to contact the hospital immediately in case of signs of obstruction. If stent obstruction was suspected, ERC was performed. The stent was switched to a SEMS in cases of occluded plastic stent. In cases of occluded metal stent, a plastic stent was inserted inside the metal endoprosthesis. Records from hospices and other primary care facilities were evaluated for signs of stent dysfunction. Complications Sample size calculation	During 10 month follow up plastic stent group: 22/49 covered SEMS group: 9/49 Median stent patency time (SEMS vs plastic) plastic stent group: 1.8 months covered SEMS group: 3.6 months HR: 1.94 (95% CI 1.24-2.95), p=0.002 Stent-related complications Plastic (n=51) / SEMS (n=49) Pancreatitis 0 / 1 Cholangitis 2 / 0 Bleeding* 0 / 1 Aspartate aminotransferase – rate of change at 2 days P=0.036 favouring SEMS Serum bilirubin – rate of change at 2 days P=0.267 favouring SEMS	affect outcome measurement) •Incomplete outcome data: low risk (missing data unlikely to be related to true outcome) •Selective reporting: low risk (all outcomes reported as expected) •Other sources of bias: low risk (appears free from other sources of bias)

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
	(<4 weeks) 8.5F plastic stent severe coagulation disturbance		We expected a failure rate of up to 50% in the PE stent group (at 3 months), with failure defined as clinical cholangitis and/or confirmed stent occlusion with or without ERC intervention. To show a reduction to 15% (70% reduction) with a metal stent, with α error of 0.05 and a power of 0.8, at least 75 patients would have to be included. Therefore, we included 100 patients.		
Full Citation Song, T. J., Lee, S. S., Yun, S. C., Park, D. H., Seo, D. W., Lee, S. K., Kim, M. H. Paclitaxel-eluting covered metal stents versus covered metal stents for distal malignant biliary obstruction: a prospective comparative pilot study, Gastrointestinal Endoscopy, 73, 727-733, 2011 Country/ies where the study was carried out: South Korea Study type: Single centre RCT Aim of the study:	N= 52 patients with unresectable distal malignant biliary obstruction (25 PC patients) who did not want to undergo chemotherapy or radiotherapy N=26 Paclitaxel-eluting SEMS (13 PC patients) N=26 covered SEMS (12 PC patients) Inclusion Patients had distal malignant biliary obstruction Exclusion Loss at follow up	Arm 1: Paclitaxel-eluting SEMS with ERCP Arm 2: Covered SEMS with ERCP	Randomisation Randomization of the patients was performed before the procedure by 1 endoscopist using computer-generated Numbers. All patients provided written informed consent, and this study was approved by the institutional review board of our hospital. Treatment ERCP was performed by 5 expert pancreatobiliary endoscopists. The covering membranes of both paclitaxel-eluting SEMS (PESEMS) and covered SEMS have a double-layer structure. Other than covering of outer layer, both stents had same shape and structure. The inner layer of both stents was covered with	Overall Survival Time to stent obstruction Stent malfunction (occlusion) Complications Survival for all patients (n=49; PESEMS vs covered SEMS) HR=1.18, 95%CI (0.64-2.17), p=0.596 Survival for PC patients (PESEMS vs covered SEMS) HR=0.85, 95%CI (0.35-2.08), p=0.729 Time to stent obstruction for all patients HR=0.53 (95%CI, 0.16-1.78), p=0.307 Time to stent obstruction for PC patients HR=0.52 (95%CI, 0.1-3.09), p=0.468 Stent malfunction (occlusion) PESEMS (n=24) Covered SEMS (n=25)	Overall high risk of bias (Only 51% PC patients DOWNGRADED for INDIRECTNESS) • Random sequence generation: Low risk (computer-generated numbers) •Allocation concealment: Unclear (No details provided) •Blinding of participants and personnel assessments: low risk (no blinding

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
To compare the efficacy and complication rates of PECMSs and the control covered metal stents (CCMSs) in patients with malignant biliary obstruction Study dates: November 2006 to June 2008 Source of funding: None reported			a silicone membrane to protect the polyurethane membrane from bile flow. The inner silicone membrane also prevents paclitaxel leakage into the luminal side. To minimize the risk of sepsis or abscess formation, before the procedure, all patients were given prophylactic antibiotics to cover both gram-positive and gram–negative bacteria. Both the PECMSs and covered SEMS were 10 mm wide and 60 to 80 mm long when fully expanded. They were mounted on an 8.5F stent introducer set. Stents were inserted by using a standard ERCP technique after a biliary sphincterotomy to facilitate stent insertion. The length of the stents was determined according to the length of the bile duct stricture. A stent was inserted to 1.5 to 2 cm proximal to the end of the stricture. Paclitaxel-eluting SEMS: The outer layer of was covered with a polyurethane solution containing 20% (wt/vol) paclitaxel (Taxol; SamYang, Daejeon, South Korea). Covered SEMS: The outer layer was covered	Tumour ingrowth 5 4 Distal stent migration 0 4 No sig diff in stent malfunction betweer groups, p=0.376 Early complications PESEMS (n=24) Covered SEMS (n=25) Cholangitis-like symptoms 3 0 Pancreatitits (mild) 1 1 No sig diff in complications between groups, p=0.189	but unlikely to affect outcomes) •Blinding of outcome assessment: Unclear (no details provided) •Incomplete outcome data: Low risk (2 patients in PESEMS group and 1 patient in covered SEMS group excluded due to loss at follow up within 1 month of stent insertion) •Selective reporting: Unclear (no protocol available) •Other sources of bias: High risk (no power calculation; participants were selected from patients who did not want chemotherapy nor radiotherapy)

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
			with a polyurethane solution that did not contain paclitaxel. Complications An early complication was defined as any complication during the procedure or within 1 week of insertion, including cholangitis, pancreatitis, cholecystitis, bleeding, or stent migration. A late complication was defined as any stent-related event, including stent migration and occlusion, occurring later than a week from the insertion of the stent. Stent occlusion was diagnosed when signs of cholangitis developed or when the total serum bilirubin level increased twofold or more above the baseline level after stent insertion. Stent migration was defined as the proximal or distal displacement of the stent from the initial insertion site. Tumour ingrowth was defined as the direct growth of a tumour into the stent lumen. Tumour overgrowth was defined as the growth of a tumour proximal to the end of the stent. Follow up		

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
			Follow-up was based on findings at outpatient examinations. Serum bilirubin and liver enzyme levels (alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyl transpeptidase) were routinely checked before and after stent placement and were also checked at 1, 2, 4, and 12 weeks after placement of the stent unless there was clinical evidence of complications. Imaging, including US and CT, was routinely performed every 3 months. If stent occlusion was suspected clinically or radiologically, we performed ERCP with balloon sweeping and endobiliary biopsy/brush cytology. Sample size calculation No power calculation was performed		
Full Citation Travis, S.& Nicholson, T. Palliation of unresectable pancreatic malignant biliary obstruction: Results of a randomized trial comparing percutaneously placed	N= 62 PC patients with unresectable malignant biliary obstruction (10 patients excluded due to subsequent clinical course,	Arm 1: Plastic stent with percutaneous transhepatic cholangiography	Randomisation Sealed envelope. Randomization occurred when decision to palliate with stent was made. Treatment Unresectable status determined in all patients by	Overall survival* Stent malfunction (occlusion) Complications* Study stopped after recruiting 62 patients due to clear differences in pain and complications between groups.	Overall high/unclear risk of bias • Random sequence generation: unclear risk (no details of method provided)

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
metal and plastic endoprostheses, Journal of Interventional Radiology, 12, 17-21, 1997 Country/ies where the study was carried out: UK Study type: Single centre RCT Aim of the study: To study safety, patient comfort, effectiveness and costs involved in percutaneous insertion of Wallstents compared to plastic stents in palliation of malignant biliary obstruction. Study dates: Not reported Source of funding: None reported	histology, or post-mortem examination demonstrated benign disease or bile duct neoplasia) N= 20 Plastic stent N=32 SEMS Inclusion Malignant obstructive jaundice caused by pancreatic cancer Informed consent Exclusion Patients with resectable PC (Stage 1 or 2a) Bismuth 2-4 lesions considered to be cholangiocarcinomas Hepato-renal failure in patients over 80 years old	Arm 2: SEMS with percutaneous transhepatic cholangiography	transabdominal ultrasound (3.5 MHz transducer, Aloka) and contrast-enhanced scan (Siemens DRH scanner, 4mm slices through liver and pancreas). Twelve of these also had percutaneous CT or ultrasound-guided biopsy. Twenty-eight patients had previous ERCP but endoscopic palliation proved too difficult. Patient provided with information about level of pain to expect, and consented 24 h before intervention. All received broad spectrum cephalosporim (1.5 g Cephuroxime) 2h prior to, and opiate analgesia (100 mg pethidine) immediately prior, to intervention. Four liters of oxygen were also given via nasal cannulae throughout procedure and intravenous benziodiazepine (2.5 mg Midazolam) was given once mandrill wire in place. Patients monitored for blood pressure and pulse oximetry. In all patients, initial percutaneous transhepatic cholangiography (PTC) performed using 21 gauage Chiba needle (Cook UK Ltd). Plastic stent: 8.3-F Ring-Lunderquisy catheter (Cook UK ltd) placed with side holes	All patients' serum bilirubin levels returned to within 2SD of normal mean (5-17 mmoles/l). Survival (weeks) Plastic: 46 (range 12-101) SEMS: 48 (range 8-102) Stent-related complications Total: Plastic (n=20) 19; SEMS (n=32) 0 Fever: Plastic 5; SEMS 0 Bile leakage>24 h: Plastic 1; SEMS 0 Bile leakage + fever: Plastic 10; SEMS 0 Occlusion # recurrent jaundice + cholangitis Plastic: 4/20 SEMS: 2/32 #recurrent jaundice + requiring 2nd reintervention Plastic: 3/20 SEMS: 0/32	•Allocation concealment: unclear risk (insufficient information) •Blinding of participants and personnel assessments: unclear risk (insufficient information) •Blinding of outcome assessment: unclear risk (insufficient information) •Incomplete outcome data: high risk (imbalance in group numbers) •Selective reporting: high risk (incomplete outcome reporting) •Other sources of bias: low risk (appears free from other sources of bias)

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
			above and below obstructing lesion. Bile aspirated to decompress ducts and after 24h drainage, catheter exchanged for 12-Fr peel-away sheath through which a 12F double mushroom Miller endoprosthesis was placed. After confirming position and free flow of contrast into duodenum catheter were withdrawn. Intravenous cephuroxime continued for 24h. SEMS: standard 7F vascular sheath inserted over Amplatz wire, and 1x10cm Wallstent released over wire with tip in duodenum. Patency checked by contrast injection through sheath side arm and bile ducts decompressed via same route. Sheath left for 24 h to tamponade track. Intravenous cephuroxime continued for 24h. Follow up All major and minor complications noted, degree of pain (measured by amount of analgesia required during inpatient stay), and length of stay from procedure. Sample size calculation None reported		

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Full Citation Telford, J. J., Carr-Locke, D. L., Baron, T. H., Poneros, J. M., Bounds, B. C., Kelsey, P. B., Saltzman, J. R. et al. (2010). A randomized trial comparing uncovered and partially covered self-expandable metal stents in the palliation of distal malignant biliary obstruction. Gastrointestinal endoscopy, 72(5), 907-914. Country/ies where the study was carried out: USA Study type: Multicentre tertiary care RCT Aim of the study: To prospectively compare an uncovered and partially covered SEMS in the palliation of distal malignant biliary obstruction Study dates: October 2002 to May 2008 Source of funding:	N = 129 patients with malignant distal biliary obstruction (82% PC patients) Uncovered SEMS=61 Partially covered SEMS=68 Inclusion ≥18 years-old Malignant distal (≥1 cm distal to biliary hilum) biliary obstruction amenable to stent placement Not eligible for curative surgical resection due to tumour stage, operative risk or patient wishes Exclusion Inability to obtain informed consent Contraindication to ERCP Prior biliary SEMS placement Prior biliary surgery Characteristics ucSEM pcSE	Arm 1: Uncovered SEMS Arm 2: Partially covered SEMS	Randomisation Subjects randomized at time of ERCP after successful placement of guidewire across malignant stricture. Subjects received either an uncovered or a Permalume partially convered Wallstent. Randomisation conducted in permuted blocks to balance stent assignment over 4 sites using random number generator. Stent assignment written on card, sealed in identical opaque envelopes and distributed to sites. Assignment concealed until this interim analysis. Patient and research assistant conducting interviews were both blinded to group assignment. Treatment All stents inserted during ERCP in the usual fashion by experienced pancreaticobiliary endoscopists. Performance of sphincterotomy or biliary dilation before stent insertion was at the discretion of the endoscopist. Opacification of the cystic duct during cholangiography and whether the stent traversed the cystic duct orifice were recorded	Survival Time to stent obstruction Adverse events Follow up (days) Uncovered SEMS=125 (range 0-793)/mean=217 (208) pcSEMS=201 (range 0-1302)/mean=244 (231) Median survival (days) Uncovered SEMS=239 (IQR 84-401) pcSEMS=227 (IQR 99-365) log rank p=0.997 Days to biliary obstruction Uncovered SEMS=711 (IQR 283-upper CI not provided due to censoring) pcSEMS=357 (IQR 264-1302) HR=1.27 (95%CI, 0.6-2.7), p=0.53 [pcSEMS vs ucSEMS] Probability of no obstruction at 6 months Uncovered SEMS=0.9 pcSEMS=0.87 Probability of no obstruction at 12 months Uncovered SEMS=0.55 pcSEMS=0.47 Adverse events ucSEMS (n=61) pcSEMS (n=68) Serious AEs 27 42	Overall high/unclear risk of bias • Random sequence generation: Low risk (permuted blocks using random number generator) •Allocation concealment: Unclear risk (insufficient information) •Blinding of participants and personnel assessments: Low risk (Blinding unlikely to affect outcomes) •Blinding of outcome assessment: low risk (Blinding unlikely to affect outcomes) •Incomplete outcome data: High risk (imbalance in numbers due to failure to attain adequately powered groups)

Study details	Participants		Interventions	Methods	Outcomes and Results			Limitation (risk of bias)
Funded in part by an American Society for Gastrointestinal Endoscopy Outcomes and Effectiveness Award. Boston Scientific Corporation provided paper case report forms and an electronic database as well as an unrestricted grant that provided partial support for a research assistant once funding from the American Society for Gastrointestinal Endoscopy award was finished.		S (n=61)	MS (n=68)	Follow up Follow-up data collected by telephone interview conducted by research assistant 1 week after stent insertion and then monthly until patient death. The interview questions evaluated for biliary obstruction, adverse events, and adjuvant therapy. In addition to the scheduled interviews, the patient was instructed to call a pager if symptoms of recurrent biliary obstruction developed. The research assistant also obtained reports of any pertinent investigations conducted at outside hospitals. Patients were considered to be lost to follow-up if they could not be contacted or declined to participate with the telephone interview within 6 months of randomization. Multiple attempts were made to contact a patient before classifying him or her as lost to follow-up. Patients lost to follow-up were analysed in an intention-to-treat fashion and censored at the time of their last follow-up interview. Sample size calculation	Recurrent biliary obstruction	11	20	•Selective reporting: High risk (outcomes of interest incompletely reported) •Other sources of bias: low risk (no other apparent sources of bias)
	Mean age	65	66		Stent migration	0	8	
	Male, n	31	30		Pancreatitis	1	0	
	Mean Karnofsky score (SD)	74 (17)	77 (18)		Cholecystitis (patients with gallbladder)	3/45	3/46	
	Pancreatic cancer, n	47	59		Other	12	17	
	Metastatic disease, n	30	31					
	Gallbladder in situ	45	46					

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
	Prior plastic stent 42 40 Adjuvant therapy* Chemotherapy 14 26 Radiation therapy 0 4 Both 6 5 *Sig. more in pcSEMS group received adjuvant therapy (p=0.037)		To demonstrate a 20% difference in the time to recurrent biliary obstruction between the two stents, with a beta error of 0.20 and an alpha error of 0.05, we estimated that 125 patients were required. An interim analysis was planned once 100 patients had been randomized and followed for 6 months. The results of the interim analysis have been presented in abstract form. There was no difference in time to recurrent biliary obstruction, time to death, or total serious adverse events between the two groups. To account for the interim analysis, the total sample size was increased by 10% to 136 patients.		
Full Citation Ung, K. A., Stotzer, P. O., Nilsson, Å., Gustavsson, M. L., & Johnsson, E. (2013). Covered and uncovered self-expandable metallic Hanarostents are equally efficacious in the drainage of extrahepatic	N = 71 patients with incurable malignant distal biliary obstruction (84% PC) cSEMS=34 ucSEMS=34 Inclusion Jaundice due to incurable	Arm 1: Covered SEMS Arm 2: Uncovered SEMS	Randomisation Patients were randomized to receive a covered or an uncovered stent using sealed, numbered, opaque envelopes half containing a card marked “Covered” and half containing a card marked “Uncovered”. The randomization procedure was performed in the ERCP	Survival Stent patency Adverse events Survival (median) cSEMS=154 days (IQR 65-217; range 21-609) ucSEMS=157 (IQR 70-273; range 20-690) Mortality with patent stent	Overall high risk of bias • Random sequence generation: unclear risk (method not described) •Allocation concealment: low

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
malignant strictures. Results of a double-blind randomized study. Scandinavian journal of gastroenterology, 48(4), 459-465. Country/ies where the study was carried out: Sweden Study type: Multicentre double-blind RCT Aim of the study: (1) To compare the patency of covered and uncovered bile duct SEMS and (2) to study the efficacy of drainage, the technical success and the complication rate. Study dates: October 2006 to April 2009 Source of funding: Supported by grants from the R&D Council in Western Götaland Region, the Faculty of Medicine and the Faculty of Surgery, University of Gothenburg. Supported with a grant of SEK30.000 from Olympus Sweden, the	malignant distal biliary obstruction [Criteria for 'incurable' obstruction: Distant metastases Locally advanced malignancy with arterial involvement, venous involvement to more than 50% of circumference and length of >2cm or signs of inability to perform an R0 resection Ineligible for major surgery (e.g. high age, concomitant diseases, affected general well being.] Exclusion Hilar strictures Expected survival time <3 months Characteristics cSEMS ucSEMS		suite by opening the sealed envelopes consecutively The stent type was documented in the endoscopy report using a code. The code lock was kept at a research centre and could only be broken if there was an urgent need for clinical reasons. The endoscopists and the staff at the endoscopy suite were not involved in the care or follow-up of the patient after the stenting procedure and the type of stent was thus blinded to all investigators involved in the follow-up as well as to the patients. Treatment All procedures performed by one of 3 experienced endoscopists at one of 2 centres. ERCPs performed under conscious sedation. Stricture length was measured using a guidewire and a stent was chosen that was about 2 cm longer than the distance between the upper limit of the stricture and the papilla. A covered or uncovered Hanarostent with a length of 40, 60 or 80 mm was used and the distal end of the stent was placed in the duodenum.	cSEMS=30/34 ucSEMS=28/34 Stent patency (median) cSEMS=153 days (IQR 65-217; range 20-609) ucSEMS=127 (IQR 70-196; range 18-486) Stent occlusion cSEMS=4/30 ucSEMS=6/34 Adverse events Two occurrences of early complications both in covered SEMS group (1 pancreatitis, 1 sepsis). No statistically significant difference in adverse events (data not reported)	risk (numbered, sealed, opaque envelopes; independent trial centre) •Blinding of participants and personnel assessments: low risk (double blinded but not likely to affect outcomes) •Blinding of outcome assessment: low risk (assessor blinded but not likely to affect outcomes) •Incomplete outcome data: Low risk (reasons for missing data unlikely to be related to true outcome) •Selective reporting: high risk (outcomes of interest reported incompletely) •Other sources of bias: high risk

Study details	Participants		Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
agent that sells Hanarostents in Sweden.	Age	77 (range 54-88)	79 (range 54-92)	These stents are made of braided nitinol wires. The covered SEMS used in this study were coated for their entire length with a silicone membrane. A small sphincterotomy using a pull-type sphincterotome or a needleknife precut papillotomy was performed before the insertion of the stent, if this was considered necessary. The procedure was performed under fluoroscopic guidance but radiological control of stent expansion after the procedure was not carried out routinely. Follow up Follow-up was performed 18 h, 48 h and 2 weeks after stent insertion and thereafter every month until the patients died or there were signs of stent dysfunction. The follow-up was conducted by a study nurse during the hospital stay and by telephone contact after discharge. A structured interview with the patient was conducted at each follow-up. Patients asked about adverse events. If patient unable to answer the questions, information was obtained from relatives or from homecare or hospice staff. The patients and care providers were also		(>80% died with patent stents)
	Male/female*	18/16	9/25			
	Gallbladder in situ	29	29			
	Diagnosis					
	Pancreatic cancer	30	27			
	Gallbladder cancer	2	5			
	Ampullary cancner	1	3			
	Unclassified	2	1			
	Liver Metastases	7	9			

Study details	Participants		Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
	Chemotherapy	8 9		asked about hospital admittance and in those cases the hospital notes were reviewed. Sample size calculation Assuming 30% stent dysfunction for uncovered stents, a sample size of 60 patients in each treatment arm was calculated from a 20% difference in stent dysfunction with a power of 80% at a 0.05 significance level.		
	Bilirubin (µmol/l)	78 (range 6-490) 182 (range 9-380)				
	Alkaline phosphatase (µkat/l)	12.2 (range 4-28.8) 5 (range 3-49)				
	C-reactive protein (mg/l)	27 (range 11-140) 73 (range 5-190)				
	*Sig. difference between groups, p=0.03					
Full Citation 1. van der Gaag, N. A., Rauws, E. A., van Eijck, C. H., Bruno, M. J., van der Harst, E., Kubben, F. J., Gerritsen, J. J.,	N = 202 participants (181 [92%] PC patients) with obstructive jaundice due to		Arm 1: Endoscopic preoperative biliary drainage	Randomisation Randomisation was performed with a computer program at the co-ordinating trial centre, with stratification according to study centre. All participants	Mortality/Overall Survival at 120 days/2 years Time to surgery Time to complications Pre-surgery/surgery-related complications	Overall unclear risk of bias • Random sequence generation: low

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Greve, J. W., Gerhards, M. F., de Hingh, I. H., Klinkenbijl, J. H., Nio, C. Y., de Castro, S. M., Busch, O. R., van Gulik, T. M., Bossuyt, P. M., Gouma, D. J. Preoperative biliary drainage for cancer of the head of the pancreas, New England Journal of Medicine, 362, 129-37, 2010 2. Eshuis, W. J., van der Gaag, N. A., Rauws, E. A., van Eijck, C. H., Bruno, M. J., Kuipers, E. J., ... & Gerhards, M. F. (2010). Therapeutic delay and survival after surgery for cancer of the pancreatic head with or without preoperative biliary drainage. Annals of surgery, 252(5), 840-849. Country/ies where the study was carried out: Netherlands Study type: Multicentre RCT Aim of the study: To assess the rates of serious complications and death, and the length of hospital stay,	suspected pancreatic head cancer (n = 6 excluded) n = 94 early surgery group (89 PC patients) n = 102 preoperative biliary drainage plus surgery group (92 PC patients) Inclusion aged 18 to 85 years serum bilirubin level 40 to 250 µmol/L no evidence on CT of distant metastasis or local vascular involvement Exclusion Serious coexisting illness (Karnofsky performance score <50) other contraindication to major surgery ongoing cholangitis	then Surgery Arm 2: Surgery only	provided written informed consent. Treatment Endoscopic biliary drainage then surgery: ERCP was performed with plastic stent placement. If the procedure was unsuccessful, the participant was referred to a tertiary centre for a second attempt. Percutaneous transhepatic cholangiography with stent placement was considered a rescue option in case of failed ERCP. Biliary drainage was defined as successful if serum bilirubin levels declined by 50% or more within 2 weeks. A new stent was placed if signs of inadequate bile drainage developed. After 4-6 weeks of drainage, patients underwent surgery. Surgery: The standard surgical procedure for resectable tumours was a pylorus-preserving pancreaticoduodenectomy, including removal of all lymph nodes on the right side of the portal vein and mesenteric artery. If metastasis into the proximal duodenum or pylorus was suspected, a classic Whipple procedure was	Stent malfunction (occlusion) Time to surgery Treatment-related hospital readmission Note that 5 patients assigned to the early surgery group underwent biliary drainage for the following reasons: surgical facility not available in time for early surgery (n=3), intercurrent cholangitis developed after previous ERCP without drainage (n = 1), hyperglycaemia (n=1). Overall mortality from any cause at 120 days Early surgery group: 12/94 (13%) Preoperative biliary drainage group: 15 (15%) Relative risk: 0.85 (95% CI 0.42 to 1.72) Overall 2 year mortality (data from Eshuis 2010) Early surgery group: 76/90 (84%) Preoperative biliary drainage group: 77/95 (81%) Log rank p=0.91 HR=0.98 (95%CI, 0.72-1.34), calculated from # deaths and log-rank p-value, Tierney et al 2007 method 7. Survival after resection: 2 year mortality (data from Eshuis 2010) Early surgery group: 47/60 (78%) Preoperative biliary drainage group: 35/53 (66%)	risk (computer program used) •Allocation concealment: unclear (insufficient detail provided) •Blinding of participants and personnel assessments: low risk (unclear whether blinded but unlikely to affect outcome) •Blinding of outcome assessment: low risk (blinded adjudication committee used) •Incomplete outcome data: low risk (reasons for missing data unlikely to be related to true outcome) •Selective reporting: unclear risk (protocol available but study does not report QoL measure)

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
for preoperative biliary drainage followed by surgery compared to surgery alone in patients with tumours of the pancreatic head. Study dates: November 2003 to June 2008. Source of funding: The Netherlands Organization for Health Research and Development	previous preoperative biliary drainage with stenting by ERCP or percutaneous transhepatic cholangiography currently receiving neoadjuvant chemotherapy serious gastric outlet obstruction Resectability status after surgical exploration (n=180) BD->Surgery: Unresectable 38; Resectable 57 Surgery: Unresectable 29; Resectable 61		performed, with resection of the distal stomach. If limited metastasis into the portal or superior mesenteric vein was found, a wedge resection of these vessels was included. Palliative treatment generally consisted of the creation of a hepaticojejunostomy with or without gastroenterostomy and coeliac plexus neurolysis. If a hepaticojejunostomy was not feasible, an expandable metal stent was inserted postoperatively by ERCP. Follow up Outpatient visits were arranged for 2, 6 and 12 weeks after discharge. A standardised evaluation of symptoms and, if indicated, laboratory tests and radiologic studies were performed. Data regarding hospital admissions and procedures were collected, with particular attention to complications. Where necessary, the participant's physician was contacted for further information. Complications An adjudication committee reviewed all complications in a blinded fashion, to exclude bias in evaluation.	Treatment-related mortality Early surgery: 4/94 Preoperative biliary drainage group: 9/102 Time to complications after randomization (surgery vs BD->surgery) HR=0.54 (95%CI 0.41-0.71) Overall complications Overall, n(%): BD->Surgery (n=102) 75 (74); Surgery (n=94) 37 (39) Complications related to preoperative drainage within 120 days of randomisation Any: BD->Surgery (n=102) 47 (46); Surgery (n=94) 2 (2) Pancreatitis: 7 (7); 0 Cholangitis: 27 (26); 2 (2) Perforation: 2 (2); 0 Haemorrhage after ERCP: 2 (2); 0 Complications related to stent within 120 days of randomisation BD->Surgery (n=102); Surgery (n=94)	•Other sources of bias: low risk (appears free of other sources of bias)

Study details	Participants	Interventions	Methods	Outcomes and Results			Limitation (risk of bias)
			Sample size calculation A complication rate of 38% in the early-surgery group, and 48% in the pre-operative drainage group was assumed. The authors stated that early surgery would be considered non-inferior if the occurrence of serious complications was less than 10% above that in the pre-operative drainage group. With a one sided significance level of 0.05 and a power of 80%, 94 patients were required in each arm to demonstrate non-inferiority of early surgery.		(n=102)		
				Occulsion	15 (15)	1 (1)	
				Need for exchange	31 (30)	2 (2)	
				Complications related to surgery within 120 days of randomisation			
					BD->Surgery (n=102)	Surgery (n=94)	
				Any	48 (47)	35 (37)	
				Pancreaticojejunostomy leak	8 (8)	11 (12)	
				Grade A	0	1 (1)	
				Grade B	4 (4)	4 (4)	
				Grade C	4 (4)	6 (6)	
				Haemorrhage after pancreatectomy	2 (2)	4 (4)	
				Delayed gastric emptying	18 (18)	9 (10)	
				Biliary leakage	1 (1)	3 (3)	
				Gastro- or duodenojejunostomy leak	4 (4)	2 (2)	
				Intrabdominal abscess	2 (2)	3 (3)	
				Wound infection	13 (13)	7 (7)	

Study details	Participants	Interventions	Methods	Outcomes and Results			Limitation (risk of bias)
				Portal-vein thrombosis	0	1 (1)	
				Pneumonia	9 (9)	5 (5)	
				Cholangitis	3 (3)	3 (3)	
				Myocardial infarction	4 (4)	0	
				Need for repeated laparotomy	12 (12)	13 (14)	
				Mean time to surgery Pre-operative biliary drainage group: 5.2 weeks (95% CI 4.8 to 5.5) Early surgery group: 1.2 weeks (95% CI 0.9 to 1.4) Treatment-related hospital readmission Early surgery : 11/94 Preoperative biliary drainage group: 34/102			
Full Citation Walter, D., van Boeckel, P. G. A., Groenen, M. J., Weusten, Blam, Witteman, B. J., Tan, G., Brink, M. A., Nicolai, J., Tan, A. C., Alderliesten, J., Venneman, N. G., Laleman, W., Jansen, J. M., Bodelier, A., Wolters, F. L., van der Waaij, L. A., Breumelhof, R., Peters, F. T. M., Scheffer, R. C. H., Leenders, M., Hirdes, M.	N= 240 patients with unresectable extrahepatic malignant bile duct obstruction (181 PC patients) N=171 Primary stent placement (148 PC patients) N=57 Plastic stent N=54 Partially covered SEMS	Arm 1: Plastic stent with ERCP Arm 2: Uncovered SEMS with ERCP Arm 3: Partially covered SEMS with ERCP	Randomisation A web-based randomisation program was used, with stratification for centre of inclusion and for primary or secondary stent placement (i.e. stent replacement due to a first episode of stent dysfunction). Randomisation to the three types of stent was performed in a 1:1:1 fashion. No blinding was performed. Written, informed consent was obtained before randomisation.	Survival* Stent malfunction (pCovered, Uncovered)/time to malfunction Treatment-related complications Note: 8 patients included in both primary and secondary stent groups. Patient survival Deaths at 1-yr follow up 182/219 deaths, 30 patients alive, 7 lost to FU (includes patients in primary and secondary stent placement groups)			Overall high/unclear risk of bias • Random sequence generation: low risk (web-based randomisation program) •Allocation concealment: low risk (central web-based allocation) •Blinding of participants and

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
M. C., Steyerberg, E. W., Vleggaar, F. P., Siersema, P. D. Cost Efficacy of Metal Stents for Palliation of Extrahepatic Bile Duct Obstruction in a Randomized Controlled Trial, Gastroenterology, 149, 130-138, 2015. Country/ies where the study was carried out: Netherlands Study type: Multicentre RCT Aim of the study: To evaluate whether plastic stent or SEMS is superior to the other for the palliation of extrahepatic bile duct obstruction. Study dates: February 2008 to February 2013. Source of funding: Supported by ZON-MW, The Netherlands Organization for Health Research and Development (unrestricted grant) and Boston Scientific (unrestricted grant).	N=60 Uncovered SEMS N=48 Secondary stent placement (33 PC patients) N=16 Plastic stent N=17 Partially covered SEMS N=15 Uncovered SEMS Inclusion Patients presenting with an increased bilirubin level (≥30mmol/L) and/or clinical symptoms of obstructive jaundice resulting from an inoperable obstructive malignancy at the level of the extrahepatic common bile duct. A patient was considered inoperable if the tumour was locally irresectable, distant		Treatment All procedures were performed under conscious sedation. After successful cannulation of the bile duct and guidewire placement across the stricture, retrograde cholangiography was performed. If no stricture was seen, or intrahepatic involvement was noted, the patient was excluded. If an extrahepatic stricture without hilar involvement was seen, the assigned stent was inserted. Stent length was chosen according to the stricture location and length. Sphincterotomy was performed at the discretion of the endoscopist. In cases of failed stent placement, insertion was conducted during a second attempt, either with ERCP, percutaneous transhepatic cholangiography or using a combined approach. Plastic stent: these included 10F polyurethane stents (Boston Scientific Corporation, Natick MA) or 10F polyethylene stents (Cook, Inc, Winston-Salem, NC) in lengths of 5-10cm. Plastic stent:	Authors report no difference in cumulative survival for the different stent types (p = 0.241). Stent dysfunction (the presence of symptoms of obstructive jaundice or cholangitis in combination with confirmation of stent obstruction or migration during ERCP) Primary stent group Plastic stent: 23/57 (40%) uncovered SEMS: 10/60 (17%) partially covered SEMS: 9/54 (17%) Secondary stent group Plastic stent: 8/16 (50%) uncovered SEMS: 1/15 (7%) partially covered SEMS: 2/17 (12%) Functional stent time Primary stent group Plastic stent: 172 days (95% CI 126-219) uncovered SEMS: 268 days (95% CI 219-317) partially covered SEMS: 286 days (95% CI 240-332) Secondary stent group Plastic stent: 170 days (95% CI 85-255) uncovered SEMS: 367 days (95% CI 282-391) partially covered SEMS: 326 days (95% CI 274-378)	personnel assessments: unclear risk (no blinding and unclear whether blinding would affect outcome [diary used to record symptoms of obstructive jaundice]) •Blinding of outcome assessment: low risk (no blinding but unlikely to affect outcome measurement) •Incomplete outcome data: low risk (reasons for missing data unlikely to be related to true outcome) •Selective reporting: high risk (not all/incomplete reporting of outcomes) •Other sources of bias: low risk (appears free of other sources of bias)

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
	metastases were present, or the patient was in poor medical condition. Exclusion Malignancy involving the intrahepatic bile ducts or duodenum Known history of cholecystitis (unless a cholecystectomy had been performed) A history of surgery to the bile duct World Health Organisation performance score of 4 (100% of time in bed).		Uncovered and partially covered SEMS: 10mm Wallstent RX (Boston Scientific Corporation) were used, either uncovered or with a partial permalume cover in lengths of 4, 6 or 8cm. Adverse events Serious adverse events were defined as short-term (<7 days) and long term (≥7 days). Follow up Participants were followed up with home visits or telephone calls at 14 days, 1 month, then monthly until 6 months and bimonthly until 1 year. Patients were given a diary in which to score symptoms of obstructive jaundice every day for 1 month, and weekly thereafter. Participants with symptoms of obstructive jaundice were evaluated in the hospital, and ERCP was performed (if suitable, given the patient's condition). Further treatment was at the discretion of the treating physician, and included stent replacement, additional stent placement or stent cleaning. Sample size calculation Based on a hazard ratio of at least 0.5 for the comparison of the two treatment groups	Hazard ratio for stent dysfunction Primary stent group uncovered SEMS compared to plastic stent: HR 0.33 (95% CI 0.16-0.69) partially covered SEMs compared to plastic stent: HR 0.32 (0.15-0.69) Secondary stent group uncovered SEMS compared to plastic stent: HR 0.10 (95% CI 0.01-0.082) partially covered SEMs compared to plastic stent: HR 0.15 (95% CI 0.03-0.70) Short-term serious stent-related complications (primary and secondary stent groups combined) Plastic stent (n=73) / Uncovered SEMS (n=75) / Partiall covere SEMS (n=71) Total 5 / 5 / 3 Postprocedural fever 3 / 1 / 2 Post ERCP pancreatitis 0 / 1 / 0 Other* 2 / 3 / 1 * includes pneumonia [n=2], pulmonary embolism [n=2], cardiac arrest [n=1] and urosepsis [n=1])	

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
			(plastic versus uncovered SEMS, and plastic versus partially covered SEMS), estimating a stent failure rate of 30-50% for plastic stents, 15-35% for uncovered SEMS, and 10-20% for partially covered SEMS. For an α-value of 0.05 and statistical power of 0.8, 80 participants were required in each stent group.	Long-term serious stent-related complications (primary and secondary stent groups combined) Total Cholecystitis Pancreatitis Gastric outlet obstruction Other* *Includes hospital admission for dehyd [n=1], leakage of PTC drain [n=1], retr arrest [n=1], rectal blood loss [n=1], ha	

F.11 1 Duodenal obstruction

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitations
Full citation Gurusamy Kurinchi, Selvan, Kumar, Senthil, Davidson Brian, R., Prophylactic GJJ for unresectable periampullary carcinoma, Cochrane Database of Systematic Reviews, 2013 Ref ID 456864 Country/ies where the study was carried out:	Where possible data was extracted from the Cochrane SR. The full copy of the study was checked for accuracy and completeness. Sample size This review includes 2 RCTs: Lillemoe et al, 1999 Van Heek 2003 Characteristics Lillemoe et al, 1999	CR: Routine prophylactic GJJ (open or laparoscopic) against a comparator of no prophylactic GJJ Included studies: Where possible data was extracted from the Cochrane SR. The full copy of the study was	Included studies: Where possible data was extracted from the Cochrane SR. The full copy of the study was checked for accuracy and completeness. Lillemoe et al, 1999 Design: Single-centre unblinded randomised controlled trial Randomization method: computer-generated random numbers Van Heek 2003	CR: Relief of obstruction (gastric outlet obstruction) Adverse effects (Peri-operative morbidity) Overall Survival Health Related Quality of Life Included studies: Where possible data was extracted from the Cochrane SR. The full copy of	CR: AMSTAR score= 11/11: low risk of bias Included studies: Where possible data was extracted from the Cochrane SR. The full copy of the study was checked for accuracy and completeness. Lillemoe et al, 1999 Random sequence generation: Low risk ("Patients were randomized using a computer-generated random number pattern")

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitations
The Netherlands, USA Study type: Systematic review with meta-analysis (Cochrane review) Aim of the study: To determine whether prophylactic GJJ should be performed routinely in people with unresectable periampullary cancer based on differences in survival, peri-operative morbidity, quality of life, and the incidence of gastric outlet obstruction. Study dates: Publication date: December 2013 Searches up to August 2012 Source of funding: National Institute for Health Research.	N=87 participants were randomly assigned to two groups (G1; G2) M/F=50/37 Mean age: 67 years Other – 1) Location of the cancer: Pancreatic cancer: 84 (96.6%) Ampullary cancer: 0 (0%) Duodenal cancer: 1 (1.1%) Bile duct cancer: 2 (2.3%) Other – 2) Biliary obstruction: 65 (74.7%) Van Heek 2003 N=65 participants were randomly assigned to two groups (G1; G2) M/F= 40/30 Mean age: 64 years Other – 1) Location of the cancer: Pancreatic cancer: 57 (87.7%) Ampullary cancer: 2 (3.1%) Duodenal cancer: 0 (0%)	checked for accuracy and completeness. Lillemoe et al, 1999 G1- intervention: GJJ (n = 44). Further details: a retrocolic (open) GJJ performed to the most dependent portion of the gastric antrum. G2-comparison: No GJJ (n = 43). Patients with biliary tract obstruction underwent hepaticojejunostomy in both groups. Van Heek 2003 G1 - intervention: GJJ (n = 36). Further details: retrocolic; open G2 -comparison: No GJJ (n = 29). Co-interventions: All patients underwent hepaticojejunostomy irrespective of	Design: Multicentre unblinded randomised controlled trial Randomization method: Centralised randomization stratified by centre and presence of metastases.	the study was checked for accuracy and completeness. Lillemoe et al, 1999 Relief of obstruction (gastric outlet obstruction) Adverse effects (Peri-operative morbidity) Overall Survival Van Heek 2003 Relief of obstruction (gastric outlet obstruction) Adverse effects (Peri-operative morbidity) Overall Survival Health Related Quality of Life	Allocation concealment: Unclear risk (No details given in the text) Blinding of participants and personnel Assessments: Unclear risk Blinding of outcome assessment: Low risk Incomplete outcome data: Unclear risk (There were no post-randomisation drop-outs) Selective reporting: Low risk (All important outcomes were reported) Other sources of bias: Unclear risk (None detected) Van Heek 2003 Random sequence generation: Unclear risk (No details given in the text) Allocation concealment: Unclear risk Blinding of participants and personnel Assessments: Low risk Blinding of outcome assessment: High risk Incomplete outcome data: High risk (Post-randomisation drop-outs could influence the effect estimate) Selective reporting: Unclear risk Other sources of bias: High risk (early stopping bias: The trial was stopped early)

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitations
	Bile duct cancer: 6 (9.2%) Other – 2) Biliary obstruction: 51 (78.5%) Inclusion criteria Lillemoe et al, 1999 Patients undergoing surgery for peri-ampullary cancer with intention to resect. Van Heek 2003 Patients undergoing surgery for peri-ampullary cancer with intention to resect. Exclusion criteria Lillemoe et al, 1999 1. Resectable disease on laparotomy. 2. Considered to be at high risk of gastric outlet obstruction based on radiological features or intraoperative findings Van Heek 2003 Resectable disease on laparotomy.	biliary tract obstruction			
Full citation Jeurnink, S. M., Polinder, S., Steyerberg, E. W., Kuipers, E. J.,	Sample size N=39 patients randomised randomized in 2 groups (G1 - G2)	Interventions G1: GJJ (GJJ) G2: duodenal stent placement	Details Design: Multicentre unblinded RCT Randomization method: Centralised	Results Relief of obstruction Change in symptoms Nutritional status	Random sequence generation: Unclear risk (No details given in the text) Allocation concealment: Unclear risk (No details given in the text)

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitations
Siersema, P. D. Cost comparison of GJJ versus duodenal stent placement for malignant gastric outlet obstruction, Journal of gastroenterology, 45, 537-43, 2010 Ref ID 456449 Country/ies where the study was carried out: The Netherlands Study type: Randomised controlled trial (RCT) Aim of the study: To study in detail the total direct and indirect costs of GJJ (GJJ) and duodenal stent placement in the palliation of malignant gastric outlet obstruction (GOO) within the framework of a randomized trial Study dates: Publication date: December 2010 Data collection/patients enrolment: January 2006 to May 2008	Characteristics M/F=20/19 Mean age: 66 +-11 years (G1) 66 +-13 years (G2) Other- Location of the cancer: Pancreas=13 (G1), 15 (G2) Bile duct=1 (G1), 0 (G2) Duodenum=1 (G1), 3 (G2) Stomach=1 (G1), 2 (G2) Papilla= 1 (G1), 0 (G2) Inclusion criteria Exclusion criteria	The GJJ was open (n = 16) or laparoscopic (n = 2), and either antecolic (n = 12) or retrocolic (n = 6). For stent placement, an Enteral Wallstent was used Duration: 14 days, 1 month, and monthly until patients' death	randomization (by computer-generated) lists stratified by centre and treatment for obstructive jaundice (defined as a treatment given 1 week or more prior to study inclusion).	Adverse events	Blinding of participants and personnel Assessments: Low risk Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: Low risk (There were no post-randomisation drop-outs) Selective reporting: High risk (All important outcomes were reported, but many important primary –e.g. relief of obstruction, and secondary outcomes –e.g. overall survival, are reported income incompletely so that they cannot be entered in a meta-analysis) Other sources of bias: Unclear risk (None detected)

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitations
Source of funding: Not reported					
Full citation Mehta S, Hindmarsh A, Cheong E, Cockburn J, Saada J, Tighe R, Lewis MP, Rhodes M. Prospective randomized trial of laparoscopic GJJ versus duodenal stenting for malignant gastric outflow obstruction. Surg Endosc. 2006 Feb;20(2):239-42. Ref ID 456449 Country/ies where the study was carried out: UK Study type: Randomised controlled trial (RCT) Aim of the study: To compare laparoscopic GJJ (GJJ) with duodenal stenting as a means of palliating malignant gastric outflow obstruction (GOO). Study dates:	Sample size N=27 patients randomised randomized in 2 groups (G1 - G2) Characteristics M/F=13/14 (G1-G2) Mean age: 67.6 +-2.9 years (G1) 70.4+-4.9 years (G2) Other – 1) Location of the cancer: Pancreatic= 15 (56%) Gastric=4 (15%) Cholangiocarcinoma= 2 (7%) Gallbladder=1(3.5%) Disseminated metastasis from other sources=4 (15%) Benign gastric ulcer=1 (3.5%) Inclusion criteria Patients with malignant gastric outlet obstruction (defined as patients with typical symptoms of nausea, vomiting, and abdominal pain - diagnosis was confirmed with	Interventions G1: GJJ (GJJ) n=14 G2: duodenal stent placement n=12 The GJJ was laparoscopic For stent placement, an Enteral Wallstent was used Duration: 3 years	Details Design: Single centre unblinded RCT Randomization method: computer-generated list	Results Overall Survival Health Related Quality of Life PROMS	Random sequence generation: Low risk Allocation concealment: Low risk (“Randomization was performed using a computer-generated list concealed from the investigators at the time of enrolment”) Blinding of participants and personnel Assessments: Low risk Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: Low risk (2 patients died after the randomization, but this censoring data to be introduced used) Selective reporting: Low risk (All important outcomes were reported) Other sources of bias: Unclear risk (None detected)

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitations
Publication date: December 2005 Data collection/patients enrolment: not reported Source of funding: Not reported	gastroscopy, contrast swallow, or CT) Exclusion criteria Not reported				
Full citation Okuwaki, K., Kida, M., Yamauchi, H., Imaizumi, H., Miyawaza, S., Iwai, T., Masutani, H., Matsumoto, T., Hasegawa, R., Koizumi, W. Randomized controlled exploratory study comparing the usefulness of two types of metallic stents with different axial forces for the management of duodenal obstruction caused by pancreatobiliary cancer, Journal of Hepato-biliary-pancreatic SciencesJ Hepatobiliary Pancreat Sci, 23, 289-97, 2016 Ref Id	Sample size N=34 patients randomised in 2 groups (G1 - G2) Characteristics M/F=17/14 (G1-G2) Median age [IQR]: 72 [69-79] years (G1) 72 [66-75] years (G2) Other – 1) Location of the cancer: Pancreas=12 (G1), 13 (G2) Bile duct=2 (G1), 4 (G2) Other – Site of obstruction: 1ST part of duodenum= 1 (G1), 1 (G2) 2ND part of duodenum= 7 (G1), 12 (G2) 3RD part of duodenum=	Interventions G1: WallFlex™ duodenal stent group (W-group) n=16 G2: Niti-S™ pyloric/duodenal D-type stent group (N-group) n=18 The WallFlex duodenal stent is an uncovered, self-expandable metallic stent (SEMS) composed of nitinol. The Niti-S pyloric/duodenal D-type stent is also an uncovered SEMS composed of nitinol. These two stents have different “axial forces,” which is required	Details Design: Single centre unblinded RCT Randomization method: Centralised randomization (method not given) adjusted by Performance status [PS; 0–2 vs. 3 or 4] and type of cancer [pancreatic cancer vs. biliary cancer]	Results Relief of obstruction Change in symptoms Nutritional status Adverse events Overall Survival	Random sequence generation: Unclear risk (No details given in the text) Allocation concealment: Low risk (Centralised allocation) Blinding of participants and personnel Assessments: Low risk Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: Low risk (missing outcome data balanced between interventions groups [n=3, 2 in G1 and 1 in G2], with similar across groups [patients found not to have severe DO requiring duodenal stent placement] Selective reporting: (All important outcomes were reported according to the research protocol) Other sources of bias: Low risk (None detected)

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitations
457142 Country/ies where the study was carried out: Japan Study type: Randomised controlled trial (RCT) Aim of the study: To compare two types of duodenal stent placement (DSP) with different axial forces (AF) for duodenal obstruction (DO) with pancreatobiliary cancer. Study dates: Publication date: December 2016 Anticipated trial start date: 2012 November 07 Last follow-up date: 2015 September 30 Source of funding: None	6 (G1), 2 (G2) Inclusion criteria Patients in whom a malignant duodenal obstruction (DO) was clinically diagnosed Exclusion criteria Patients in whom a DO was not severe DO and a duodenal stent placement (DSP) was not required.	to keep stents straight Duration: Until patients' death			
Full citation Shyr, Y. M., Su, C. H., King, K. L., Wang, H. C., Lo, S. S., Wu, C. W., Lui, W. Y. Randomized trial of three types of GJJ in unresectable	Sample size N=45 patients randomised randomized in 3 groups (G1 - G2 – and G3) Characteristics M/F=37/8 (G1-G2)	Interventions G1-Type I by-pass (GJJ): n=15 G2-Type II by-pass (GJJ): n=15 G3-Type III by-pass (GJJ): n=15	Details Design: Single centre unblinded RCT Randomization method: Random number table.	Results Change in symptoms Nutritional status Adverse events	Random sequence generation: Low risk (Random number table) Allocation concealment: Unclear risk (No details given in the text) Blinding of participants and personnel Assessments: Low risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitations
periampullary cancer, Surgery, 121, 506-512, 1997 Ref ID 455465 Country/ies where the study was carried out: China Study type: Randomised controlled trial (RCT) Aim of the study: To compare a GJJ with duodenal partition (designed to clarify whether so-called circulus vomiting exists) with two other types of GJJ (GJJ) commonly used for gastric bypass in unresectable periampullary cancer. Study dates: Data collection/patients enrolment: May 1992 to November 1995. Source of funding: Not reported	Mean age: 70.4 +- 7.0 years (G1) 68.0 +- 14.3 years (G2) 66.9 +-12.3 years (G3) Other- Location of the cancer: Pancreas= 11 (G1), 12 (G2), 12 (G3) Ampulla of voter= 4 (G1), 2 (G2), 1 (G3) Duodenum= 0 (G1), 1 (G2), 2 (G3) Bile duct= 0 (G1), 0 (G2), 0 (G3) Inclusion criteria Patients with unresectable periampullary cancer by pathologic conditions or a malignant clinical course with: clinical symptoms of gastric outlet obstruction (GOO) including anorexia, epigastric fullness, nausea, and vomiting; prolonged mean value of gastric emptying time by isotope gastric emptying study;	Differences among them were the site of jejunum for GJJ and partition of duodenum. (a), Type I GJJ was performed at the proximal jejunal limb 20 cm distal to the ligament of Trek. (b), Type II GJJ was similar to type I except duodenal partition at duodenal bulb was 1 cm beyond pylorus by linear stapler. (c), Type III GJJ was performed at Roux-limb jejunum 60 cm distal to biliojejunostomy but not proximal limb. Duration: 1 month			Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: Low risk (All important outcomes were reported) Selective reporting: Unclear risk (No study protocol to permit judgement on this criterion) Other sources of bias: Unclear risk (None detected)

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitations
	or impending DO evidenced by tumour spread toward duodenum at operation. Exclusion criteria Not reported				

F.12.1 Neoadjuvant treatment

Study details	Participants	Interventions	Methods	Outcomes and Results*	Limitations
Full citation Evans DB, Varadhachary GR, Crane CH, Sun CC, Lee JE, et al. Preoperative GEM-based CRT for patients with resectable adenocarcinoma of the pancreatic head. J Clin Oncol 2008; 26:3496- 3502 Ref Id Evans et al. 2008 Country/ies where the study was carried out: USA Study type:	Sample size N=86 patients with resectable PC Characteristics M/F (n): 55/31 Median age (range): 64 (42-80) years Current or past smoker (yes, n): 59 Inclusion criteria Patients with: potentially resectable disease on the basis of physical examination and the following objective CT criteria: (1) no evidence of extrapancreatic disease; (2) no evidence of tumor extension to the superior mesenteric artery (SMA) or celiac axis; and (3) no evidence of occlusion of	Interventions G1: CRT before surgery Further details: GEM and 30 Gy (in 10 fractions over 2 weeks) Not comparative study	Details Design: single-arm phase II clinical trial Duration: 2002-2006 Country: USA	Results Overall Survival Resection rate Time from initiating treatment to Surgery Adverse Events	Limitations Selection: Low risk of bias Comparability: not applicable Outcome: Low risk of bias Other information

Study details	Participants	Interventions	Methods	Outcomes and Results*	Limitations
Prospective phase II clinical trial Aim of the study: To assess the outcomes of patients who received preoperative GEM-based CRT and pancreatoduodenectomy (PD) for stage I/II PC. Study dates: Publication date: December 2008 Data collection/patients enrolment: 1998-2001 Source of funding: Not reported	the superior mesenteric vein (SMV) or SMV–portal vein (PV) confluence a Karnofsky performance status of at least 70, an absolute neutrophil count (ANC) more than 1,500 cells/mm3 a platelet count of at least 100,000 cells/mm3 a serum creatinine level less than 1.6 mg/dL a serum bilirubin level less than 5 mg/dL Exclusion criteria Patients with: evidence of fever, active infection, hepatic transaminases (ALT and AST) greater than 5× the upper limits of normal significant medical comorbidity precluding consideration of major pancreatic surgery.				
Full citation Festa V, Andriulli A, Valvano MR, Uomo G, Perri F, et al. Neoadjuvant chemo-radiotherapy for patients with borderline resectable PC: a meta-analytical evaluation	Sample size This review includes 5 phase II trials Pipas et al. 2005 Le Scodan et al. 2009 Small et al. 2011 Sahora et al. 2011a Sahora et al. 2011b	SR: Pre-operative administration of chemotherapy, alone or in combination with radiotherapy Included studies: Where possible data was extracted from the Cochrane SR. The full copy of the study was checked for accuracy and completeness.	SR~: Identification of studies: MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials from 1966 to September 2012 Data collection and analysis:	Where possible data was extracted from the Cochrane SR. The full copy of the study was checked for accuracy	Limitations SR: AMSTAR score= 10/11 Low risk of bias Included studies: Where possible data was extracted from the

Study details	Participants	Interventions	Methods	Outcomes and Results*	Limitations
of prospective studies. JOP 2013;14(6):618-25. Ref Id Festa et al. 2013 Country/ies where the study was carried out: Austria, France, Italy, Korea, Lebanon, USA Study type: Systematic review (SR) Aim of the study: To evaluate the effectiveness of chemo-radiotherapy delivered pre-operatively in down staging the disease in patients with borderline resectable PC, with emphasis on tumour response, resectability, and survival. Study dates: Publication date: December 2013 Searches up to September 2012 Source of funding: None	and 5 prospective observational studies Mehta et al. 2001 Magnin et al. 2003 Massucco et al. 2006 Leone et al. 2012 Lee et al. 2012 Characteristics Where possible data was extracted from the SR. The full copy of the study was checked for accuracy and completeness. Pipas et al. 2005 N=6* M/F= not specified Median age (range)= 65 (not specified) years Le Scodan et al. 2009 N=41 M/F=25/16 Median age (range)= 59 (33-75) years Small et al. 2011 N=10* M/F= not specified Median age (range)= 62 (not specified) years Sahora et al. 2011a N=12* M/F= not specified Median age (range)= 61 (not specified) years	Pipas et al. 2005 G1- intervention: CRT (CRT) followed by surgery^ (n= 6). Further details: GEM + Docetaxel and 50.4 Gy Not comparative study Le Scodan et al. 2009 G1- intervention: CRT followed by surgery^ (only for patients presenting with resectable disease at restaging) (n= 41). Further details: 5-fluorouracil + Cisplatin and 50 Gy Not comparative study Small et al. 2011 G1- intervention: CRT followed by surgery^ (n= XX). Further details: GEM + Bevacizumab and 50 Gy Not comparative study Sahora et al. 2011a G1- intervention: Chemotherapy followed by surgery^ (n= 12). Further details: GEM + Docetaxel Not comparative study Sahora et al. 2011b G1- intervention: Chemotherapy followed by surgery (n= 15). Further details: GEM + Oxaliplatin Not comparative study	Quality of each study was evaluated by means of the Evidence Evaluation Process, for assessing non randomized trials Data were analysed using the Comprehensive Meta-Analysis statistical software and were presented as proportions along with corresponding 95% confidence intervals Included studies: Where possible data was extracted from the SR. The full copy of the study was checked for accuracy and completeness Pipas et al. 2005 Design: single-arm phase II clinical trial Duration: 2002-2004 Country: Lebanon Le Scodan et al. 2009 Design: single-arm phase II clinical trial Duration: 1998-2003 Country: France Small et al. 2011 Design: single-arm phase II clinical trial Duration: 2005-2007 Country: USA Sahora et al. 2011a	and completeness. SR: Response to neoadjuvant treatment pre-surgery OverResection rate Adverse Events The outcomes 'Disease-free interval'; Relapse-free survival'; Time from initiating treatment to Surgery'; Health Related Quality of Life' and 'Patient experience' were not included in this SR. Each paper was checked for these outcomes and no additional outcome was found	Cochrane SR. The full copy of the study was checked for accuracy and completeness. Pipas et al. 2005 Selection: High risk of bias Comparability: not applicable Outcome*: Low risk of bias Le Scodan et al. 2009 Selection: Low risk of bias Comparability: not applicable Outcome*: Low risk of bias Small et al. 2011 Selection: High risk of bias Comparability: not applicable Outcome*: Low risk of bias Sahora et al. 2011a Selection: Low risk of bias Comparability: not applicable

Study details	Participants	Interventions	Methods	Outcomes and Results*	Limitations
	Sahora et al. 2011b N=15* M/F= not specified Median age (range)= 63 (not specified) years Mehta et al. 2001 N=15* M/F= not specified Median age (range)= 54 (not specified) years Magnin et al. 2003 N=32 M/F= 20/12 Median age (range)= 62 (39-76) years Massucco et al. 2006 N=18* M/F= not specified Median age (range)= not specified Leone et al. 2012 N=15* M/F= not specified Median age (range)= not specified Lee et al. 2012 N=18* M/F= not specified Median age (range)= not specified Inclusion criteria Pipas et al. 2005	Mehta et al. 2001 G1- intervention: CRT followed by Surgery^ (n= 15). Further details: 5-fluorouracil and 50.4-56 Gy Not comparative study Magnin et al. 2003 G1- intervention: CRT followed by surgery^ (n= 32). Further details: 5-fluorouracil and 45 Gy Not comparative study Massucco et al. 2006 G1- intervention: CRT followed by surgery^ (n= 18). Further details: GEM and 45 Gy Not comparative study Leone et al. 2012 G1- intervention: CRT followed by surgery^(n= 15). Further details: GEM + Oxaliplatin and 50.4 Gy Not comparative study Lee et al. 2012 G1- intervention: Chemotherapy followed by surgery^ (n= 18). Further details: GEM + Capecitabine Not comparative study	Design: single-arm phase II clinical trial Duration: 2001-2003 Country: Austria Sahora et al. 2011b Design: single-arm phase II clinical trial Duration: 2003-2006 Country: Austria Mehta et al. 2001 Design: prospective observational study Duration: 1994-2000 Country: USA Magnin et al. 2003 Design: prospective observational study Duration: 1996-2001 Country: France Massucco et al. 2006 Design: prospective observational study Duration: 1999-2004 Country: Italy Leone et al. 2012 Design: prospective observational study Duration: 2003-2009 Country: Italy Lee et al. 2012 Design: prospective observational study Duration: 2006-2008		Outcome*: Low risk of bias Sahora et al. 2011b Selection: Low risk of bias Comparability: not applicable Outcome*: Low risk of bias Mehta et al. 2001 Selection: Low risk of bias Comparability: not applicable Outcome*: Low risk of bias Magnin et al. 2003 Selection: Low risk of bias Comparability: not applicable Outcome*: Low risk of bias Massucco et al. 2006 Selection: Low risk of bias Comparability: not applicable Outcome*: Low risk of bias Leone et al. 2012

Study details	Participants	Interventions	Methods	Outcomes and Results*	Limitations
	Biopsy-proven PC with Measurable stage I to III disease Age >18 years Karnofsky performance status of >70%. Le Scodan et al. 2009 Patients with localized, potentially resectable PC Small et al. 2011 Patients with 18+ years were eligible if they had radiographically assessable, localized PC without evidence of metastatic disease and had not undergone chemotherapy for PC, chemotherapy for any malignancy within the previous 5 years, or prior RT to the target volume Patients with Eastern Cooperative Oncology Group performance status of 0 or 1; malignancy that could be encompassed within a single irradiation field; no evidence of proteinuria Sahora et al. 2011a Patients with locally advanced non-metastatic PC, without concurrent contraindications age >18 years		Country: Korea		Selection: Low risk of bias Comparability: not applicable Outcome*: Low risk of bias Lee et al. 2012 Selection: Low risk of bias Comparability: not applicable Outcome*: Low risk of bias Other information ~ Resectability was determined according to NCCN criteria; if resectability criteria were not clearly stated, tumours were considered according to the stated resectability category * Patients were stratified as (1) unresectable or (2) borderline resectable. The number of patients refers to those participants

Study details	Participants	Interventions	Methods	Outcomes and Results*	Limitations
	Histologically proven PC, Eastern Cooperative Oncology Group performance status <2, life expectancy of >12 weeks, no other coexisting malignancy or malignancy diagnosed within the last 5 years for operation Female patients of childbearing age had to have a negative pregnancy test to be included Sahora et al. 2011b see Sahora et al. 2011a criteria Mehta et al. 2001 Not specified Magnin et al. 2003 Patients with histologically proven adenocarcinoma of the pancreas on examination of a biopsy obtained by endoscopy under ultrasound guidance. Massucco et al. 2006 Patients with a cytological diagnosis of ductal adenocarcinoma obtained by computed tomography (CT)-guided fine needle aspiration Leone et al. 2012 Patients with LAPC histologically or cytologically proven PC with tumour				with borderline resectable disease (those patients included in the meta-analysis) ^ only for patients presenting with resectable disease at restaging

Study details	Participants	Interventions	Methods	Outcomes and Results*	Limitations
	infiltration of the celiac axis, the superior mesenteric artery, or the superior mesenteric-portal vein Patients aged >18 years No prior chemotherapy or radiation to the upper abdomen Lee et al. 2012 Histologically documented ductal carcinoma of the pancreas; cT3-4 or cN1 tumour according to the AJCC Staging system26; Borderline resectable (BR) or unresectable (UR) tumour; Age 18+ years; Eastern Cooperative Oncology Group performance status Adequate organ function Exclusion criteria Pipas et al. 2005 Patients with a history of chemotherapy/XRT or malignancy (except treated basal cell or squamous cell skin cancer or in situ cervical cancer) Le Scodan et al. 2009 Not specified (see inclusion criteria) Small et al. 2011				

Study details	Participants	Interventions	Methods	Outcomes and Results*	Limitations
	Patients with central nervous system metastases; a history of abdominal fistula, gastrointestinal perforation, or other intra-abdominal abscess within the previous 6 months; gross involvement of the duodenum; clinically significant heart disease; or evidence of bleeding diathesis or coagulopathy Sahora et al. 2011a Not specified (see inclusion criteria) Sahora et al. 2011b Not specified (see inclusion criteria) Mehta et al. 2001 Not specified Magnin et al. 2003 Patients with tumours of neuroendocrine origin or with carcinoma of the duodenum, distal common bile duct, or ampulla of Vater Massucco et al. 2006 Not specified (see inclusion criteria) Leone et al. 2012 Not specified (see inclusion criteria) Lee et al. 2012 Not specified (see inclusion criteria)				

Study details	Participants	Interventions	Methods	Outcomes and Results*	Limitations
Full citation Grose D., McIntosh D., Jamieson N., Carter R., Dickson E., Chang D., Marashi H., Wilson C., Alfayez M., Kerr A., O'Donoghue R. The role of induction chemotherapy+ chemoradiotherapy in localised pancreatic cancer: initial experience in Scotland. Journal of Gastrointestinal Oncology. 2017 Ref ID Grose et al. 2017 Country/ies where the study was carried out: UK Study type: Retrospective review of prospective database Aim of the study: (1) To evaluate effect of pre-surgery CRT on overall survival, radiological response, pathological	N=85 patients with locally advanced (non-metastatic) pancreatic cancer Inclusion criteria Potentially R1 resectable tumour T3 tumour adjacent to SMV or short segment narrowing/adjacent to SMA/HA (no deformation), or T3 tumour adjacent to vessels including sig narrowing or SMA/HA contour deformation (<180○) Exclusion criteria Potentially R0 resectable tumours (small tumour(≤T2) with no proximity to vessel) M/F: 47/38 Median age=65 years (range 42-79) Tumour site: 12 body/tail, 9 uncinate, 45 head, 19 neck Resectability criteria: B=45, C=19, D1=19, Multivisceral=2 Performance status: PS0=46, PS1=37, PS2=2 Neoadjuvant CT regimen: FOLFIRINOX=65, GEMcap=20	Interventions Group 1: Neo-adjuvant CT (GEMcap or FOLFIRINOX) then CRT followed by surgery then adjuvant GEM Group 2: Neo-adjuvant CT (GEM/cap or FOLFIRINOX) followed by surgery then adjuvant GEM	Retrospective review of prospective database Neoadjuvant CT was either FOLFIRINOX if fit and <70 years old, otherwise GEMcap. Patients considered for CRT in Group 1 if disease stable or better on CT Chest Abdomen Pelvis ~ 4 weeks after CT completion. CRT was Volumetric Modulated Arc Therapy delivering 50.4 Gy in 28 fractions over 5.5 weeks with concurrent Capecitabine. Adjuvant CT was Gemcitabine 1,000 mg/m2 D1, 8, 15 q28 Resectability defined according to Glasgow resection /NCCN criteria (A=potential for R0 resection; B=likely R1 resection; C=inoperable but candidate for resection if sig downstaging response; D1 or D2=inoperable and not candidate for resection; unfit). Adverse Events assessed using CTC v4.	Results Neoadjuvant FOLFIRINOX vs Gemcitabine Response to neoadjuvant treatment Overall survival Adverse Events CRT+Surgery vs Surgery Overall survival Resection rate	Limitations Selection: Low risk of bias Comparability: High risk of bias (confounders: GEMcap received if not fit for FOLIRINOX; CRT received if fit) Outcome: Low risk of bias Other information

Study details	Participants	Interventions	Methods	Outcomes and Results*	Limitations
response; (2) to define tolerability of this approach in terms of toxicity from chemotherapy and surgical morbidity. Study dates: 2012-2015 Source of funding: Not reported					
Full citation Liu W, Fu XL, Yang JY, Liu DJ, Li J, et al. Efficacy of Neo-Adjuvant CRT for Resectable PC: A PRISMA-Compliant Meta-Analysis and Systematic Review. Medicine (Baltimore) 2016;95(15):e3009. Ref ID Liu et al. 2016 Country/ies where the study was carried out: Italy, Germany, USA, Japan, Finland Study type Systematic review (SR) Aim of the study:	Sample size This review includes 3 RCTs Casadei et al. 2015 Golcher et al. 2015 Golcher et al. 2008 and 5 retrospective cohort studies: Papalezova et al. 2012 Satoi et al. 2009 Sho et al. 2013 Tzeng 2014 Vento et al. 2007 Characteristics Where possible data was extracted from the SR. The full copy of the study was checked for accuracy and completeness. Casadei et al. 2015 N=38 participants were randomly assigned to two groups (G1; G2)	SR: Neo-adjuvant CRT followed by surgery against a comparator of surgery (pancreaticoduodenectomy) alone for resectable PC. Included studies: Where possible data was extracted from the Cochrane SR. The full copy of the study was checked for accuracy and completeness. Casadei et al. 2015 G1-intervention: Neo-ad CRT and surgery (n= 18) Further details: GEM + 45 Gy G2-comparison: Surgery Alone (n = 20) Golcher et al. 2015 G1-intervention: Neo-ad CRT and surgery (n= 33). Further details: GEM mitomycin (or cisplatin) + 55.8 Gy	SR: Identification of studies: Medline and Cochrane were searched until November 2014 Data collection and analysis: The quality of the included RCT was assessed using the Cochrane “assessing risk of bias” table The quality of retrospective studies was assessed using the Newcastle–Ottawa scale All statistical analyses were performed by use of the statistical software Comprehensive Meta-Analysis Included studies: Where possible data was extracted from the SR.	Where possible data was extracted from the SR. The full copy of the study was checked for accuracy and completeness. SR: Overall Survival Resection rate Included studies: The outcomes ‘Response to neoadjuvant treatment pre-surgery’; Disease-free interval’; Relapse-free	Limitations SR: AMSTAR score= 10/11 Low risk of bias Included studies: Where possible data was extracted from the Cochrane SR. The full copy of the study was checked for accuracy and completeness*. Casadei et al. 2015 Random Sequence Generation: Low risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results*	Limitations
To determine the overall survival, mortality rate, and complete resection rate of neo-adjuvant CRT followed by surgery against a comparator of surgery alone for resectable PC Study dates: Publication date: 2016 Searches up to November 2014 Source of funding: None	M/F=22/16 Median age (range)= 70 (48–79) years Potentially resectable tumour/borderline: 38/0 (all participants) Golcher et al. 2015 N=66 participants were randomly assigned to two groups (G1; G2) M/F=35/31 Median age (range)= 63.9 (33–76) years Potentially resectable tumour/borderline: 66/0 (all participants) Golcher et al. 2008 N=79 participants were randomly assigned to two groups (G1; G2) M/F=48/31 Median age = 60 (G1) years; 66 (G2) years; Potentially resectable tumour/borderline: 79/0 (all participants) Papalezova et al. 2012 N=236 participants were assigned to two groups (G1; G2) M/F=127/109 Mean age [SD] = 64[12] (G1) years; 65[12] (G2) years;	G2-comparison: Surgery Alone (n = 33). Golcher et al. 2008 G1- intervention: Neo-ad CRT and surgery (n= 21). Further details: GEM + cisplatin + 50.4 Gy G2-comparison: Surgery Alone (n = 58). Papalezova et al. 2012 G1- intervention: Neo-ad CRT and surgery (n= 144). Further details: 5-FU-based chemotherapy + 45 Gy G2-comparison: Surgery Alone (n = 92). Satoi et al. 2009 G1- intervention: Neo-ad CRT and surgery (n= 27). Further details: 5-FU + cisplatin (or GEM) + 40 Gy G2-comparison: Surgery Alone (n = 41). Sho et al. 2013 G1- intervention: Neo-ad CRT and surgery (n= 61). Further details: GEM + 50 (or 54) Gy G2-comparison: Surgery Alone (n = 71). Tzeng 2014 G1- intervention: Neo-ad CRT and surgery (n= 115).	The full copy of the study was checked for accuracy and completeness. Casadei et al. 2015 Design: Randomized controlled trial Randomization method: computer-generated 1:1 randomization Duration: 2007-2013 Country: Italy Golcher et al. 2015 Design: randomised controlled trial Randomization method: unclear Duration: 2003-2009 Country: Germany Golcher et al. 2008 Design: randomised controlled trial Randomization method: unclear Duration: 1995-2003 Country: Germany Papalezova et al. 2012 Design: retrospective cohort study Duration: 1999-2007 Country: USA Satoi et al. 2009 Design: retrospective cohort study	survival'; Time from initiating treatment to Surgery ; Adverse Events'; Health Related Quality of Life' and 'Patient experience' were not included in this SR. Each paper was checked for these outcomes: Casadei et al. 2015 Response to neoadjuvant treatment pre-surgery Adverse Events Golcher et al. 2015 Response to neoadjuvant treatment pre-surgery Adverse Events Golcher et al. 2008	Allocation Concealment: Low risk of bias Blinding of Participants and Personnel: High risk of bias Blinding of Outcome Assessment: Unclear risk of bias Incomplete Outcome Data: Low risk of bias Selective Reporting: Low risk of bias Golcher et al. 2015 Random Sequence Generation: Low risk of bias Allocation Concealment: Low risk of bias Blinding of Participants and Personnel: Unclear risk of bias Blinding of Outcome Assessment:

Study details	Participants	Interventions	Methods	Outcomes and Results*	Limitations
	Tumour type: resectable PC (all participants) Potentially resectable tumour/borderline: 236/0 (all participants) Satoi et al. 2009 N=68 participants were assigned to two groups (G1; G2) M/F= 33/35 Median age [range] = 64[47-74] (G1) years; 66[50-83] (G2) years; Potentially resectable tumour/borderline: n= 16/11 (G1); n=24/17(G2) Sho et al. 2013 N=132 participants were assigned to two groups (G1; G2) M/F=73/59 Median age [range] = 65[36-78] (G1) years; 66[33-82] (G2) years; Potentially resectable tumour/borderline: 22/39 (G1); 39/32 (G2); Tzeng 2014 N=167 participants were assigned to two groups (G1; G2) M/F=91/76	Further details: GEM + cisplatin + 30 Gy G2-comparison: Surgery Alone (n = 62). Vento et al. 2007 G1- intervention: Neo-ad CRT and surgery (n= 22). Further details: GEM + 50.4 Gy G2-comparison: Surgery Alone (n = 25).	Duration: 2000-2005 Country: Japan Sho et al. 2013 Design: retrospective cohort study Duration: 2008-2011 Country: Japan Tzeng 2014 Design: retrospective cohort study Duration: 2002-2007 County: USA Vento et al. 2007 Design: retrospective cohort study Duration: 1999-2002 Country: Finland	No additional outcome Papalezova et al. 2012 No additional outcome Satoi et al. 2009 No additional outcome Sho et al. 2013 Response to neoadjuvant treatment pre-surgery Adverse Events Tzeng 2014 Adverse Events Vento et al. 2007 Adverse Events	Unclear risk of bias Incomplete Outcome Data: Low risk of bias Selective Reporting: Low risk of bias Golcher et al. 2008 Random Sequence Generation: Unclear risk of bias Allocation Concealment: Unclear risk of bias Blinding of Participants and Personnel: Unclear risk of bias Blinding of Outcome Assessment: Unclear risk of bias Incomplete Outcome Data: Low risk of bias Selective Reporting: Low risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results*	Limitations
	Median age [range] = 66[38-79] (G1) years; 62[25-79] (G2) years; Potentially resectable tumour/borderline: 167/0 (all participants) Vento et al. 2007 N=47 participants were assigned to two groups (G1; G2) M/F=25/22 Median age [range] = 65[49-83] (G1) years; 63[43-87] (G2) years; Potentially resectable tumour/borderline: 47/0 (all participants) Inclusion criteria Casadei et al. 2015 Age, between 18 and 80 years Medical history without previous pancreatic resection or PC Eastern Cooperative Oncology Group (ECOG)=0 – 1 American Society of Anesthesiologists (ASA) score <4 Good renal, hepatic, cardiac, and hematological functions Golcher et al. 2015				Papalezova et al. 2012 Selection: Low risk of bias Comparability*: High risk of bias (no adjustment for confounders between comparison groups) Outcome: Low risk of bias Satoi et al. 2009 Selection: Low risk of bias Comparability*: High risk of bias (even though, it is stated that “There were no significant differences in patient and operative characteristics between … groups”; no adjustment for confounders between comparison groups) Outcome: Low risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results*	Limitations
	Histologically confirmed ductal adenocarcinoma of the pancreatic head No infiltration of extrapancreatic organs with the exception of the duodenum No more than 1 enlarged (> 1cm) regional lymph node in thin slice spiral CT, without signs of vessel infiltration (omitted in amendment 2005) No distant metastasis No peritoneal spread Age at treatment initiation at least 18 years and not older than 75 Karnofsky index ≥ 70 Golcher et al. 2008 See Golcher et al. 2015 Papalezova et al. 2012 Patients with adenocarcinoma of the pancreatic head or uncinate process see exclusion criteria Satoi et al. 2009 Patients with a clinical diagnosis of pancreatic ductal adenocarcinoma Sho et al. 2013 Patients with adenocarcinoma of the pancreatic head				Sho et al. 2013 Selection: Low risk of bias Comparability*: High risk of bias (even though, it is stated that “There were no significant differences in patient and operative characteristics between … groups”; no adjustment for confounders between comparison groups. As well the comparison groups differed in terms of resectability status) Outcome: Low risk of bias Tzeng 2014 Selection: Low risk of bias Comparability: Comparability*: High risk of bias (even though, it is stated that “There were no

Study details	Participants	Interventions	Methods	Outcomes and Results*	Limitations
	Tzeng 2014 Patients included in this study had potentially resectable tumour anatomy that met the following radiographic criteria: (1) no extra-pancreatic disease, (2) no tumour extension to the superior mesenteric artery or celiac axis, and (3) no occlusion of the superior mesenteric vein (SMV) or the SMV-portal vein (PV) confluence Vento et al. 2007 Patients who underwent pancreaticoduodenectomy for cure with extended lymphadenectomy for pancreatic carcinoma Exclusion criteria Casadei et al. 2015 CRT therapy in the past 6 months Other neoplastic diseases diagnosed in the past 5 years Major surgery, biopsy, or traumatic event in the past 28 days; HIV positivity Golcher et al. 2015 Ampullary carcinoma Carcinoma of the pancreatic corpus or tail Non-ductal adenocarcinoma of the pancreas				significant differences in patient and operative characteristics between … groups"; no adjustment for confounders between comparison groups) Outcome: Low risk of bias Vento et al. 2007 Selection: Low risk of bias Comparability: Comparability*: High risk of bias (even though, it is stated that "There were no significant differences in patient and operative characteristics between … groups"; no adjustment for confounders between comparison groups)

Study details	Participants	Interventions	Methods	Outcomes and Results*	Limitations
	Tumour-specific prior treatment Peritoneal spread Distant metastases 2 or more enlarged lymph nodes (> 1cm) with suspicion of metastatic spread based on morphology in CT scan (omitted in amendment 2005) Recurrent tumour Infiltration of extrapancreatic organs with the exception of the duodenum Vascular involvement > 180° of at least one of the major peripancreatic vessels HIV-infection pregnancy or insufficient contraception Age < 18 years Karnofsky performance status < 70 Golcher et al. 2008 See Golcher et al. 2015 Papalezova et al. 2012 Patients with adenocarcinoma of the pancreatic body and tail patients with other diagnoses, such as adenocarcinoma arising from the duodenum, common bile duct, or ampulla of Vater; cystadenocarcinoma;				Outcome: Low risk of bias Other information

Study details	Participants	Interventions	Methods	Outcomes and Results*	Limitations
	neuroendocrine tumours and papillary tumours Patients with medical contraindications to major abdominal surgery Patients with radiographically borderline resectable or unresectable disease were excluded. Satoi et al. 2009 Patients with endocrine tumour of the pancreas, intraductal papillary mucinous cancer, acinar cell cancer, anaplastic cancer, duodenal cancer, distal common bile duct cancer, or ampullary cancer Sho et al. 2013 No details given Tzeng 2014 Patients with disease that met MDACC clinical criteria for borderline resectable cancer on the basis of advanced tumour anatomy Vento et al. 2007 Patients with metastases to the liver Patients with a poor general condition Patients with a fractured femur and died from a pulmonary embolism before the operation.				

Study details	Participants	Interventions	Methods	Outcomes and Results*	Limitations

Full citation
Takahashi H, Ohigashi H, Gotoh K, Marubashi S, Yamada T, Murata M, Ioka T, Uehara H, Yano M, Ishikawa O. Preoperative GEM-based CRT therapy for resectable and borderline (BR) resectable PC. Ann Surg 2013;258(6):1040-50
Ref ID
Takahashi 2013
Country/ies where the study was carried out:
Japan
Study type:
Prospective phase II clinical trial
Aim of the study:
To evaluate the outcome of preoperative GEM-based CRT therapy (CRT) for resectable and borderline resectable PC (PC), with a focus on the differences in surgical outcomes
	Sample size
	n= 268 patients with resectable (n=188) and BR resectable (n=80) PC
	Characteristics
	M/F (n):
	Total=170/98;
	resectable PC= 123/65;
	BR resectable PC= 47/33;
	Mean age <=65/>65 years (n):
	Total=130/138;
	resectable PC= 91/97;
	BR resectable PC= 39/41;
	Tumour location, head/body tail (n):
	Total=181/87;
	resectable PC= 126/62;
	BR resectable PC= 55/25;
	Inclusion criteria
	Patients with:
	definite radiographic evidence of tumor extension beyond the confines of the pancreas;
	no evidence of distant disease (M0);
	no evidence of tumour abutment greater than 180 degrees of the circumference of the superior mesenteric artery (SMA), celiac axis
		Interventions
		G1- intervention: CRT followed by surgery^ (n= 268).
		Further details: GEM and 50 Gy (with a daily fraction of 2 Gy 5 times per week)
		Not comparative study
			Details
			Design: single-arm phase II clinical trial
			Duration: 2002-2011
			Country: Japan
				Results
				Overall Survival
				Resection rate
				Adverse Events
					Limitations
					Selection: Low risk of bias
					Comparability: not applicable
					Outcome*: Low risk of bias
					Other information

Study details	Participants	Interventions	Methods	Outcomes and Results*	Limitations
and patterns of recurrence between these 2 categories. Study dates: Publication date: December 2013 Data collection/patients enrolment: 2002-2011 Source of funding: Otsuka Research Fund - not a commercial organization	(CA), or common hepatic artery (CHA) and/or no evidence of encasement of these arteries; no evidence of cancer invasion into the confluent point of the right colic vein to the superior mesenteric vein (SMV); and no evidence of occlusion of the SMV and portal vein (PV) without an appropriate option for venous resection and reconstruction. Patients whose PC showed abutment/partial encasement or a short segment of occlusion of the SMV/PV with the option for venous resection and reconstruction were eligible for preoperative CRT. Exclusion criteria Patients with: performance status, according to the Eastern Cooperative Oncology Group criteria, of grade 2 or worse; inadequate bone marrow reserves as measured by a total white blood cell count of 3000 cells/mm3 or less and a platelet count of 100,000 cells/mm3 or less; laboratory tests indicating abnormal data				

Study details	Participants	Interventions	Methods	Outcomes and Results*	Limitations
	or a significant medical comorbidity precluding consideration for major pancreatic surgery.				
Full citation Varadhachary GR, Wolff RA, Crane CH, Sun CC, Lee JE, Pisters PW, Vauthey JN, Abdalla E, Wang H, Staerkel GA, Lee JH, Ross WA, Tamm EP, Bhosale PR, Krishnan S, Das P, Ho L, Xiong H, Abbruzzese JL, Evans DB. Preoperative GEM and cisplatin followed by GEM-based CRT for resectable adenocarcinoma of the pancreatic head. J Clin Oncol 2008; 26: 3487-3495 Ref ID Varadhachary et al. 2008 Country/ies where the study was carried out USA Study type	Sample size N=90 patients with resectable PC Characteristics M/F (n): 50/40 Median age (range): 64 (42-80) years Current or past smoker (yes, n): 56 Inclusion criteria Patients with: potentially resectable disease on the basis of physical examination and the following objective CT criteria: (1) no evidence of extrapancreatic disease; (2) no evidence of tumor extension to the superior mesenteric artery (SMA) or celiac axis; and (3) no evidence of occlusion of the superior mesenteric vein (SMV) or SMV–portal vein (PV) confluence a Karnofsky performance status of at least 70, an absolute neutrophil count (ANC) more than 1,500 cells/mm3 a platelet count of at least 100,000 cells/mm3	Interventions G1: Chemotherapy followed by CRT before surgery (n=90) Further details: GEM + cisplatin followed by GEM and 30 Gy Not comparative study	Details Design: single-arm phase II clinical trial Duration: 2002-2006 Country: USA	Results Overall Survival Time from initiating treatment to Surgery Adverse Events	Limitations Selection: Low risk of bias Comparability: not applicable Outcome*: Low risk of bias Other information

Study details	Participants	Interventions	Methods	Outcomes and Results*	Limitations
Prospective phase II clinical trial Aim of the study To evaluate the outcome of pre-operative GEM and cisplatin followed by GEM-based CRT (Gem-Cis-XRT) in stage I/II adenocarcinoma of the pancreatic head. Study dates Publication date: December 2008 Data collection/patients enrolment: 2002-2006 Source of funding Not reported	a serum creatinine level less than 1.6 mg/dL a serum bilirubin level less than 5 mg/dL Exclusion criteria Patients with: evidence of fever, active infection, hepatic transaminases (ALT and AST) greater than 5× the upper limits of normal significant medical comorbidity precluding consideration of major pancreatic surgery.				

F.131 Resectable and borderline resectable pancreatic cancer

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Data taken from the review only					
Full Citation de Rooij T, Lu MZ, Steen MW et al. (2016) Minimally invasive versus open pancreatoduodenectomy: systematic review and meta-analysis of comparative cohort and	N=716 (Minimally invasive [MI]=266/open=450) _____ Abdelgadir Adam et al (2015), N=7061 (MI=983/open=6078)	Inclusion Studies comparing minimally invasive (robotic or laparoscopic) pancreaticoduodenectomy and open pancreaticoduodenectomy reporting at least 1 outcome of interest	Abdelgadir Adam et al (2015): Registry study of 246 centres 2010-2011 (National Cancer Database), no details of type of MI surgery used Cho et al (2009): single centre	Body mass index Tumour size Cancer Diagnosis Operation time Blood loss R0 resection rate Retrieved lymph nodes	Overall High Risk of bias Studies were not randomised. All were cohort or Registry studies. Not clear if there was blinding of patients,

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
registry studies. Annals of Surgery 264(2): 257-67 Country/ies where the study was carried out: Abdelgadir Adam et al. (2015) - USA Cho et al. (2009) Hakeem et al. (2014) Kuroki et al. (2012) Langan et al. (2014) Sharpe et al. (2015) - USA Speicher et al. (2014) Tee et al. (2015) Tran et al. (2016) – USA Wang et al. (2014) Wellner et al. (2014) Study type Systematic review and meta-analysis Aim of the study To compare minimally invasive (laparoscopic or robotic) pancreaticoduodenectomy with open approach. Study dates Searches conducted to August 2015 Source of funding	_____ Cho et al. (2009), N=60 (MI=30/open=30) Age: MI=64 (10)/open=68 (9). Malignant: MI=7/open=15 _____ Hakeem et al. (2014), N=24 (MI=12/open=12 [matched]) _____ Kuroki et al. (2012) , N=51 (MI=20/open=31) _____ Langan et al. (2014), N=53 (MI=28/open=25 [matched]) Age (median): MI=64 (IQR 45-84)/open=65 (IQR 34-85). Malignant: MI=16/open=16 _____ Sharpe et al. (2015), N=4422 (MI=385/open=4037) _____	Exclusion Articles including non-pancreaticoduodenectomy procedures; Review articles; Articles not reporting on postoperative outcomes; ≤10 participants in each arm; Non-English language articles; Opinion papers; Proceedings; Editorials; or Studies on children or animals	laparoscopically-assisted pancreaticoduodenectomy Hakeem et al. (2014): single centre laparoscopic pancreaticoduodenectomy/ laparoscopically-assisted pancreaticoduodenectomy Kuroki et al. (2012): single centre laparoscopically-assisted pancreaticoduodenectomy Langan et al. (2014): single centre laparoscopically-assisted pancreaticoduodenectomy Sharpe et al. (2015): Registry study of 365 centres 2010-201 (National Cancer Database), no details of type of MI surgery used Speicher et al. (2014): single centre laparoscopic pancreaticoduodenectomy/ laparoscopically-assisted	Mortality Pancreatic fistula (Grade B-C) Delayed Gastric Emptying (clinically relevant) Hospital stay	treatment administrators or investigators however as this was a surgical comparison it is unlikely that patients/treatment administrators were blinded. No information was recorded as to whether intent to treat analysis was performed Selection Bias There is a potentially high risk of selection bias across the included studies as these are not randomised comparisons and the type of surgery may be determined based on the patient's suitability. Performance Bias There is a high risk of performance bias across the included studies. Although participants and treatment administrators were not blinded, this would not be possible in surgical comparison. Registry studies combined data for 133-365 centres in USA: operator and centre differences highly likely. Attrition Bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Three of the authors received educational grant from Ethicon Endo-Surgery for Dutch Pancreatic Cancer Group LAELAPS nationwide training program in MI pancreaticoduodenectomy	Speicher et al. (2014), N=107 (MI=25/open=84) Age (median): Totally laparoscopic=61 (IQR 57-69)/hand-assisted=69 (62-72))/open=64 (IQR 58-72). Malignant: Totally laparoscopic=20/hand-assisted=25/open=62 _____ Tee et al. (2015), N=338 (MI=113/open=225) _____ Tran et al. (2016), N=15,574 (MI=681/open=14,893) _____ Wang et al. (2014), N=33 (MI=13/open=20) _____ Wellner et al. (2014), N=80 (MI=40/open=40 [matched]) _____ Other studies alrady included in more recent reviews.		pancreaticoduodenectomy Tee et al. (2015): single centre laparoscopic pancreaticoduodenectomy Tran et al. (2016): Registry study of 133 centres from 2000-2010 (Nationwide Inpatient Sample), no details of type of MI surgery used Wang et al. (2014): single centre laparoscopically-assisted pancreaticoduodenectomy Wellner et al. (2014): multicentre laparoscopically-assisted pancreaticoduodenectomy		There is a low risk of attrition bias Detection Bias The risk of detection bias is low as outcomes are primarily short-term post-operative outcomes therefore follow-up is likely to be adequate. Investigators were not blinded to patient exposure or to potential confounders however which presents a high risk of bias.

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
	Information regarding age and surgical pathology from review by Doula et al. (2016)				
Data taken from the review only					
Full Citation Doula et al. (2016) Comparison between minimally invasive and open pancreaticoduodenectomy: A systematic Review Surg Laparosc Endosc Percutan Tech 26;1:6-16 Country/ies where the study was carried out: Pugliese et al. (2008) - Italy Gumbs et al. (2008) USA Study type: Systematic review and meta-analysis Aim of the study: To compare minimally invasive (laparoscopic or robotic) pancreaticoduodenectomy with open approach. Study dates: Searches conducted to July 2014	N=68 (open=46/minimally invasive=22) _____ Pugliese et al. (2008 (Italy) N=60 (open=41/minimally invasive=19) Age: MI=64 (12)/open= not applicable Malignant: MI=18/open=not applicable _____ Gumbs et al. (2008 (USA) N=8 (open=5/minimally invasive=3) Malignant: MI=0/open=0 _____ Other studies are already included in more recent reviews.	Inclusion Original articles published in English Studies comparing minimally invasive (robotic or laparoscopic) pancreaticoduodenectomy and open pancreaticoduodenectomy Various types of pancreatic pathology Exclusion Non comparative studies; Non-English language studies; Case reports; reviews; or animal studies. Pugliese et al. (2008 (Italy) Laparoscopic (6 total, 7 HA, 6 converted) versus open Gumbs et al. (2008 (USA) Laparoscopic versus open	Pugliese et al. (2008 (Italy) Open: No details Minimally invasive: resection=14/preserving=-5 Gumbs et al. (2008 (USA) Not reported	Number of retrieved lymph nodes Surgical margin Duration of operation Amount of blood loss Number of transfused patients Transfused blood units Conversions to open operation and reoperation Length of hospital stay Complications including: Pancreatic fistula Bile leak Delayed gastric emptying Intraoperative deaths Postoperative deaths Cost of operation	Overall High Risk of bias Studies were not randomised All were cohort studies. Not clear if there was blinding of patients, treatment administrators or investigators however as this was a surgical comparison it is unlikely that patients/treatment administrators were blinded. No information was recorded as to whether intent to treat analysis was performed Selection Bias There is a potentially high risk of selection bias across the included studies as these are not randomised comparisons and the type of surgery may be determined based on the patient's suitability. Performance Bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Source of funding: N/A					There is a low risk of performance bias across the included studies. Although participants and treatment administrators were not blinded, this would not be possible in surgical comparison. Attrition Bias There is a low risk of attrition bias Detection Bias The risk of detection bias is low as outcomes are primarily short-term post-operative outcomes therefore follow-up is likely to be adequate. Investigators were not blinded to patient exposure or to potential confounders however which presents a high risk of bias.
Data taken from the review only					
Full Citation Giovinazzo F. et al. (2016) Meta-analysis of benefits of portal-superior mesenteric vein resection in pancreatic resection for ductal adenocarcinoma BJS 103;179-191	N=27 studies N=9005 patients N=1587 patients underwent pancreatic resection with VR N=7418 underwent pancreatic resection only Inclusions	Pancreatic resection with vein resection Pancreatic resection Only	N=13 studies reported type of venous reconstruction End to end anastomosis (46.5%, n=368) Venorrhaphy/patch (19.2%, n=34.3%)	Overall Survival (1,3 and 5 year) Perioperatie outcomes including: Duration of surgery Blood loss Postoperative morbidity	Overall – high risk Studies are all retrospective comparisons and are not randomised. No blinding of patients, treatment administrators or investigators Selection Bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Country/ies where the study was carried out: Sperti et al. (1996) Martin et al. (2009) Chakravarty et al. (2010): Taiwan Bachellier et al. (2001): France Fukuda et al. (2007) Shrikhande et al. (2011) Castleberry et al. (2012) Fuhrman et al. (1996) Harrison et al. (1996): USA Leach et al. (1998): USA Launois et al. (1999): France Shibata et al. (2001): Japan Hartel et al. (2002): Germany Nakagohri et al. (2003): Japan Poon et al. (2004): Hong Kong Tseng et al. (2004) Carrere et al. (2006): France Riediger et al. (2006): Germany Shimada et al.(2006): Japan	Patients diagnosed with pancreatic adenocarcinoma Comparative At least one outcome of interest Exclusion: Pancreatic neuroendocrine neoplasia Other histology Reviews without original data Case reports Studies without a control group Sperti et al. (1996) With VR:99 Without VR:14 Martic et al. (2009) With VR:557 Without VR:36 Chakravarty et al. (2010) With VR:75 Without VR:12 Bachellier et al. (2001) With VR:66 Without VR:21 Fukuda et al. (2007) With VR:84 Without VR:37		Interposition of a graft (19.2%, n=152)	Postoperative mortality (30 day or during hospital stay) Histopathology findings including: Results of pathology reports for the presence of metastatic lymph nodes and resection margin status	There is a high risk of selection bias as the studies are not randomised and it is likely that patients selected for surgery are selected based on the suitability and likelihood of a positive outcome. Performance Bias There is a low risk of performance bias across the included studies. Although participants and treatment administrators were not blinded, this would not be possible in surgical comparison. Attrition Bias There is a low risk of attrition bias Detection Bias There is an unclear risk of bias. Follow-up time for each study are not reported it is therefore not clear whether follow-up was sufficient to allow reporting of long term outcomes such as overall survival.

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Al-Haddad et al. (2007): USA Kurosaki et al. (2008): Japan Ouaissi et al. (2010): Belgium Ravikumar et al. (2014) Gong et al. (2013) Kelly et al. (2013) Murakami et al. (2013) Kawada et al. (2002) Study type Systematic review and meta-analysis Aim of the study: To evaluate the perioperative outcomes and overall survival of patients undergoing pancreatic resection combined with vein resection, compared with those without vein resection to evaluate the feasibility and influence on patient outcomes Study dates: Articles published anytime up to 31st December 2013 Source of funding: None reported.	Shrikhande et al. (2011) With VR:6 Without VR:1 Castleberry et al. (2012) With VR:3301 Without VR:281 Fuhrman et al. (1996) With VR:36 Without VR:23 Harrison et al. (1996) With VR:274 Without VR:58 Leach et al. (1998) With VR:44 Without VR:31 Launois et al. (1999) With VR:74 Without VR:14 Shibata et al. (2001) With VR:46 Without VR:28 Hartel et al. (2002) With VR:203 Without VR:68 Nakagohri et al. (2003) With VR:48 Without VR:33 Poon et al. (2004) With VR:38				

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
	Without VR:12 Tseng et al. (2004) With VR:181 Without VR:110 Carrere et al. (2006) With VR:88 Without VR:45 Riediger et al. (2006) With VR:169 Without VR:53 Shimada et al. (2006) With VR:63 Without VR:86 Al-Haddad et al. (2007) With VR:54 Without VR:22 Kurosaki et al. (2008) With VR:42 Without VR:35 Ouaissi et al. (2010) With VR:82 Without VR:59 Ravikumar et al. (2014) With VR:840 Without VR:230 Gong et al. (2013) With VR:447 Without VR:119 Kelly et al. (2013) With VR:422 Without VR:70				

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
	Murakami et al. (2013) With VR:64 Without VR:61 Kawada et al. (2002) With VR:15 Without VR:28				
Data taken from the Cochrane Review. Original publications were not checked					
Full citation Huttner et al. (2016) Pylorus-preserving pancreaticoduodenectomy (pp Whipple) versus pancreaticoduodenectomy (classic whipple) for surgical treatment of periampullary and pancreatic carcinoma Cochrane Database of Systematic Reviews Country/ies where the study was carried out: Bloechle: Germany Lin: Taiwan Paquet: Germany Seiler: Germany Srinarmwong: Thailand Taher: Bangladesh Tran: Netherlands Wenger: Germany Study type: Cochrane Review Inclusion	Sample size Total N=512 (PPW=255/CW=257) Bloechle 1999 N= 44 (PPW=23/CW=21) Inclusion Criteria People with periampullary cancer (cT1-4, cN0-1, cM0) Exclusion Criteria None listed Lin 1999 N=33 (PPW=14/CW=19 Inclusion Criteria People with pancreatic head cancer Exclusion Criteria None listed Paquet 1998 N=40 (PPW=17/CW=23	Interventions Bloechle: PPW and CW (no operation details) Erythromycin/Somastostatin application unknown Lin: PPW and CW (no operation details) No Somastostatin Erythromycin application unknown Paquet: Anastomoses: retrocolic end to end pancreaticojejunostomy with a drain in the pancreatic duct, end to end hepaticojejunostomy, end to end duodenojejunostomy Erythromycin/Somastostatin application unknown Seiler:	Bloechle: Randomisation method not reported Allocation concealment: unknown Intention to treat analysis: no Sample size calculation: none Lin: Randomisation method not reported Allocation concealment: unknown Intention to treat analysis: no Sample size calculation: none Paquet: Randomisation method: sealed envelopes Allocation concealment: unknown	Primary Outcomes Pancreatic Fistula Delayed Gastric emptying Biliary Leakage Secondary Outcomes Survival Postoperative Mortality Perioperative Parameters including: Intraoperative blood loss Red blood cell transfusion Operating time Postoperative bleeding Wound infection Pulmonary complications Necessity for reoperation duration of hospital stay Quality of Life Status of resection margin (R0/R1)	Bloechle: Random sequence generation: Unclear risk (Not reported) Allocation concealment: Unclear risk (Not reported) Blinding: Unclear risk (Not reported) Blinding of participants and personnel Assessments: Unclear risk (Not reported) Blinding of outcome assessment: Unclear risk (Not reported) Incomplete outcome data: High risk (randomisation dropouts could have influenced effect estimates) Selective reporting: unclear risk (no study protocol available).

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
RCTs comparing classic whipple with pp whipple procedures Aim of the study: To compare the effectiveness of pylorus preserving Whipple and classic Whipple techniques for the surgical treatment of cancer of the pancreatic head and the periampullary region. Study dates: 1946 – 2015 Source of funding: None reported.	Inclusion Criteria People with pancreatic adenocarcinoma or periampullary cancer and an R0 resection Exclusion Criteria None listed Seiler 2005 N=130 (PPW=64/CW=66) Inclusion Criteria All patients suitable for surgery with suspected pancreatic or periampullary cancer considered resectable on the basis of CT or MRI with no history of previous gastric resection Exclusion Criteria Direct tumour invasion of the proximal duodenum, pylorus or stomach Peripyloric lymph node metastases confirmed by intraoperative frozen section examination Distant metastases or locally unresectable tumours due to major	Reconstruction performed by means of a an interrupted 2 layer end to side pancreaticojejunostomy 10-15cm distal to the pancreatic anastomosis, and an end to end gastrojejunostomy/duodenojejunostomy approximately 40cm distal to the biliodigestive anastomosis, followed by a Braun jejunostomy Somatostatin: 100-200µg three times a day for seven days Erythromyacin: None Perioperative treatment: antibiotic prophylaxis Srinarmwong: Resection line: 2cm distal to the pylorus (PPW group); 20-40% of the stomach resected (CW group) Reconstruction: end to side invaginated pancreaticojejunostomy, an end to side hepaticojejunostomy and an end to side dudenojejunostomy in the PPW group or a side to side	Intention to treat analysis: no Sample size calculation: none Seiler: Randomisation method: sealed envelopes Allocation concealment: unknown Intention to treat analysis: no Sample size calculation: yes Srinarmwong: Randomisation method: computer-generated random lists Allocation concealment: sealed, opaque Intention to treat analysis: no Sample size calculation: none Taher: Randomisation method not reported Allocation concealment: unknown Intention to treat analysis: no Sample size calculation: none Tran:	Bloechle: Operation time (minutes) Postoperative Mortality Delayed Gastric Emptying Lin: Operation time (minutes) Intraoperative blood loss (ml) Blood replacement (units) Postoperative mortality Delayed Gastric Emptying Bleeding Fistula Bile Leak Wound infection Intra-abdominal abscess Paquet: Postoperative mortality Delayed gastric emptying Fistula Radicality Seiler: Opertion time (minutes) Intraperative blood loss (ml) Blood replacement (units) Hospital stay (days)	Other sources of bias: High Risk (sample size calculation not reported) Lin: Random sequence generation: Unclear risk (Not reported) Allocation concealment: Unclear risk (Not reported) Blinding: Unclear risk (Not reported) Blinding of participants and personnel Assessments: Unclear risk (Not reported) Blinding of outcome assessment: Unclear risk (Not reported) Incomplete outcome data: High risk (randomisation dropouts could have influenced effect estimates) Selective reporting: unclear risk (no study protocol available). Other sources of bias High Risk (sample size calculation not reported) Paquet: Random sequence generation: Unclear risk (Not reported) Allocation concealment: Unclear risk (information

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
	retroperitoneal infiltration Emergency resections Necessity for total pancreatectomy to achieve clear margins Srinarmwong 2008 N=27 (PPW=14/CW=13) Inclusion Criteria All people with suspected pancreatic or periampullary cancer evaluated to have resectable disease Exclusion Criteria Previous gastric resection Distant metastases Unresectable tumours Tumour invasion of pylorus or stomach Refusal to participate Taher 2015 N=20 (PPW=12/CW=8) Inclusion Criteria All people suitable for surgery with carcinoma of the head of the pancreas	gastrojejunostomy in the CW group Somatostatin: 100µg 3 times/day for seven days Erythromycin application unknown Perioperative treatment: antibiotic prophylaxis (cefazolin+metronidazole); postoperative: H2 antagonists Taher: PPW and CW (no operation details) Erythromycin/Somastostatin application unknown Perioperative treatment detaisl unknown Tran: End to side invaginated pancreaticojejunostomy, end to side hepaticojejunostomy, side to side gastroenterostomy, end to side pylorus jejunostomy Somatostatin: 100µg three times a day for a total of seven Erythromycin application unknown Perioperative treatment: antibiotic prophylaxis,	Randomisation method: sealed envelopes Allocation concealment: sealed opaque envelopes Intention to treat analysis: yes Sample size calculation: yes Wenger: Randomisation method not reported Allocation concealment: unknown Intention to treat analysis: no Sample size calculation: none	Postoperative mortality Delayed gastric emptying Bleeding Fistula Bile leak Infection (wound or abscess) Positive lymph nodes Radicality (R0) Srinarmwong: Operation time (minutes) Intraoperative blood loss (ml) Hospital Stay (days) Postoperative mortality Delayed gastric emptying Bleeding Fistula Bile Leak Positive lymph nodes Taher: Operation time (mins) Blood replacement (units) Hospital Stay (days) Postoperative mortality Delyaed gastric emptying Bleeding Fistula	obtained from study author –'sealed envelopes') Blinding: Unclear risk (Not reported) Blinding of participants and personnel Assessments: Unclear risk (Not reported) Blinding of outcome assessment: Unclear risk (Not reported) Incomplete outcome data: Low risk (no post-randomisation drop outs reported) Selective reporting: unclear risk (no study protocol available) Other sources of bias: High risk (sample size calculation not reported) Seiler: Random sequence generation: Unclear risk (Not reported) Allocation concealment: Unclear risk (envelopes used for randomisation but no detail as to whether they were opaque) Blinding: Unclear risk (Not reported) Blinding of participants and personnel

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
	or periampullary region Exclusion Criteria People with distant metastases Tran 2004 N=170 (PPW=87/CW=83) Inclusion Criteria Consecutive patients with suspected pancreatic or periampullary cancer assumed to be resectable according to preoperative diagnostic imagin Exclusion Criteria Previous gastric resection Distant metastases or local unresectable tumours Direct invasion of the pylorus or stomach Postivie peripyloric lymph nodes Wenger 1999 N=48 (PPW=24/CW=24) Inclusion Criteria People with a preoperative diagnosis of a ductal carcinoma of the	H2 antagonists, drain in operation area Wenger: PPW and CW (no operation details) Erythromycin/Somastostatin application unknown		Bile leak Re-laparotomy Tran: Operation time (minutes) Intraoperative blood loss (ml) Blood replacement (units) Hospital stay (days) Postoperative mortality Delayed gastric emptying Bleeding Fistula Bile leak Intra-abdominal abscess Re-laparotomy Positive lymph nodes Radicality (R0) Wenger: Operation time (minutes) Blood replacement (units) Hospital stay (days) Wound infections Positive lymph nodes Radicality (R0)	Assessments: Unclear risk (Not reported) Blinding of outcome assessment: Unclear risk (Not reported) Incomplete outcome data: Low risk (no post randomisation dropouts) Selective reporting: Unclear risk (Not reported) Other sources of bias: Low Risk Srinarmwong: Random sequence generation: Low risk (computer generated random list) Allocation concealment: Low risk (sealed, opaque envelopes) Blinding: Unclear risk (Not reported) Blinding of participants and personnel Assessments: Unclear risk (Not reported) Blinding of outcome assessment: Unclear risk (Not reported) Incomplete outcome data: Low risk (no post randomisation drop out) Selective reporting: Unclear risk (Not reported)

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
	pancreatic head or periampullary carcinoma R0 resection Postoperative affirmation of the diagnosis Exclusion Criteria Tumour infiltration of the stomach, the superior part of the duodenum or the pylorus Age >75 years Peritoneal carcinosis Reduced general condition Heart insufficiency Renal insufficiency Hepatic insufficiency Pulmonary insufficiency				Other sources of bias: High risk (sample size calculation not reported) Taher: Random sequence generation: Unclear risk (No details given in the text) Allocation concealment: Unclear risk (Not reported) Blinding: Unclear risk (Not reported) Blinding of participants and personnel Assessments: Unclear risk (Not reported) Blinding of outcome assessment: Unclear risk (Not reported) Incomplete outcome data: Low risk (no post randomisation drop outs) Selective reporting: Unclear risk (Not reported) Other sources of bias: High risk (no sample size calculations; ambiguities in report of the trial) Tran: Random sequence generation: Unclear risk (Not reported)

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
					Allocation concealment: Low Risk Blinding: Unclear risk (Not reported) Blinding of participants and personnel Assessments: Unclear risk (Not reported) Blinding of outcome assessment: Unclear risk (Not reported) Incomplete outcome data: Low risk (reasons for exclusion from long-term survival analysis are provided) Selective reporting: Unclear risk (Not reported) Other sources of bias: Low Risk Wenger: Random sequence generation: Unclear risk (Not reported) Allocation concealment: Unclear risk (Not reported) Blinding: Unclear risk (Not reported) Blinding of participants and personnel Assessments: Unclear risk (Not reported)

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
					Blinding of outcome assessment: Unclear risk (Not reported) Incomplete outcome data: Low risk (no post randomisation dropouts) Selective reporting: Unclear risk (Not reported) Other sources of bias: High risk (sample size calculation not reported)
Full citation Kawai et al. (2014) Pylorus resecting pancreaticoduodenectomy offers long-term outcomes similar to those of pylorus-preserving pancreaticoduodenectomy: results of a prospective study Country/ies where the study was carried out: Japan Study type: Randomised Trial Aim of the study: To assess whether Pylorus resecting pancreaticoduodenectomy leads to better long term outcomes compared with pylorus-preserving	N= 130 patients randomised (64 pylorus preserving/66 pylorus resecting) N= 40 pancreatic adenocarcinoma (n=17 pylorus preserving/n=23 pylorus resecting) Inclusion No details Exclusion Data following tumour recurrence or metastasis were excluded from analysis.	Pylorus-resecting Pancreaticoduodenectomy versus Pylorus-preserving Pancreaticoduodenectomy In malignant disease, lymph node removal in two procedures: hepatoduodenal ligament, circumferentially around the common hepatic artery and the right half circumference of the superior mesenteric artery. All patients underwent pancreaticoduodenectomy with duct-to-mucosa, end to side pancreaticojejunostomy.	Randomised Controlled Trial No details provided on method of randomisation Patients agreed to 24 months of post-surgery follow-up Assessments of nutritional status by body weight change and serum nutritional parameters was performed before surgery and at 6, 12, 18 and 24 months post-surgery Quality of life was assessed at 6, 12, and 24 months after surgery using FACT-Ga questionnaire (27 items assessing physical, social,	Outcomes Long-term outcomes Body weight change Gastric empyting Quality of life Late post-operative complications Effect of delayed gastric emptying in the early period on long-term outcomes Median follow-up PpPD Group: 37.5 months (3-78 months) PrPD Group: 41.5 months (1-76 months) 45/130 patients died due to cancer recurrence (PpPD=19/PrPD=26) Complete data were available for 52.7% of patients at 2 year follow-	Random sequence generation: Unclear risk (Not reported) Allocation concealment: Unclear risk (Not reported) Blinding: Unclear risk (Not reported) Blinding of participants and personnel Assessments: Unclear risk (Not reported) Blinding of outcome assessment: Unclear risk (Not reported) Incomplete outcome data: Low risk (no post randomisation dropouts) Selective reporting: Unclear risk (Not reported) Other sources of bias: High risk (sample size calculation not reported)

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
pancreaticoduodenectomy. Study dates: October 2005 – March 2009 Source of funding: None reported			emotional and functional well-being and a newly validated 19 item section assessing gastric cancer specific domains)	up (body weight and nutritional assessment) Late postoperative complications and long-term outcomes There was no significant difference between the two procedures in relation to any of the late post-operative complications (dumping syndrome, peptic ulcer; diarrhoea, new onset/worsening diabetes) or in relation to any of the nutritional status measurements at any time point. Long term body weight changes There was no significant difference in mean body weight preoperatively and 24 months postoperatively between the groups. PpPD PrPD Change in BW (Kg) Preoperative 54.9 ±10 55± 9 6 months post-op 50.9 ±11 20± 8	

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
				Weight loss>grade 2 — 23 (41.1%) — 24 (45.3%) 12 months post-op — 51±11 — 50.7±8.9 Weight loss>grade 2 — 22 (43%) — 12 (27.3%) 18 months post-op — 51.2±11 — 52±9.1 Weight loss>grade 2 — 18 (39.1%) — 6 (15.8%) 24 months post-op — 51.1±11 — 53±9.5 Weight loss>grade 2 — 19 (42.2%) — 6 (16.2%) Long-term Gastric emptying and quality of life Measured as Tmax – time to peak CO2 content Tmax was significantly delayed in the PpPD group compared with the PrPD group at all three time points PpPD — PrPD	

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
				(n=64) (n=66) Gastric emptying by C-ac breath test 6 months 26.7 ±18.8 17.4 ±13.2 12 months 23.4 ±16.9 14.2 ±4.5 24 months 20.9 ±15.6 14± 5.5 QoL assessments available: 6 months=109 (83%) 12 months=95 (73%) 18 months=84 (63.9%) 24 months=82 (63.1%) Return rate at each time point was 100% No significant differences in QoL scores were observed between the two groups at any time point. PpPD (n=64) PrPD (n=66) Quality of Life (total FACT score) 6 months 139 ±22.9 139.6±21.4	

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
				12 months 144.7±20 145.9±24.8 24 months 149.5±20.1 148.8±23.2 FACT-Ga subscale 6 months 59.6±11 60.1±11.3 12 months 61.3±10 60.8±11.6 24 months 63.5±10.5 62.7±10.9 Short-term and long-term outcomes after early post-operative DGE There was no significant difference between patients with or without DGE for pancreatic fistula (p=0.381) or intraabdomial abscess (p=0.206) Body weight at 24 months post surgery improved significantly in patients without DGE (p=0.010) Serum albumin was significantly higher at 24 months in patients without DGE (p=0.013)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
				Tmax at 24 months post surgery was significantly delayed in patients with early post-op DGE compared to patients without early post-op DGE (p=0.023). There were no significant differences in the results on the QoL assessments	
Original Publications were checked to ascertain the risk of bias and also for inclusion/exclusion criteria, interventions and methods.					
Ke et al. (2014) Standard and extended lymphadenectomy for adenocarcinoma of the pancreatic head: A meta-analysis and systematic review Journal of Gastroenterology and Hepatology 29;453-462 Country/ies where the study was carried out: Pedrazzoli: Italy Farnell: USA Riall: USA Nimura: Japan Study type: Systematic review and meta-analysis Aim of the study: To investigate whether pancreaticoduodenectomy with extended lymphadenectomy	Total N=428 (lymphadenectomy=215/Extended lymphadenectomy=213) Inclusions RCTs comparing outcomes between standard and extended lymphadenectomy in pancreatoduodenectomy for adenocarcinoma of the pancreas head. Exclusions Non RCTs, case reports, retrospective studies, conference proceedings, abstracts and non-peer reviewed publications.	Pedrazzoli: Standard lymphadenectomy: removal of the anterior and posterior pancreatoduodenal, pyloric and biliary duct, superior and inferior pancreatic head and body lymph node stations Extended: As standard plus reoval of lymph nodes from the hepatic hilum and along the aorta from the diaphragmatic hiatus to the inferior mesenteric artery and laterally to both renal hila, with circumferential clearance of the origin of the celiac trunk and superior mesenteric artery.	Pedrazzoli: Pancreatoduodenectomy with or without pylorus preservation (surgeons choice) Farnell: Standard lymphadenectomy versus extended lymphadenectomy Riall: Standard lymphadenectomy versus extended lymphadenectomy Nimura: Standard lymphadenectomy versus extended lymphadenectomy	Pedrazzoli: Duration of operation Patients transfused Units transfused Total amount of drainage through abdominal drains Postoperative day abdominal drains were removed Length of post operative stay Lymph nodes retrieved Patients who underwent IORT Intraperitonel haemorrhage Pancreatic Fistula Subphrenic abscess Stump acute pancreatitis Perforated colonic diverticulum	Overall Low quality evidence for all outcomes (GRADE assessment included in the systematic review) due to lack of reporting on randomisation methods, lack of blinding (assessor), incomplete outcome data and inadequate sample sizes. Pedrazzoli: High risk of selection bias – only patients who were considered eligible after an exploratory laparoscopy were randomised. Random sequence generation: unclear risk (random number generation on a

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
improves survival in patients with adenocarcinoma of the head of the pancreas Study dates: Searches completed January 2013 Source of funding: None reported.	Distal bile duct, ampullary cancer, duodenal tumour, neuroendocrine and serous cystic tumours or pancreatic body or tail tumours Pedrazzoli: N=81 (standard=40/extended=41) Inclusions Patients considered eligible if surgeons considered that all macroscopic disease could be removed following an exploratory laparotomy for adenocarcinoma of the pancreas head. Exclusions Peritoneal or liver metastases Unresectable tumour due to local spread Post-operative Adjuvant therapy Farnell: N=79 (standard=40/extended=39) Inclusions	Farnell: Patients in both groups underwent distal gastrectomy No pylorus preservation Standard Lymphadenectomy: first echelon lymph nodes (N1) attached to the specimen were removed en bloc Extended lymphadenectomy: first echelon lymph nodes (N1) attached to the specimen were removed and second echelon (N2) were dissected separately. Riall: Standard margin negative pylorus preserving pancreaticoduodenal resection followed by standard or radical resection Standard: lymph node groups resected en bloc included anterior pancreaticoduodenal lymph nodes, posterior pancreaticoduodenal lymph nodes, nodes in the lower hepatoduodenal ligament and nodes		Other Postoperative mortality Farnell: Survival Perioperative morbidity incluiding: Early reoperation Delayed gastric emptying Pancreatic leak Wound infection Abscess Bile Leak Choloangitis Lymphocele Graft or PV thrombosis Biliary enteric anastomatic stricture Duration of stay Quality of Life Riall: Perioperative complications Length of hospital stay Survival Nimura: Long term survival Morbidity Mortality Quality of life Post-operative Complications	personal computer – no other details) Allocation concealment: Unclear risk (Not reported) Blinding: Unclear risk (Not reported) Blinding of participants and personnel Assessments: Low risk (Not possible to blind in surgical trials) Blinding of outcome assessment: Unclear risk (Not reported) Incomplete outcome data: Low risk (no post randomisation drop outs) Selective reporting: unclear risk (no study protocol available). Other sources of bias: High Risk (sample size calculation not reported) Farnell: High risk of selection bias – only patients who were considered eligible after an exploratory laparoscopy were randomised. Random sequence generation: unclear risk (no details for randomisation method)

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
	Patients with adenocarcinoma of the pancreas Exclusions Patients with ampullary, duodenal or bile duct carcinoma Patients with non-functioning islet cell neoplasms Riall: N=294 (167 pancreatic) (standard=146 (84)/extended=148 (83)) Inclusions Patients undergoing pancreaticoduodenectomy for suspected periampullary adenocarcinoma (tumour of the head, neck or unicate process of the pancreas, ampulla of Vater, distal bile duct or per-Vaterian duodenum) Exclusions Absence of informed consent Preoperative chemotherapy or radiotherapy	along the right lateral aspect of the superior mesenteric artery and vein. Extended resection added a 30-40% distal gastrectomy and a retoperitonela lymphadenectomy extending from the right renal hilum to the left lateral border of the aorta in the horizontal axis and from the portal vein to below the third portion of the duodenum in the vertical axis. Nimura: Pylorus preserving pancreatoduodenectomy Classical PD with distal gastrectomy or subtotal stomach-preserving pancreatoduodenectomy could be selected Standard: lymphadenectomy including anterior and posterior pancreatoduodenal nodes without nerve dissection Extended operation: lymphadenectomy including dissection of the nodes around the		Extended lymphadenectomy retrieved more lymph nodes and took more surgical time. Blood transfusions and length of postoperative stay were comparable between the two groups Quality of Life Farnell et al: extended group lower (worse QoL) score for diarrhoea, bowl control and appearance 4 months post surgery compared with the standard group Nimura et al: QoL was worse in the extended group compared with the standard group in the early post-operative period. QoL improved and reached similar levels 12 months post surgery	Allocation concealment: Unclear risk (Not reported) Blinding: Unclear risk (Not reported) Blinding of participants and personnel Assessments: Low risk (Not possible to blind in surgical trials) Blinding of outcome assessment: Unclear risk (Not reported) Incomplete outcome data: Low risk (reasons provided for patients excluded from analysis) Selective reporting: unclear risk (no study protocol available). Other sources of bias: Unclear Risk (sample size calculations were based on accrual of 50 patients per arm however only 79 patients were randomised) Riall: High risk of selection bias – only patients who were considered eligible after an exploratory laparoscopy were randomised.

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
	Final pathology showing disease other than adenocarcinoma primary to the ampullary region Positive resection margins Nimura: N=101 (standard=51/extended=50) Inclusions Patient <80 years Potentially curable carcinoma of the pancreatic head Exclusions Invasive mucinous cystoadenocarcinoma Intraductal papillary mucinous carcinoma Severe cardiovascular and pulmonary diseases Gross metastases to the paraaortic nodes Marked portal vein stenosis with collateral circulation	common heptatic artery, celiac artery, superior mesenteric artery and sleletonisation of the hepatoduodenal ligament. Nerve dissection circumferentially around the CHS and SMA and semicircumferentially on the right lateral aspect of the CA			Random sequence generation: low risk (random number generation) Allocation concealment: Unclear risk (Not reported) Blinding: Unclear risk (Not reported) Blinding of participants and personnel Assessments: Low risk (Not possible to blind in surgical trials) Blinding of outcome assessment: Unclear risk (Not reported) Incomplete outcome data: Low risk (no post randomisation drop outs) Selective reporting: unclear risk (no study protocol available). Other sources of bias: Low Risk (sample size calculation reported as required 121 patients per arm which was achieved) Nimura: High risk of selection bias – only patients who were considered eligible after standard resection were randomised.

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
					Random sequence generation: low risk (surgeon contacted a central office by phone to receive a randomly generated assignment) Allocation concealment: Unclear risk (Not reported) Blinding: Unclear risk (Not reported) Blinding of participants and personnel Assessments: Low risk (Not possible to blind in surgical trials) Blinding of outcome assessment: Unclear risk (Not reported although states that none of the surgeons were involved in data analysis) Incomplete outcome data: Low risk (details provided for exclusions) Selective reporting: unclear risk (no study protocol available). Other sources of bias: High Risk (sample size calculation reported as requiring 130 patients. A total of 112 were randomised and 101 were included in analysis)

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Data taken from review only					
Full Citation Lei P., Wei B., Guo W. et al. (2014) Minimally invasive surgical approach compared with open pancreaticoduodenectomy: a systematic review and meta-analysis on the feasibility and safety. Surgical Laparoscopy Endoscopy & Percutaneous Techniques 24(4): 296-305 Country/ies where the study was carried out: Ito et al 2009 – not reported Study type: Systematic review and meta-analysis Aim of the study: To compare minimally invasive (laparoscopic or robotic) pancreaticoduodenectomy with open approach. Study dates: To January 2013	N=15 (Minimally invasive [MI]=5/Open=10) Ito et al 2009: N=15 (MI=5/open=10); age: MI=69.2 (15.1)/open=68 (12.1) Other studies are already included in more recent reviews.	Inclusion Cohort or case-control studies that compare laparoscopic or robotic pancreaticoduodenectomy with open pancreaticoduodenectomy in any age group. Reports at least one outcome of interest Exclusion Non-comparative studies, non-human studies, experimental trials, review articles, editorials, letter, case reports	Ito et al. 2009: retrospective cohort study. Total laparoscopic pancreaticoduodenectomy vs open pancreaticoduodenectomy	Perioperative complications Pancreatic fistula Delayed gastric emptying Operation time Blood loss	Overall High Risk of bias Included study was retrospective cohort. Not clear if there was blinding of patients, treatment administrators or investigators however as this was a surgical comparison it is unlikely that patients/treatment administrators were blinded. No information was recorded as to whether intent to treat analysis was performed Selection Bias There is a potentially high risk of selection bias across the included studies as these are not randomised comparisons and the type of surgery may be determined based on the patient's suitability. Performance Bias There is a low risk of performance bias across the included studies. Although participants and treatment administrators

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Source of funding: None reported					were not blinded, this would not be possible in surgical comparison. Attrition Bias There is a low risk of attrition bias Detection Bias The risk of detection bias is low as outcomes are primarily short-term post-operative outcomes therefore follow-up is likely to be adequate. Investigators were not blinded to patient exposure or to potential confounders however which presents a high risk of bias.
Data taken from review only					
Full Citation Mollberg N, et al. (2011) Arterial resection during pancreatectomy for pancreatic cancer. A systematic review and meta-analysis Annals of Surgery 25;6:882-893 Country/ies where the study was carried out: Allendorf (2008): USA Amano et al. (2009): Japan Bockhorn et al. (2010): Germany Boggi et al. (2009): Italy	N=26 articles included N=2609 patients undergoing pancreatic resection N=366 (14%) underwent concomitant arterial resection Allendorf (2008): Total:198 Arterial Resection:11 Amano et al. (2009): Total:23 Arterial Resection:23	PD=Pancreaticoduodenectomy DP=Distal Pancreatectomy TP=Total pancreatectomy STP=subtotal pancreatectomy ExPD extended pancreaticoduodenectomy ExDP= extended distal pancreatectomy ExTP=extended total pancreatectomy	All included studies were retrospective analyses. Follow-up time was reported in 10 studies and ranged from 8-27.4 months	Morbidity Reoperation Rate Mortality Hospital Stay Median Survival Actuarial Survival (1, 3 and 5 year) R0 Resection Lymph Node Positive Meta-analysis (4 studies) showed a significant difference in intraoperative blood loss in favour of patients without AR	Overall – high risk of bias Studies were not randomised and seven studies were non-comparative. Two studies (Allendorf et al & Fortner et al) presented data on the whole (AR+/AR-) population as a whole and five studies (Amano et al, Denecke et al, Hirano et al, Miyakawa et al & Settmacher et al) presented data only for

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Denecke et al. (2010): Germany Fortner et al. (1977): USA Hartwig et al. (2009): Germany Hirano et al. (2007):Japan Hishinuma et al. (2007): Japan Kato et al. (2009): Japan Kinoshita et al. (2001): Japan Klempnauer et al. (1996): Germany Martin et al. (2009): USA Miyakawa et al. (2002): Japan Miyazaki et al. (2003): Japan Ogata et al. (1997): Japan Ouaissi et al. (2010):Belgium Park et al. (2001:Korea Settmacher et al. (2004): Germany Shimada et al. (2006):Japan Sperti et al. (2010): Italy Stitzenberg et al. (2004): USA:	Bockhorn et al. (2010) Total:478 Arterial Resection:29 : Boggi et al. (2009): Total:307 Arterial Resection:26 Denecke et al. (2010) Total:6 Arterial Resection:6 Fortner et al. (1977): Total:18 Arterial Resection:6 Hartwig et al (2009): Total:216 Arterial Resection:14 Hirano et al. (2007): Total:23 Arterial Resection:23 Hishinuma et al. (2007): Total:25 Arterial Resection:7 Kato et al. (2009): Total:176 Arterial Resection:17 Kinoshita et al. (2001): Total:139	ExSTP= extended subtotal pancreactetomy Allendorf (2008): Type of operation: PD (160), DP (22), TP (15), STP (1) Amano et al (2009): Type of operation PD (7); DP (1); TP (15) Artery resected SMA (12); CHA (6), RHA (3), LHA (3), rRHA (4), rCHA (2) Bockhorn et al (2010): Type of operation AR+: PD (16), DP (5), TP (4), STP (4) AR-: PD (442), DP (5), TP (4), STP (27) Artery Resected SMA (3), CA (8), HA (18) Boggi et al (2009): Type of operation AR+: PD (6), DP (10), TP (10) AR-: PD (191), DP (50), TP (40) Artery Resected SMA (6), CA (12), HA (12) Denecke et al (2010): Type of operation DP (6)		(WMD=4338.19; 95% CI, 206.17-670.14, p<0.001, I2=88%) (data not shown in the review to allow for quality assessments/forest plots etc) Meta-analysis of hospital stay data indicated a lengthier stay for patients with AR (WMD=7.97; 95% CI, 1.56-14.38, p=0.01, I2=67%) (data not shown in the review to allow for quality assessments/forest plots etc) Meta-analysis on 5 year survival rates indicated significantly worse outcomes of patients with AR (OR=0.30, 95% CI, 0.15-0.60; p<0.001; I2=0%) (data not shown in the review to allow for quality assessments/forest plots etc)	patients undergoing arterial resection) No blinding of patients, treatment administrators or investigators Selection Bias High risk of selection bias as it is likely that patients were selected for surgery depending on their suitability. Performance Bias There is a low risk of performance bias across the included studies. Although participants and treatment administrators were not blinded, this would not be possible in surgical comparison. Attrition Bias There is a low risk of attrition bias Detection Bias There is a high risk of detection bias. Not all studies reported follow up times and it is not clear whether the follow-up times that were reported were sufficiently long to allow accurate assessment of the long-term outcomes of interest.

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Sugiura et al. (2009): Japan Tamura et al. (1992): Japan Wang et al. (2008): China Wu et al. (2010): China Study type Systematic review and meta-analysis Aim of the study To evaluate peri-operative outcomes and long-term survival of patients who underwent resection for pancreatic cancer with combined arterial resection. Study dates: February 1973-November 2010 Source of funding: None reported.	Arterial Resection:6 Klempnauer et al. (1996): Total:189 Arterial Resection: 16 Martin et al. (2009): Total: 36 Arterial Resection: 5 Miyakawa et al. (2002): Total: 8 Arterial Resection: 8 Miyazaki et al (2003): Total:80 Arterial Resection:13 Ogata et al. (1997) Total:192 Arterial Resection:21 Ouaissi et al. (2010) Total:149 Arterial Resection:8 Park et al. (2001): Total:40 Arterial Resection:15 Settmacher et al. (2004) Total:18 Arterial Resection:18 Shimada et al. (2006): Total:88 Arterial Resection:12	Artery resected CA (6) Fortner et al (1977): Type of operation ExTP: (24) Artery resected SMA (3), CA (1), CHA (1), LHA (1), rRHA (1) Hartwig et al (2009): Type of operation AR+: PD (5), DP (2), TP (7) AR-: PD (42), DP (120), TP (40) Artery resected: SMA (6), CA (12), HA (12) Hirano et al (2007): Type of operation DP (23) Artery resected CA (23); CHA (23) Hishinuma et al (2007): Type of operation AR+:ExDP (7) AR-:ExDP (18) Artery resected CA + CHA (7) Kato et al. (2009): Type of operation PD (176) Kinoshita et al. (2001): Type of operation			Individual study assessments taken from the review Allendorf (2008): High Amano et al. (2009): High Bockhorn et al. (2010): Low Boggi et al. (2009): Low Denecke et al. (2010): High Fortner et al. (1977): High Hartwig et al. (2009): High Hirano et al. (2007): High Hishinuma et al. (2007): High Kato et al. (2009): Low Kinoshita et al. (2001): High Klempnauer et al. (1996): High Martin et al. (2009): High Miyakawa et al. (2002): High Miyazaki et al. (2003): High Ogata et al. (1997): High Ouaissi et al. (2010): High Park et al. (2001: High

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
	Sperti et al. (2010) Total:54 Arterial Resection:5 Stitzenberg et al. (2004): Total:252 Arterial Resection:12 Sugiura et al. (2009): Total:107 Arterial Resection:25 Tamura et al. (1992) Total:15 Arterial Resection:7 Wang et al. (2008) Total:80 Arterial Resection:19 Wu et al. (2010) Total:36 Arterial Resection:9	PD, DP, TP Artery Resected SMA (2), HA (4) Klempnauer et al. (1996): Type of operation AR-: ExPD (131), ExDP (24), ExTP (27), ExSTP (7) Artery resected SMA (7), CA (1), CHA (10) Martin et al. (2009): Artery Resected SMA (2), HA (3) Miyakawa et al. (2002): Type of operation ExDP (8) Artery Resected CA (8), CHA (8) Miyazaki et al (2003): Type of operation PD (60), DP (11), TP (9) Artery Resected SMA (2), CA (6), HA (9) Ogata et al. (1997) Type of operation AR+: PD (5), DP (4), TP (12) AR-: PD (131), DP (22), TP (39) Artery Resected			Settmacher et al. (2004): High Shimada et al. (2006):Low Sperti et al. (2010): High Stitzenberg et al. (2004): High: Sugiura et al. (2009): High Tamura et al. (1992): High Wang et al. (2008): High Wu et al. (2010): High

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
		SMA (1), CA (5), CHA (4), RHA (3), LHA (1) Ouaissi et al. (2010) Type of operation AR+: PD (8) AR-: PD (128), TP (13) Artery Resected SMA (1), CHA (2), rRHA (5) Park et al. (2001): Not reported Settmacher et al. (2004) Type of operation PD (3); DP (7) Artery resected SMA (7), CHA (9) Shimada et al. (2006): Type of operation ExDP (76) Appleby (12) Artery resected CA (12), CHA (12) Sperti et al. (2010) Type of operation: AR+: DP (5) AR_: DP (49) Artery Resected CA (5) Stitzenberg et al. (2004): Type of operation AR+: PD (6), DP (2), TP (2), STP (2) AR-: Not reported			

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
		Artery resected CA (10), CHA (1), LHA (1) Sugiura et al. (2009): Type of operation ExPD (64), ExDP (15), ExTP (28) Artery resected SMA (8), CA (7), HA (10) Tamura et al. (1992) Type of operation AR+: DP (1), TP (6) AR-: PD(5), DP (1), TP (1), STP (1) Artery resected SMA (4), CA (4), HA (2) Wang et al. (2008) Not reported Wu et al. (2010) Type of operation AR+: Modified Appleby (9) AR-: DP (36) Artery resected CA+CHA+LGA (8), CA+LGA (1)			
Data taken from the review only					
Full Citation Pędziwiatr M, Małczak P, Pisarska M et al. (2017) Minimally	N=1382 (Minimally invasive [MI]=423/Open=959)	Inclusion Studies comparing characteristics and perioperative outcomes	Boggi et al. (2016): retrospective single centre study, robotic pancreaticoduodenectomy vs open.	Operation time Blood loss Morbidity	Overall High Risk of bias Studies were not randomised

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
invasive versus open pancreatoduodenectomy—systematic review and meta--analysis. Langenbeck's Archives of Surgery 402(5): 841-851 Country/ies where the study was carried out Boggi et al. (2016) - Italy Buchs et al. (2011) - USA Delitto et al. (2016) - USA Zhou et al. (2011) - China Zureikat et al. (2016) - USA Study type Systematic review and meta-analysis Aim of the study To compare minimally invasive pancreaticoduodenectomy with open approach. Study dates Not reported, article received January 2017 Source of funding None reported	Sample characteristics (e.g. condition/type of tumour) of each study not reported. _____ Boggi et al. (2016): N=119 (MI=83/open=36) _____ Buchs et al. (2011): N=83 (MI=44/open=39) Age: MI=63 (14.5)/open=56 (15.8) Malignancy (n), MI, Open Adenocarcinoma: 31, 21 Neuroendocrine neoplasm: 2, 3 Benign/borderline (n), 11, 12 _____ Delitto et al (2016): N=138 (MI=77/open=61) _____ Zhou et al. (2011): N=14 (MI=8/open=6) Age: MI=65 (range 48-75)/open=57 (range 47-77)	of minimally invasive techniques (laparoscopic or robitic surgery) to open surgery in patients having pancreaticoduodenectomy Objective evaluation of operative time and reports of pancreatic fistula Exclusion Lack of comparative data; describes use of hand-assisted technique in surgery (especially anastomoses) or surgical technique unclear; lack of primary outcome data or insufficient data; studies on techniques other than pancreaticodudodenectomy; not possible to extract data on pancreaticoduodenectomy outcomes. Boggi et al. (2016): Vein resection, robotic=8.4%/open=11.1%; Conversion rate=2%. Neoadjuvant treatment, laparoscopic=5.8%/open=6%.	Buchs et al. (2011): retrospective single centre study, robotic pancreaticoduodenectomy vs open Delitto et al. (2016): prospective single centre study, laparoscopic pancreaticoduodenectomy vs open. Zhou et al. (2011): retrospective single centre study, robotic pancreaticoduodenectomy vs open Zureikat et al. (2016): retrospective multi centre study, robotic pancreaticoduodenectomy vs open	Delayed gastric emptying Pancreatic fistula Retrieved lymph nodes R1 resection rate Hospital stay Readmission rate	4 of the Included studies were retrospective cohort studies, 1 prospective. Not clear if there was blinding of patients, treatment administrators or investigators however as this was a surgical comparison it is unlikely that patients/treatment administrators were blinded. No information was recorded as to whether intent to treat analysis was performed Selection Bias There is a potentially high risk of selection bias across the included studies as these are not randomised comparisons and the type of surgery may be determined based on the patient's suitability. Performance Bias There is a low risk of performance bias across the included studies. Although participants and treatment administrators were not blinded, this would not be possible in

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
	Malignancy (n), MI, Open Adenocarcinoma: 8, 6 Benign/borderline (n), 0, 2 _____ Zureikat et al.(2016): N=1028 (MI=211/open=817) _____ Other studies alrady included in more recent reviews. ____ Information regarding age and surgical pathology from review by Peng et al. (2017)	Zureikat et al. (2016): Conversion rate=4.7%.			surgical comparison. High risk of bias due to operaor and centre differences. Attrition Bias There is a low risk of attrition bias Detection Bias The risk of detection bias is low as outcomes are primarily short-term post-operative outcomes therefore follow-up is likely to be adequate. Investigators were not blinded to patient exposure or to potential confounders however which presents a high risk of bias.
Data taken from the review only					
Full Citation Peng L, Lin S, Li Y et al. (2016) Systematic review and meta-analysis of robotic versus open pancreaticoduodenectomy. Surgical Endoscopy 31(8): 3085-3097 Country/ies where the study was carried out: Hammill et al. (2010) – not reported	N=77 (Minimally invasive robotic[MI]=8/Open=69) Hammill et al. (2010): Age: Robotic=55/open=62.5 Other studies alrady included in more recent reviews.	Inclusion Comparative study of robotic versus open pancreaticoduodenectomy (inc. RCTs and observational clinical studies) Reports at least one outcome of interest Study with best quality/largest sample size if more than one	Hammill et al (2010): prospective cohort study (conference abstract), technique not reported.	Margin negative resection Retrieved lymph nodes Operation time Blood loss Overall complications Wound Infection Delayed Gastric Emptyinh Reoperation Bile Leakage Pancreatic fistula	Overall High Risk of bias Study not randomised but was prospective. Not clear if there was blinding of patients, treatment administrators or investigators however as this was a surgical comparison it is unlikely that patients/treatment

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Study type: Systematic review and meta-analysis Aim of the study: To compare minimally invasive robotic pancreaticoduodenectomy with open approach. Study dates: To January 2016 Source of funding: None reported.		publication reporting on same authors/instituition Exclusion Letters, editorials, expert opinion, review w/o original dta, case reports or non-comparative studies		Pancreatic fistula (Grade B-C) Hospital stay Mortality	administrators were blinded. No information was recorded as to whether intent to treat analysis was performed Selection Bias There is a potentially high risk of selection bias across the included studies as these are not randomised comparisons and the type of surgery may be determined based on the patient's suitability. Performance Bias There is a low risk of performance bias across the included studies. Although participants and treatment administrators were not blinded, this would not be possible in surgical comparison. Attrition Bias There is a low risk of attrition bias Detection Bias The risk of detection bias is low as outcomes are primarily short-term post-operative outcomes therefore follow-up is likely to be

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
					adequate. Investigators were not blinded to patient exposure or to potential confounders however which presents a high risk of bias.
Data taken from the review only					
Full Citation Shin SH, Kim YJ, Song KB et al. (2017) Totally laparoscopic or robot-assisted pancreaticoduodenectomy versus open surgery for periampullary neoplasms: separate systematic reviews and meta-analyses. Surgical Endoscopy 31(9): 3459-3474 Country/ies where the study was carried out: Asburn et al. (2012) - USA Baker et al. (2016) - USA Bao et al. (2014) - USA Chalikonda et al. (2012) - USA Chen et al. (2015) - China Croome et al. (2014) - USA Croome et al. (2015) - USA	N=1622 (Minimally invasive [MI]=610/Open=1012) _____ Asburn et al. (2012): N=268 people with periampullary tumours (MI=53/open=215) Age: MI=62.9 (14.14)/open=67.3 (11.53) Malignant: MI=33/open=131 _____ Baker et al. (2016): N=71 people with periampullary tumours (MI=22/open=49); Age: MI=63 (range 38-82)/open=63 (26-86). Malignant (n): MI, open Adenocarcinoma: 16, 35	Inclusion Study uses either totally laparoscopic pancreaticoduodenectomy or any type of robotic surgery (e.g. pure, hybrid, robot-assisted) and compares to open pancreaticoduodenectomy Single centre study Reports at least one outcome of interest Exclusion Data on robotic techniques excluded from totally laparoscopic analysis; No comparison between types of surgery; <10 participants in each arm.	Asburn et al. (2012): retrospective single centre 2005-2011 totally laparoscopic pancreaticoduodenectomy vs open pancreaticoduodenectomy Baker et al. (2016): retrospective single centre 2012-2013 robotic-assisted pancreaticoduodenectomy vs open pancreaticoduodenectomy Bao et al. (2014): retrospective single centre 2009-2011 robotic-assisted pancreaticoduodenectomy vs open pancreaticoduodenectomy Chalikonda et al. (2012): retrospective single centre 2009-2010 robotic-assisted pancreaticoduodenectomy vs open	Operation time Blood loss Overall morbidity Delayed gastric emptying Pancratic fistula (Grade A-C; Grade B-C) Retrieved lymph nodes Margin-free resection Hospital stay	Overall High Risk of bias Studies were not randomised All were retrospective studies except for Chen et al. (2015). Not clear if there was blinding of patients, treatment administrators or investigators however as this was a surgical comparison it is unlikely that patients/treatment administrators were blinded. No information was recorded as to whether intent to treat analysis was performed Selection Bias There is a potentially high risk of selection bias across the included studies as these are not randomised comparisons and the type of surgery may be

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Dokmak et al. (2015) - France Lai et al. (2012) - China Mesleh et al. (2013) - USA Song et al. (2015) – South Korea Tan et al. (2015) - China Zureikat et al. (2011) - USA Study type Systematic review and meta-analysis Aim of the study To compare perioperative and oncologic outcomes of minimally invasive (totally laparoscopic or robot-assisted) pancreaticoduodenectomy with open pancreaticoduodenectomy. Study dates: To November 2015 Source of funding: None reported.	Neuroendocrine: neoplasm: 1, 1 IPMN: 1, 2 Other: 0, 2 Benign/borderline (n): 4, 9 _____ Bao et al. (2014): N=56 people with periampullary tumours (MI=28/open=28) Age: MI=61 (11.2)/open=66.7 (12.5). Malignant (n): MI, open Adenocarcinoma: 17, 20 Neuroendocrine: neoplasm: 2, 3 IPMN: 0,2 Benign/borderline (n): 9, 3 _____ Chalikonda et al. (2012): N=60 people with periampullary tumours (MI=30/open=30) Age: MI=62.6 (range 51-78)/open=61.1 (range 49-80). Malignant (n): MI, open		pancreaticoduodenectomy Chen et al. (2015): prospective single centre 2010-2013 robotic-assisted pancreaticoduodenectomy vs open pancreaticoduodenectomy Croome et al. (2014): retrospective single centre 2008-2013 totally laparoscopic pancreaticoduodenectomy vs open pancreaticoduodenectomy Croome et al. (2015): retrospective single centre 2007-2013 totally laparoscopic pancreaticoduodenectomy vs open pancreaticoduodenectomy Dokmak et al. (2015): retrospective single centre 2011-2014 totally laparoscopic pancreaticoduodenectomy vs open pancreaticoduodenectomy Lai et al. (2012): retrospective single centre 2000-2012		determined based on the patient's suitability. Performance Bias There is a low risk of performance bias across the included studies. Although participants and treatment administrators were not blinded, this would not be possible in surgical comparison. High risk of bias due to operator and centre differences. Attrition Bias There is a low risk of attrition bias Detection Bias The risk of detection bias is low as outcomes are primarily short-term post-operative outcomes therefore follow-up is likely to be adequate. Investigators were not blinded to patient exposure or to potential confounders however which presents a high risk of bias.

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
	Adenocarcinoma: 14, 14 Neuroendocrine: neoplasm: 4, 4 Benign/borderline (n): 12, 12 _____ Chen et al. (2015): N=180 people with periampullary tumours (MI=60/open=120) Age: MI=53.6 (13.5)/open=53.8 (14.3). Malignant (n): MI, open Adenocarcinoma: 38, 76 Benign/borderline (n): 22, 44 _____ Croome et al. (2014): N=322 people with PDAC (MI=108/open=214) _____ Croome et al. (2015): N=89 people with periampullary tumours (MI=31/open=58) _____ Dokmak et al. (2015): N=92 people with periampullary		robotic-assisted pancreaticoduodenectomy vs open pancreaticoduodenectomy Mesleh et al. (2013): retrospective single centre totally laparoscopic pancreaticoduodenectomy vs open pancreaticoduodenectomy Song et al. (2015): retrospective single centre 2007-2012totally laparoscopic pancreaticoduodenectomy vs open pancreaticoduodenectomy Tan et al. (2015): retrospective single centre 2009-2014totally laparoscopic pancreaticoduodenectomy vs open pancreaticoduodenectomy Zureikat et al. (2011): retrospective single centre totally laparoscopic pancreaticoduodenectomy vs open		

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
	tumours (MI=46/open=46 [matched]) _____ Lai et al. (2012): N=87 people with periampullary tumours (MI=20/open=67) Age: MI=66.4 (11.9)/open=62.1 (11.2). Malignant (n): MI, open Adenocarcinoma: 13, 48 Neuroendocrine: neoplasm: 0, 1 IPMN: 1, 2 Other: 1, 2 Benign/borderline (n): 5, 14 _____ Mesleh et al. (2013): N=123 people with periampullary tumours (MI=75/open=48) Malignant: MI=59/open=37 _____ Song et al. (2015): N=186 people with periampullary tumours		pancreaticoduodenectomy		

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
	(MI=93/open=93 [matched]) _____ Tan et al. (2015): N=60 people with periampullary tumours (MI=30/open=30) _____ Zureikat et al. (2011): N=28 people with periampullary tumours (MI=14/open=14) Age: MI=69.8 (10.2)/open=67.4 (11) Malignant: MI=11/open=10 _____ Information regarding age and surgical pathology from reviews by Doula et al. (2016) and Peng et al. (2017)				
Sui et al. (2012) Laparoscopic versus open distal pancreatectomy: A meta-analysis Asian Journal of Surgery 35; 1-8 Country/ies where the study was carried out: Shimura (2010) Japan	N=178 (LDP=58/ODP=120) Shimura (2010) N=13 (LDP=5/ODP=8) Kooby (2010) N=93 (LDP=23/ODP=70) Zhao (2010)	Inclusion Compare laparoscopic and open approaches among patients who underwent distal pancreatectomy for benign or malignant disease	Shimura (2010) Retrospective Matching: None reported Kooby (2010) Retrospective Matching: age, gender, pancreatic pathology,	Operative Outcomes including: Operative time Operative blood loss Number of patients requiring blood transfusion Oncologic clearance (resection margins)	Overall Unclear Risk of bias Studies were not randomised and two studies All were retrospective studies. Not clear if there was blinding of patients, treatment administrators

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Kooby (2010) USA Zhao (2010) China Study type: Systematic review and meta-analysis Aim of the study: To compare laparoscopic distal pancreatectomy versus open distal pancreatectomy Study dates: Studies published through 2010 Source of funding: None reported.	N=72 (LDP=30/ODP=42)	Report on at least one clinical outcome measure Clearly report the indications for surgery No details of the inclusion/exclusion criteria of the individual studies provided	ASA status, tumour size Zhao (2010) Retrospective Matching: age, gender, BMI, pancreatic pathology	Postoperative outcomes including: Time to oral intake Time to first flatus Hospital stay Morbidity Mortality	or investigators however as this was a surgical comparison it is unlikely that patients/treatment administrators were blinded. No information was recorded as to whether intent to treat analysis was performed Selection Bias There is a potentially high risk of selection bias across the included studies as these are not randomised comparisons and the type of surgery may be determined based on the patient's suitability. Performance Bias There is a low risk of performance bias across the included studies. Although participants and treatment administrators were not blinded, this would not be possible in surgical comparison. Attrition Bias There is a low risk of attrition bias Detection Bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
					The risk of detection bias is low as outcomes are primarily short-term post-operative outcomes therefore follow-up is likely to be adequate. Investigators were not blinded to patient exposure or to potential confounders however which presents a high risk of bias.
Data taken from the review only					
Venkat et al. (2012) Laparoscopic distal pancreatectomy is associated with significantly less overall morbid compared to the open technique Country/ies where the study was carried out: Velanovich (2006) USA Misawa (2007) Tang (2007) Hong Kong Teh (2007) USA Brunzoni (2008) USA Eom (2008) Korea Kim (2008) Korea Kooby (2008) USA Matsumoto (2008) Japan Nakamuara (2009) Baker (2009) USA	N=18 studies (no RCTs) with a total of 1814 participants (N=77s LDP/1041 ODP) Velanovich (2006) N= 30 (LDP=15/ODP=15 Misawa (2007) N=17 (LDP=8/ODP=9) Tang (2007) N=14 (LDP=9/ODP=5) Teh (2007) N=28 (LDP=12/ODP=16) Brunzoni (2008) N=11 (LDP=7/ODP=4) Eom (2008)	Inclusion Comparison of characteristics and perioperative outcomes of laparoscopic (with or without hand-assisted technique) to open approaches in patients undergoing distal pancreatectomy Objective evaluation of at least one outcome of interest Exclusion Studies focusing on laparoscopic enucleation, debridement or necrosectomy and pancreatectomy for trauma	Velanovich (2006) Retrospective Matching: Age, gender, pathological diagnosis Misawa (2007) Retrospective Matching: Location of lesion, pathological diagnosis Tang (2007) Retrospective evaluation of prospective data Matching: Pathological diagnosis Teh (2007) Retrospective Matching: None Brunzoni (2008) Retrospective	Perioperative outcomes including: Operative time Intraoperative blood loss and transfusion rate Postoperative recovery (time to ambulation, time to oral feeds, time to flatus and length of hospital stay Oncologic safety (lymph node harvest and margin status) Postoperative complications (overall complications, major complications, surgical site infections, reoperation rate, pancreatic fistula and mortality)	Overall Unclear Risk of bias Studies were not All were retrospective studies (N=8 retrospective analysis of prospectively collected data) Not clear if there was blinding of patients, treatment administrators or investigators however as this was a surgical comparison it is unlikely that patients/treatment administrators were blinded. No information was recorded as to whether intent to treat analysis was performed

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Finan (2009) USA Aly (2010) Japan Casadei (2010) Italy DiNorcia (2010) Jayaraman (2010 USA) Vijan (2010) USA Waters (2010) Study type: Systematic review and meta-analysis Aim of the study: To compare laparoscopic distal pancreatectomy versus open distal pancreatectomy Study dates: Last search conducted January 11, 2011 Source of funding: None reported.	N=93 (LDP=31/ODP=62) Kim (2008) N=128 (LDP=93/ODP=35) Kooby (2008) N=342 (LDP=142/ODP=200) Matsumoto (2008) N=33 (LDP=14/ODP=19) Nakamuara (2009) N=36 (LDP=20/ODP=16) Baker (2009) N=112 (LDP=27/ODP=85) Finan (2009) N=148 (LDP=44/ODP=104) Aly (2010) N=75 (LDP=40/ODP=35) Casadei (2010) N=44 (LDP=22/ODP=22) DiNorcia (2010) N=263 (LDP=71/ODP=192) Jayaraman (2010) N=200 (LDP=100/ODP=100) Vijan (2010)	Studies involving exclusively robotic procedures Studies not published in English Velanovich (2006) Exclusion None specified Misawa (2007) Exclusion Malignant lesions Tang (2007) Exclusion Malignant lesions Teh (2007) Exclusion Malignant lesions Brunzoni (2008) Exclusion Splenic vessels not preserved Eom (2008) Exclusion Tumours with high grade malignant potential Kim (2008) Malignant lesions Kooby (2008) None specified Matsumoto (2008) Malignant Lesions Nakamuara (2009)	Matching: None Eom (2008) Retrospective Matching: Age, gender, pathological diagnosis Kim (2008) Retrospective Matching: pathological diagnosis Kooby (2008) Retrospective evaluation of prospective data Matching: size of tumour, pathological diagnosis, ASA score, resected pancreas length, tumour type (solid/cystic/pancreatitis) Matsumoto (2008) Nakamuara (2009) Retrospective Matching: None Baker (2009) Retrospective evaluation of prospective data Matching: None Finan (2009) Retrospective with some Retrospective evaluation of		Selection Bias There is a potentially high risk of selection bias across the included studies as these are not randomised comparisons and the type of surgery may be determined based on the patient's suitability. Performance Bias There is a low risk of performance bias across the included studies. Although participants and treatment administrators were not blinded, this would not be possible in surgical comparison. Attrition Bias There is a low risk of attrition bias Detection Bias The risk of detection bias is low as outcomes are primarily short-term post-operative outcomes therefore follow-up is likely to be adequate. Investigators were not blinded to patient exposure or to potential confounders however which presents a high risk of bias.

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
	N=200 (LDP=100/ODP=100) Waters (2010) N=40 (LDP=18/ODP=22)	Invasive ductal carcinoma Baker (2009) Exclusion None specified Finan (2009) Exclusion None Specified Aly (2010) Exclusion Malignant lesions, previous major surgery Casadei (2010) Exclusion Invasive ductal cancer DiNorcia (2010) Exclusion None specified Jayaraman (2010) Exclusion None specified Vijan (2010) Exclusion None specified Waters (2010) Exclusion Concurrent major surgery	prospective data post 2005 Matching: None Aly (2010) Retrospective Matching: age, BMI, size of tumour, location of lesion, pathological diagnosis Casadei (2010) Retrospective evaluation of prospective data Matching: age, gender, pathological diagnosis, ASA score DiNorcia (2010) Retrospective evaluation of prospective data Matching: None Jayaraman (2010) Retrospective evaluation of prospective data Matching: age, size of tumour, pathological diagnosis Vijan (2010) Retrospective Matching: age, pathological diagnosis, resected pancreas length Waters (2010)		

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
			Retrospective evaluation of prospective data Matching: None		
Data taken from the review only					
Full Citation Yu et al. (2014) Benefit from synchronous portal-superior mesenteric vein resection during pancreaticoduodenectomy for cancer: a meta-analysis EJSO 40;371-378 Country/ies where studies carried out: Banz et al. (2012): UK Kunxing et al. (2010): China Kaneoka et al. (2009): Japan Illuminati et al. (2008): Italy Takahasi et al. (1994): Japan Study Type: Systematic Review and meta-analysis Aim: To provide up-to-date and an evidence based evaluation of the peri-operative outcomes and long-term benefit of	Banz et al. (2012): With VR:51 Without VR:275 Kunxing et al. (2010): With VR:12 Without VR:40 Kaneoka et al. (2009): With VR:42 Without VR:42 Illuminati et al. (2008): With VR:29 Without VR:108 Takahasi et al. (1994): With VR:63 Without VR:58	Pancreatic resection with vein resection Pancreatic resection Only	Venous reconstruction technique not reported	Resection Margin Histopathology Operation time Blood loss Lymph node metastasesDelayed gastric emptying Intra abdominal abscess Biliary complications Pancreatic fistula Post-operative mortality Overall Survival (1, 3 and 5 years)	Overall – high risk Studies are all retrospective comparisons and are not randomised. No blinding of patients, treatment administrators or investigators Selection Bias There is a high risk of selection bias as the studies are not randomised and it is likely that patients selected for surgery are selected based on the suitability and likelihood of a positive outcome. Performance Bias There is a low risk of performance bias across the included studies. Although participants and treatment administrators were not blinded, this would not be possible in surgical comparison. Attrition Bias There is a low risk of attrition bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
patients undergoing venous resection in pancreaticoduodenectomy compared with patients without venour resection. Study Dates: January 1990 to July 2013 Source of Funding: None reported					Detection Bias There is an unclear risk of bias. Follow-up time for each study are not reported it is therefore not clear whether follow-up was sufficient to allow reporting of long term outcomes such as overall survival.
Original Publications were checked to ascertain the risk of bias and also for inclusion/exclusion criteria, interventions and methods.					
Full citation Zhang et al. (2013) Robotic versus Open Pancreatectomy: A Systematic Review and Meta-analysis Annals of Surgical Oncology 20:1774-1780 Country/ies where the study was carried out: Kang: Korea Waters: USA Walsh: USA Study type: Systematic review and meta-analysis Aim of the study: To compare the clinical and oncological safety and efficacy of robotic versus open pancreatectomy Study dates:	Sample Size N=104 surgeries (robotic=47/open=57) Kang et al 2011: N=15 (robot=5/open=10) Inclusion Patients undergoing robotic surgery for a borderline malignant tumour of the pancreas located in the neck and proximal body of the pancreas Patients who underwent open central pancreatectomy for benign and borderline malignant tumours of the pancreas Exclusion	Kang: Total robotic (60%)/Hybrid robotic (40%) vs open Waters: Total robotic vs open Walsh: Hybrid robotic vs open	Kang: Retrospective analysis of surgical data collected between December 2007 and December 2009 (robotic) and January 1990 – November 2007 (open) Waters: Retrospective analysis of surgical data collected between 2008-2009 Intent to treat analysis Walsh: conference abstract, no info	Review Outcomes Overall Complication Rate Postoperative Pancreatic Fistula Postoperative Mortality Reoperation Rate Positive Margin Hospital Stay Conversion Rates Operation Time Estimated Blood Loss	Overall Unclear Risk of bias Studies were not randomised No blinding of patients, treatment administrators or investigators Selection Bias There is a potentially high risk of selection bias across the included studies as these are not randomised comparisons and the type of surgery may be determined based on the patient's suitability. Kang: High Risk Waters: High Risk Walsh: High Risk Performance Bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Searches complete up to April 2012 Source of funding: None reported.	None reported Walsh et al. 2011: N=50 (Robotic=25/Open=25) (conference abstract) Waters et al. 2010: N=40 (Robotic=17/open=22) Inclusion All resections of the distal pancreas by any surgeon and any high volume centre. Exclusion Emergent or urgent surgery Concurrent major surgery Indication of pancreatitis (chronic or acute)				There is a low risk of performance bias across the included studies. Although participants and treatment administrators were not blinded, this would not be possible in surgical comparison. Kang: Low Risk Waters: Low Risk Walsh: Unclear Risk Attrition Bias There is a low risk of attrition bias Kang: Low Risk Waters: Low Risk Walsh: Unclear Risk Detection Bias The risk of detection bias is low as outcomes are primarily short-term post-operative outcomes therefore follow-up is likely to be adequate. Investigators were not blinded to patient exposure or to potential confounders however which presents a high risk of bias. Kang: Low Risk Waters: Low Risk Walsh: Unclear Risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Extra Studies from additional reviews					
Full Citation Zhou et al. (2012) Pancreatectomy combined with superior mesenteric vein-portal vein resection: A meta-analysis Worl J Surgery 36:884-891 Country/ies where studies carried out: Allema et al. (1994): Netherlands Howard et al (2003): USA Study Type: Systematic review and meta-analysis Aim: To provide an evidence-based evaluation regarding the perioperative outcomes and long-term survival of patients undergoing VR in pancreatectomy for pancreatic cancer compared with outcomes and survival of patients without VR. Study Dates: Anytime up to July 2011 Source of Funding: None reported.	Allema et al. With VR=20 Without VR=156 Howard et al. With VR=13 Without VR=23	Pancreatic resection with vein resection Pancreatic resection Only	Venous reconstruction technique not reported	Perioperative outcomes including: Operative time Operative blood loss Number of patients requiring blood transfusion Morbidity Mortality Overall survival (1,3 and 5 year)	Overall – high risk Studies are all retrospective comparisons and are not randomised. No blinding of patients, treatment administrators or investigators Selection Bias There is a high risk of selection bias as the studies are not randomised and it is likely that patients selected for surgery are selected based on the suitability and likelihood of a positive outcome. Performance Bias There is a low risk of performance bias across the included studies. Although participants and treatment administrators were not blinded, this would not be possible in surgical comparison. Attrition Bias There is a low risk of attrition bias Detection Bias There is an unclear risk of bias. Follow-up time for each study are not

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
					reported it is therefore not clear whether follow-up was sufficient to allow reporting of long term outcomes such as overall survival.

1

2

F.143 Adjuvant treatment

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Full Citation Büchler, M., Friess, H., Schultheiss, K. H., Gebhardt, C., Kübel, R., Muhrer, K. H., Müller, G. et al. (1991). A randomized controlled trial of adjuvant immunotherapy (murine monoclonal antibody 494/32) in resectable pancreatic cancer. Cancer, 68(7), 1507-1512. Country/ies where the study was carried out: Germany Study type: RCT Aim of the study:	N= 61 Arm 1=29 Arm 2=32 Inclusion Resectability (Whipple procedure), no distant metastasis (MO according to the UICC] 1987) Histologic Grade 1 or 2 (according to UICC 1987) Karnofsky performance status > 70% Informed consent Exclusion Myelosuppression (leukocyte	Arm 1: Immunotherapy (MoAb 494/32) Arm 2: No adjuvant therapy	Randomisation No details provided Treatment The IgGl murine MoAb BW 494/32 (BI 51.01 1) was derived from BALB/c mice immunized with the DE-TA carcinoma cell line. Arm 1: intravenous infusion once a day over 10 days, starting with a dose of 100 mg Monoclonal antibody (MoAb) 494/32 and continuing with 9 X 30 mg up to a final dose of 370 mg. MoAb was diluted in 50 ml of normal saline (pH 7.4) and administered over 30 minutes to 1 hour. Adverse events	Overall survival Adverse events Immunotherapy vs No adjuvant therapy Survival Median OS by arm (days): 428 (range 248-510) vs 386 days (range 296-509), ns Mortality: 19/29 vs 17/32 Recurrent tumour and/or metastatic spread: 6/10 vs 8/15 Adverse events One patient in immunotherapy group had a Grade 3 toxicity (abdominal pain).	Overall high risk of bias. Random sequence generation: Unclear risk (Insufficient information) Allocation concealment: Unclear risk (Insufficient information) Blinding of participants and personnel assessments: Low risk (Not blinded but unlikely that outcome would be influenced by blinding)

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
To assess whether passive immunotherapy using MoAB 494/32 is effective in patients with resectable pancreatic cancer Study dates: June 1987 to November 1989 Source of funding: None reported	count ≤ 3 X 103/µl Platelet count ≤ 100 X 103/µl) Coagulation disorders (partial thromboplastin time> 50 seconds/Quick's time I 70%) Any other prior anti-cancer (cytotoxic) treatment		Patients monitored by specially trained personnel for potential toxic or allergic reactions according to WHO criteria.		Blinding of outcome assessment: Low risk (Not reported but unlikely that outcome measurement would Incomplete outcome data: Low risk (Reasons for missing outcome data unlikely to be related to true outcome) Selective reporting: High risk (Primary outcome not fully reported) Other sources of bias: High risk (Kaplan-Meier curves for overall survival cross, proportional hazards not satisfied)
Full Citation Kosuge, T., Kiuchi, T., Mukai, K., Kakizoe, T., & Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer (JSAP). (2006). A multicenter randomized controlled trial to	N= 89 resected PC patients from 11 Japanese institutions Arm 1=45 (ITT) Arm2=44 (ITT) Inclusion	Arm 1: Chemotherapy (Cisplatin + 5-FU) Arm 2: No adjuvant therapy	Randomisation Patients registered with randomisation centre by fax within 10 weeks of surgery and randomly assigned to CT group or no adjuvant therapy group. Patients stratified according to institution and tumour stage	Overall survival Recurrence-free survival Adverse events Chemotherapy vs No adjuvant therapy Overall survival Median OS by arm: 12.5 vs 15.8 months Estimated OS at 5 years by arm: 26.4 vs 14.9% (p=0.94)	Overall high risk of bias. • Random sequence generation: Low risk (Randomisation 1:1 using

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
evaluate the effect of adjuvant cisplatin and 5-fluorouracil therapy after curative resection in cases of pancreatic cancer. Japanese journal of clinical oncology, 36(3), 159-165. Country/ies where the study was carried out: Japan Study type: Open-label RCT Aim of the study: To evaluate the efficacy of adjuvant chemotherapy with cisplatin and 5-FU after margin-negative resection in patients with pancreatic cancer. Study dates: April 1992 to March 2000 Source of funding: Grant-in-aid for cancer research from the Ministry of Health and Welfare (currently the Ministry of Health, Labor and Welfare) of Japan.	Patients with ductal PC Written informed consent Exclusion Other pancreatic and periampullary neoplasms, such as intraductal papillary mucinous neoplasm, cystadenocarcinoma and endocrine tumour Presence of distant metastases, even if resected, or of peritoneal seeding		using minimization technique. (Tumour stage determined according to UICC TNM classification [4th or 5th edition]). Resection procedures and the range of dissection were determined according to institutional policy. Treatment Arm 1: CT started within 1 week of randomisation. Cisplatin 80 mg/m2 on first day of treatment and 5-FU 500 mg/m2 per day as a continuous infusion for first 5 days, repeated 4–8 weeks after the start. All patients in trial followed up at 3 month intervals. Second course withheld if toxicity of grade 3 or above severity was observed or if the patient's condition did not improve sufficiently to fit the eligibility criteria for registration within 8 weeks of the start of the initial course. Adverse events Assessed according to WHO classification criteria. Statistical analysis ITT efficacy analysis Safety analysis based on all eligible patients who had started CT	Observed events of death: 35/45 vs 36/44 Recurrence-free survival Median RFS by arm: 8.6 vs 10.2 months Estimated Recurrence rate at 5 years by arm: 73.6 vs 80.8% (p=0.8) Observed events of recurrence: 32/44 vs 34/44 Adverse events (n=38) in CT group One patient died from sepsis due to severe post-operative complication not documented at trial registration after one course of CT. Among 38 eligible patients who received CT, minor toxicity commonly observed, especially nausea and vomiting, with Grade 3+ severity observed in small number of patients. All toxicities were reversible and resolved with conservative treatment. # patients with Grade 3 or 4 toxicities Toxicity / Grade 3 / Grade 4 Nausea/vomiting / 5 / 0 Leukopenia / 2 / 0 Granulocytopenia / 3 / 1 Mucositis / 2 / 0 Hepatic / 3 / 0	minimisation technique) •Allocation concealment: Unclear risk (Not reported) •Blinding of participants and personnel assessments: Low risk (No blinding but unlikely that outcome would be influenced by blinding) •Blinding of outcome assessment: Low risk (Not clear whether blinded but unlikely that outcome measurement would be influenced by blinding) •Incomplete outcome data: Low Risk (Missing outcome data unlikely to be related to true outcome) •Selective reporting: Unclear

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
					risk (Insufficient information) •Other sources of bias: High Risk (Kaplan-Meier curves for overall survival and recurrence-free survival cross, proportional hazards not satisfied).
Full Citation Lygidakis, N. J., Sgourakis, G., Georgia, D., Vlachos, L., & Raptis, S. (2002). Regional targeting chemoimmunotherapy in patients undergoing pancreatic resection in an advanced stage of their disease: a prospective randomized study. Annals of surgery, 236(6), 806-813. Country/ies where the study was carried out: Greece Study type: RCT Aim of the study: To evaluate in a prospective randomized study the long-term	N=85 resected PC patients from 1 centre Arm 1=45 Arm 2=40 (Arm 3=43) Inclusion Stage 3 pancreatic duct carcinoma based on diagnostic screening and mainly on histologic confirmation of resected specimens Written informed consent Exclusion Stage 1 or 2 disease	Arm 1: Chemotherapy (Gemcitabine, Carboplatin + mitoxantrone + mitomycin C + fluororacil + folinic acid) Arm 2: No adjuvant therapy Arm 3: Chemoimmunotherapy	Randomisation All patients randomized after resection to optimize intraoperative staging and to include patients with similar mechanical and anatomic peculiarities. Special emphasis given to items such as histologic evaluation via frozen biopsies of resected specimen, presence of lymph node involvement, and presence of residual pathology in the pancreatic remnant. At the end of intervention and after pathology report, anaesthesiologist assigned each patient to groups according to chosen sealed envelope. Treatment Before closing abdomen, patients in arm 1 had arterial	Overall survival Disease-free survival Adverse events Chemotherapy vs No adjuvant therapy Survival Mean OS by arm: 25.02 (15.777) vs 18.83 (11.745), log rank p=0.05 OS at 1 years by arm: 72% vs 65% OS at 2 years by arm: 53% vs 29% OS at 3 years by arm: 31% vs 15% OS at 4 years by arm: 16% vs 0% Observed deaths=22/45 vs 15/40 Disease-free survival Mean DFS by arm: 21.54 (15.713) vs 15.22 (9.619), log rank p=0.05 DFS rate at 1 years by arm: 62% vs 50% DFS rate at 2 years by arm: 35% vs 20% DFS rate at 3 years by arm: 22% vs 10% DFS rate at 4 years by arm: 0% vs 0%	Overall high risk of bias. Random sequence generation: Unclear risk (Insufficient information about sequence generation method) Allocation concealment: Unclear risk (Insufficient information) Blinding of participants and personnel assessments: Low risk (Not blinded but unlikely that outcome would be influenced by blinding)

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
results of adjuvant locoregional chemoimmunotherapy in a number of patients with stage III pancreatic duct cancer who underwent pancreatic resection Study dates: November 1993 to October 2000 Source of funding: None reported	Underwent total pancreatectomy Arterial vascular involvement (hepatic artery, superior mesenteric artery) Underwent regional vascular resection reconstruction (of either the portal or superior mesenteric vein) Found during either screening or at initial exploration to have liver secondaries, peritoneal dissemination, ascites, or lung or bone metastases.		catheter introduced via a side arterial branch through the jejunal artery under fluoroscopic control into the superior mesenteric artery (SMA) to receive adjuvant treatment. If this was not technically feasible, catheter was inserted into the SMA postoperatively in department of radiology through the left subclavian artery under ultrasound guidance. To maintain patency of the catheters, infusion of 10 mL normal saline 0.9% with 1 mL heparin was given every 2 weeks during the time patients were not undergoing treatment. Arm 1: 5 days after surgery, patients had 5-day course of CT consisting of: Day 1: Gemcitabine 1.5 mg/ m2 diluted in 250 mL normal saline 0.9%, given as a 6-hour infusion through the superior mesenteric catheter Day 2: Carboplatin 300 mg/ m2 and mitoxantrone HCl 14 mg/ m2 diluted in 250 mL normal saline 0.9%, given as a 6-hour infusion via the superior mesenteric arterial catheter	Observed recurrence: 19/45 vs 15/40 Adverse events Only 1 patient in CT group had Grade 3 toxicity (nausea) Chemotherapy vs chemoimmunotherapy Survival Mean OS by arm: 25.05 (15.777) vs 31.07 (17.315), log rank p=0.02 OS at 1 years by arm: 72% vs 92% OS at 2 years by arm: 53% vs 65% OS at 3 years by arm: 31% vs 49% OS at 4 years by arm: 16% vs 28% OS at 5 years by arm: 0% vs 18% Observed deaths=22/45 vs 20/43 Disease-free survival Mean DFS by arm: 21.54 (15.713) vs 26.69 (14.458), log rank p=0.03 DFS rate at 1 years by arm: 62% vs 81% DFS rate at 2 years by arm: 35% vs 58% DFS rate at 3 years by arm: 22% vs 39% Observed recurrence: 19/45 vs 21/43 Adverse events # patients with Grade 3 toxicities CT (n=45) CIT (n=43) Vomiting 0 2 Nausea 1 0 Chemoimmunotherapy vs No adjuvant therapy	Blinding of outcome assessment: Low risk (Not reported but unlikely that outcome measurement would be influenced by blinding) Incomplete outcome data: Low Risk (Missing outcome data unlikely to be related to true outcome) Selective reporting: High risk (Fails to report survival results in expected manner) Other sources of bias: High risk (Sample size calculation not reported; Kaplan-Meier curves for overall survival cross, proportional hazards not satisfied)

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
			Day 3: Mitomycin C 10 mg/ m2, fluorouracil 750 mg/ m2, and folinic acid 200 mg/m2 diluted in 250 mL normal saline 0.9%, given as a 6-hour infusion via the superior mesenteric arterial catheter Days 4 and 5: Fluorouracil 750 mg/m2 and folinic acid 200 mg/ m2 diluted in 250 mL normal saline 0.9%, given as a 6-hour infusion via the superior mesenteric arterial catheter Adverse Events Assessment method not reported	Survival Mean OS by arm: 31.07 (17.315) vs 18.83 (11.745), log rank p=0.02 OS at 1 years by arm: 92% vs 65% OS at 2 years by arm: 65% vs 29% OS at 3 years by arm: 49% vs 15% OS at 4 years by arm: 28% vs 0% OS at 5 years by arm: 18% vs 0% Observed deaths=20/43 vs 15/40 Disease-free survival Mean DFS by arm: 26.69 (14.458) vs 14.22 (9.619), log rank p=0.001 DFS rate at 1 years by arm: 81% vs 50% DFS rate at 2 years by arm: 58% vs 20% DFS rate at 3 years by arm: 39% vs 10% DFS rate at 4 years by arm: 25% vs 0% DFS rate at 5 years by arm: 0% vs 0% Observed recurrence: 21/43 vs 15/40 Adverse events Only 2 patients in CIT group had Grade 3 toxicity (vomiting).	
Full Citation Neoptolemos, J. P. (2001). ESPAC-1: A European randomized controlled study of adjuvant chemoradiation and chemotherapy in resectable pancreatic	N=188 resected PC patients from 61 centres in 11 countries Arm 1=95 (25/97 received background CRT)	Arm 1: Chemotherapy (Folinic acid + 5-Fluororacil) Arm 2: No adjuvant therapy	ESPAC—1+ Data from CT only vs Obs only pragmatic RCT trial only (recorded whether patient has background chemoradiotherapy or not) Randomisation ESPAC-1 trial expanded to allow participating	Overall survival Quality of life Chemotherapy vs No adjuvant therapy Overall survival Individual patient data: 44/92 vs 63/96, O-E=-20.2, Var=24.4 [from Neoptolemos 2009]	Overall high risk of bias. Random sequence generation: Unclear risk (1:1 but insufficient information about sequence

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
cancer. Lancet, 358, 1576-1585. Country/ies where the study was carried out: 11 European countries (inc. UK, Switzerland, Germany, France, and Italy) Study type: Multicentre RCT Aim of the study: To assess whether adjuvant chemotherapy alone has a role in improving survival of patients with resectable pancreatic cancer. Study dates: February 1994 to April 2000 Source of funding: Principally funded by the Cancer Research Campaign, UK; the Fonds de Recherche de la Société National Française de Gastroentérologie; the Consorzio Studi Universitari di Verona, Cariverona, and the Ministero Università e Ricerca Scientifica e Tecnologica (Cofin 9906195987), Rome,	Arm 2=97 (19/95 received background CRT) Inclusion Histologically proven, macroscopically resected ductal adenocarcinoma of the pancreas with no evidence of local spread or distant metastases. Fully recovered from surgery Life expectancy > 3 mo Fit enough for treatment Given informed consent Exclusion Pancreatic cystadenocarcinoma Endocrine tumours of the pancreas Tumours of the duodenum		institutions to choose randomisation to 2x2 trial, CT only vs Obs, or CRT only vs Obs. Randomisation was by phone call or fax to one of four randomisation centres (UK, Switzerland, Germany, and France), where eligibility was checked before treatment was allocated. Randomisation was stratified by randomisation centre and resection-margin status (positive or negative). Treatment Median time from resection to randomisation (days)=21 (IQR 13-36). Median follow up of 40 alive patients (months)=64 (IQR 20-89). Arm 1: Intravenous bolus folinic acid 20 mg/m2 followed by intravenous bolus fluororacil 425 mg/m2 for 5 consecutive days every 28 days for 6 cycles. Adverse events UICC Common Toxicity Criteria with clearly defined protocol for modifications and delays. Quality of life	Median OS: 17.4 (95%CI, 15.8-21.7), HR=1.03 (95%CI, 0.81, 1.32), log rank p=0.33 Median OS by arm: 24 (95%CI, 18.8-36.3) vs 12.8 (95%CI, 10.2-16.9), HR=0.58 (95%CI, 0.42-0.8) Observed deaths=72/97 vs 80/95 Estimated OS at 1, 2 and 5 years: 66%, 38%, 19%. Quality of life Chemotherapy vs no chemotherapy ESPAC-1 QoL Mean change from baseline (after surgery) to 3 months: 12.6 (95% CI 5.7-19.5) vs 11.6 (4.1-19.1), p=0.96 # patients with improving scores on ESPAC-1 QoL Role Functioning subscale: p=0.003 (favours no adjuvant therapy group) Note that Chemotherapy group (n=238) includes 74 CT only and 72 CT+CRT patients from ESPAC-1 trial, and 92 CT only from ESPAC-1+ trial; No chemotherapy group (n= 235) includes 69 no adjuvant therapy and 70 CRT only patients from ESPAC-1 trial, and 96 No CT patients from ESPAC-1+ trial. This outcome is downgraded for indirectness in GRADE.	generation method) Allocation concealment: Low risk (Central allocation) Blinding of participants and personnel assessments: Low risk for survival data (Not blinded but unlikely that outcome would be influenced by blinding)/High risk for QoL data (Not blinded and outcome likely to be influenced by this) Blinding of outcome assessment: Low risk (Not reported but unlikely that outcome measurement would be influenced by blinding) Incomplete outcome data: Low risk (Missing outcome data unlikely to be

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Italy; Associazione Italiana Ricerca Cancro (AIRC) Milan, Italy; and European Community grant BIOMED 2 CE-Contract number BMH4-CT98-3805.			Mean observed QoL assessed with standardized AUC methods within 12 months after resection using ESPAC-1 QoL form (modified EORTC QLQ-C30 v1 with ESPAC-1 disease-specific questions) Statistical analysis All analyses were carried out according to the intention-to-treat principle, and all reported P values are two-sided. ITT Kaplan-Meier survival analysis; for patients lost to follow-up, data were censored on the date the patient was last seen alive. Stratified log-rank analyses and Cox proportional-hazards modelling used to investigate and adjust for major prognostic and stratification factors. QoL group differences assessed using nonparametric Wilcoxon two-sample test.		related to true outcome) Selective reporting: High risk (One or more outcomes of interest reported incompletely) Other sources of bias: High risk (Clinicians chose which ESPAC-1 trial patients were randomised to; Kaplan-Meier curves for overall survival cross, proportional hazards not satisfied)
Full Citation Neoptolemos, J. P., Stocken, D. D., Friess, H., Bassi, C., Dunn, J. A., Hickey, H., Falconi, M. et al. (2004). A randomized trial of	N= 144 resected PC patients from 53 hospitals in 11 countries Arm 1=75 Arm2=69	Arm 1: Chemotherapy (Folinic acid + 5-FU)	ESPAC—1 2x2 trial Data from 2x2 RCT, chemotherapy only and observation arms only Randomisation	Overall survival Adverse events Quality of life Chemotherapy vs No adjuvant therapy Overall survival (from Neoptolemos 2009)	Overall high risk of bias. Random sequence generation: Unclear risk (1:1 but insufficient information about

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
chemoradiotherapy and chemotherapy after resection of pancreatic cancer. New England Journal of Medicine, 350(12), 1200-1210. Country/ies where the study was carried out: 11 countries in Europe Study type: RCT Aim of the study: To investigate the possible benefits of adjuvant chemoradiotherapy and maintenance chemotherapy in patients with pancreatic cancer. Study dates: February 1994 to June 2000 Source of funding: Supported by Cancer Research United Kingdom and the Fonds de Recherche de la Société Nationale Française de Gastroentérologie; by a grant (9906195987) from the Consorzio Studi Universitari di Verona, Cariverona, and the	Inclusion Histologically proven, macroscopically resected ductal adenocarcinoma of the pancreas with no evidence of local spread or distant metastases. Fully recovered from surgery Life expectancy > 3 mo Fit enough for treatment Given informed consent Exclusion Pancreatic cystadenocarcinoma Endocrine tumours of the pancreas Tumours of the duodenum	Arm 2: No adjuvant therapy	Randomisation by phone or fax to one of four randomisation centres (UK, Germany Switzerland, and France), where eligibility was checked before treatment allocated. Randomisation stratified by randomisation centre and resection-margin status (positive or negative). After resection patients were randomly assigned to receive chemotherapy or chemoradiotherapy, neither treatment, or both. Treatment Median time from resection to randomisation (days)=21 (IQR 14-35) Median follow up of 25 alive patients (months)=78 (IQR 45-92) Arm 1 median time from resection to start of assigned treatment (days)=46 (IQR 34-67) (N=289, includes combined CT and CRT arm) Arm 1: Intravenous bolus folinic acid 20 mg/m2 followed by intravenous bolus fluororacil 425 mg/m2 for 5 consecutive days every 28 days for 6 cycles. Adverse events UICC Common Toxicity Criteria with clearly defined	Median OS: 18.6 (95%CI, 15.7-23.6) Estimated OS at 1, 2 and 5 years: 67%, 42%, 18%. Median OS by arm: 21.7 (95% CI, 14.8-27.3) vs 16.9 (95% CI, 12.3-24.8), HR=0.7 (95%CI, 0.49-1.01) Observed deaths: 57/75 vs 63/69 Estimated OS at 1 year by arm: 70% vs 64% Estimated OS at 2 years by arm: 44% vs 39% Estimated OS at 5 years by arm: 27% vs 10% Adverse Events Grade 3 or 4 toxicities Grade 3 or 4 toxicities: CRT+CT (n=75) / Obs (n=69) Haematological events: 2 / 0 Stomatitis: 4 / 0 Diarrhoea: 2 / 0 Other: 3 / 0 Quality of life No significant difference between CT (n=147) vs no CT (n=142), p=0.75 (direction of effect not reported) CRT->Chemotherapy vs No adjuvant therapy Overall survival Median OS by arm: 19.9 (95% CI, 14.2-22.5) vs 16.9 (95% CI, 12.3-24.8)	sequence generation method) Allocation concealment: Low risk (Central allocation) Blinding of participants and personnel assessments: Low risk for survival data (Not blinded but unlikely that outcome would be influenced by blinding) Blinding of outcome assessment: Low risk (Not reported but unlikely that outcome measurement would be influenced by blinding) Incomplete outcome data: Low risk for data (Missing outcome data unlikely to be related to true outcome) Selective reporting: High risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Ministero Università e Ricerca Scientifica e Tecnologica, Rome; by the Associazione Italiana Ricerca Cancro, Milan, Italy; and by a European Community Grant (BMH4-CT98-3805). Dr. Neoptolemos reports having received grant support from Solvay Pharmaceuticals and KS Biomedix.			protocol for modifications and delays. Quality of life Mean observed QoL assessed with standardized AUC methods within 12 months after resection using ESPAC-1 QoL form (modified EORTC QLQ-C30 v1 with ESPAC-1 disease-specific questions) Statistical analysis All analyses were carried out according to the intention-to-treat principle, and all reported P values are two-sided. ITT Kaplan-Meier survival analysis; for patients lost to follow-up, data were censored on the date the patient was last seen alive. Stratified log-rank analyses and Cox proportional-hazards modelling used to investigate and adjust for major prognostic and stratification factors. QoL group differences assessed using nonparametric Wilcoxon two-sample test.	Observed deaths: 60/72 vs 60/69 Estimated OS at 5 years by arm: 13% vs 11% Adverse Events Grade 3 or 4 toxicities: CRT+CT (n=72) 5; Obs (n=69) 0 Haematological events: 5; 0 Stomatitis: 5; 0 Diarrhoea: 4; 0 Other: 2; 0 Quality of life Not reported for separate groups Chemotherapy vs CRT Overall survival Median OS by arm: 21.6 (95% CI, 13.5-27.3) vs 13.9 (95% CI, 12.2-17.3) HR= 0.7 (95%CI, 0.49-1.02) (estimated by Liao 2013) Observed events: 52/75 vs 65/73 Estimated OS at 5 years: 13% vs 29%. Adverse Events Grade 3 or 4 toxicities: CT (n=75) 2; CRT (n=73) 0 Haematological events: 2; 0 Stomatitis: 4; 0 Diarrhoea: 2; 0	(One or more outcomes of interest reported incompletely) Other sources of bias: high risk (Clinicians chose which ESPAC-1 trial patients were randomised to; Study not powered to compare CT only group and no adjuvant therapy group; Kaplan-Meier curves for overall survival cross, proportional hazards not satisfied)

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
				Other 3 2 CRT->Chemotherapy vs Chemotherapy only Overall survival Median OS by arm: 19.9 (95%CI, 14.2-22.5) vs 21.6 (95%CI, 13.5-27.3) Observed events: 60/72 vs 52/75 Observed-Expected=7.5, Variance=27.3 Estimated OS at 5 years: 13% vs 29% Adverse Events Grade 3 or 4 toxicities: CRT+CT (n=72) CT (n=75) Haematological events: 5 2 Stomatitis: 5 4 Diarrhoea: 4 2 Other: 2 3 Quality of life Not reported for separate groups Chemotherapy->CRT vs CRT Overall survival Median OS by arm: 19.9 (95%CI, 14.2-22.5) vs 13.9 (95%CI, 12.2-17.3) Observed events: 60/72 vs 65/73 Observed-expected=-11.9, variance=29.7 Estimated OS at 5 years by arm: 13% vs 7% Adverse Events Haematologic events: 5/75 vs 0/69	

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
				Stomatitis: 5/75 vs 0/69 Diarrheoa: 4/75 vs 0/69 Other AEs: 2/75 vs 2/69 Quality of life Not reported for separate groups	
Full Citation Neoptolemos, J. P., Stocken, D. D., Smith, C. T., Bassi, C., Ghaneh, P., Owen, E., Büchler, M. W. et al. (2009). Adjuvant 5-fluorouracil and folinic acid vs observation for pancreatic cancer: composite data from the ESPAC-1 and-3 (v1) trials. British journal of cancer, 100(2), 246-250. Country/ies where the study was carried out: ESPAC-3 v1 (17 countries in Europe, Australasia, Japan, Canada) Study type Multicentre RCT Aim of the study: To provide an unbiased randomised comparison of adjuvant 5FU/FA vs observation following the resection of	N=122 resected PC patients from 159 centres in 17 countries Arm 1=61 Arm 2=61 Inclusion Histologically proven, macroscopically resected ductal adenocarcinoma of the pancreas with no evidence of local spread or distant metastases. Fully recovered from surgery Life expectancy > 3 mo Fit enough for treatment Given informed consent Exclusion	Arm 1: Chemotherapy (5-FU + Folinic acid) Arm 2: No adjuvant therapy	ESPAC-3 v1 data only Randomisation Randomisation on 1:1 basis according to computer-generated variable size blocked randomisation method. Patients stratified at randomisation by country and resection margin status (R0 vs R1). Treatment Median follow up of 30 alive patients (months)=54 (IQR 34-60) Arm 1: Intravenous bolus folinic acid 20 mg/m2 followed by intravenous bolus fluororacil 425 mg/m2 for 5 consecutive days every 28 days for 6 cycles. Adverse events UICC Common Toxicity Criteria with clearly defined protocol for modifications and delays. Quality of life Mean observed QoL assessed with standardized	Overall survival Chemotherapy vs No adjuvant therapy Survival Median OS: 24.3 (95%CI, 19.8- 30.9), HR=0.86 (95%CI, 0.66-1.11), log rank p=0.33 Estimated OS at 1, 2 and 5 years: 80%, 51%, 20%. Median OS by arm: 25.9 (95%CI, 18.3-36.3) vs 20.3 (95%CI, 18.1-31.7), HR=0.89 (95%CI, 0.59-1.33) Observed deaths: 45/61 vs 47/61 Estimated OS at 1 year by arm: 82% vs 79% Estimated OS at 2 years by arm: 54% vs 48% Estimated OS at 5 years by arm: 20% vs 20%	Overall high risk of bias. Random sequence generation: Unclear risk (1:1 but insufficient information about sequence generation method) Allocation concealment: Low risk (Central allocation) Blinding of participants and personnel assessments: Low risk (Not blinded but unlikely that outcome would be influenced by blinding) Blinding of outcome assessment: Low risk (Not reported but unlikely that primary outcome

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
pancreatic ductal adenocarcinoma. Study dates: July 2000 to June 2003 Source of funding: Funded by Cancer Research UK; plus the Fonds de Recherche de la Societe Nationale Franc¸aise de Gastroenterologie; the Consorzio Studi Universitari di Verona, Cariverona and the Ministero Universita e Ricerca Scientifica e Tecnologica (Cofin 9906195987) Rome, Italy; Associazione Italiana Ricerca Cancro (AIRC) Milan, Italy; European Community Grant BIOMED 2 CE-contract no. BMH4-CT98-3805; National Cancer Institute, Canada; and Medical Research Council, Australia.	Pancreatic cystadenocarcinoma Endocrine tumours of the pancreas Tumours of the duodenum		AUC methods within 12 months after resection using ESPAC-1 QoL form (modified EORTC QLQ-C30 v1 with ESPAC-1 disease-specific questions) Statistical analysis All analyses were carried out according to the intention-to-treat principle, and all reported P values are two-sided. ITT Kaplan-Meier survival analysis; for patients lost to follow-up, data were censored on the date the patient was last seen alive. Stratified log-rank analyses and Cox proportional-hazards modelling used to investigate and adjust for major prognostic and stratification factors. QoL group differences assessed using nonparametric Wilcoxon two-sample test.		measurement would be influenced by blinding) Incomplete outcome data: Low risk (Missing outcome data unlikely to be related to true outcome) Selective reporting: High risk (Toxicity and QoL data not reported) Other sources of bias: High risk (Originally part of 3-arm trial comparing 5FU+FA vs gemcitabine vs no adjuvant therapy, discontinued due to results of ESPAC-1 2x2 trial; Kaplan-Meier curves for overall survival cross, proportional hazards not satisfied)
Full Citation 1. Neoptolemos, J. P., Stocken, D. D., Bassi, C., Ghaneh, P.,	N= 1088 resected PC patients from 159	Arm 1: Chemotherapy-1	ESPAC-3, v2 Study protocol available at clinicaltrials.gov, NCT00058201	Overall survival Disease-free survival (from Valle 2014) Adverse events Quality of life	Overall low risk of bias Random sequence generation: Low

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Cunningham, D., Goldstein, D., Wente, M. N. et al. (2010). Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. Jama, 304(10), 1073-1081. 2. Valle, J. W., Palmer, D., Jackson, R., Cox, T., Neoptolemos, J. P., Ghaneh, P., O'Reilly, D. et al. (2014). Optimal duration and timing of adjuvant chemotherapy after definitive surgery for ductal adenocarcinoma of the pancreas: ongoing lessons from the ESPAC-3 study. Journal of Clinical Oncology, JCO-2013. Country/ies where the study was carried out: ESPAC—3, v2 (17 countries in Europe, Australasia, Japan, Canada) Study type: Phase 3 RCT Aim of the study:	centres in 17 countries Arm 1=537 Arm 2=551 Inclusion Undergone complete macroscopic (R0 or R1) resection for ductal adenocarcinoma of the pancreas with histological confirmation No evidence of malignant ascites, peritoneal metastasis, or spread to the liver or other distant abdominal or extra-abdominal organs (type and extent of resection determined using an established international classification) Fully recovered from resection operation	(Gemcitabine) Arm 2: Chemotherapy-2 (Folinic Acid + 5-FU)	Randomisation Patients were randomly assigned to each treatment group on a 1:1 basis according to a computer-generated variable-size blocked randomisation method. Patients were stratified at randomisation by country and resection margin status (R0 vs R1). Treatment Median time from randomisation to chemotherapy: 8 days (IQR5-14) vs 10 (IQR 5-18). Median follow up of 335 alive patients (months)=34.2 (IQR, 27.1-43.4) Median time receiving CT (months): 5.1 (IQR4-5.3) vs 4.7 (IQR 3.1-5) Median dose intensity: 89% (range 6-122) vs 79% (range 3-141) Arm 1: Intravenous infusion 1000 mg/m2 gemcitabine (lyophilized powder diluted in normal saline) administered once a week for 3 out of every 4 weeks (1 cycle) for 6 cycles (24 weeks). Arm 2: Intravenous bolus 20 mg/m2 folinic acid followed by intravenous bolus 425 mg/m2 for 5 consecutive	Chemotherapy-1 vs chemotherapy-2 Overall survival Median OS (months): 23.2 (95%CI, 21.7-24.9) Estimated OS at 12 months=79.3% (95%CI, 76.9-81.8) Estimated OS at 24 months=48.6% (95%CI, 45.6-51.6) Median OS by arm: 23.6 (95%CI, 21.4-26.4) vs 23 (95%CI, 21.1-25), HR=0.94 (95%CI, 0.81-1.08), log rank p=0.39 Observed events: 365/537 vs 388/551 Median OS by arm (including CA 19-9): HR=0.88 (95%CI, 0.75-1.05), log rank p=0.15 (Cox proportional model) Median OS by arm (excluding CA 19-9): HR=0.9 (0.78-1.04), log rank p=0.16 (Cox proportional model) Estimated OS at 12 months by arm: 80.1% (95%CI, 76.7-93.6) vs 78.5% (95%CI, 75-82) Estimated OS at 24 months by arm: 49.1% (95%CI, 44.8-53.4) vs 48.1% (95%CI, 43.8-52.4) Progression-free/Disease-free survival (arm 1=486, arm 2=499) [from Valle 2014] Median DFS by arm (months) : 14.06 (95%CI, 13.44-15.7) vs 14.55 (95%CI, 12.81-16.06), HR=0.995 (95%CI, 0.868-1.141), log rank p=0.946 [from Valle 2014] Observed events: 408/486 vs 417/499 [from Valle 2014]	risk (1:1 using computer-generated variable-size blocks) Allocation concealment: Low risk (Central allocation) Blinding of participants and personnel assessments: Low risk for survival data (Not blinded but unlikely that outcome would be influenced by blinding); High risk for QoL data (Not blinded and outcome likely to be influenced by this) Blinding of outcome assessment: Low risk (Not blinded but unlikely that outcome measurement would be influenced by blinding) Incomplete outcome data: Low

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Limitation (risk of bias)</th></tr>
<tr>
<td>To determine whether fluorouracil or gemcitabine is superior in terms of overall survival as adjuvant treatment following resection of pancreatic cancer.
Study dates:
July 2000 to January 2007
Source of funding:
Supported by Cancer Research UK; National Cancer Institute of Canada, Canadian Cancer Society; Fonds de Recherche de la Societe Nationale Francaise de Gastroenterologie; Fondazioone Italiana Malattie del Pancreas; Health and Medical Research Council of Australia, Cancer Councils of New South Wales, Queensland, Victoria, and South Australia. Dr Cunningham’s work is funded in part by the National Institute for Health Research Biomedical Research</td>
<td>WHO performance score ≤ 2
Life expectancy> 3 months
Exclusion
Previous use of neoadjuvant chemotherapy or other concomitant chemotherapy and with pancreatic lymphoma, macroscopically remaining tumour (R2 resection)
TNM stage IVb disease</td>
<td></td>
<td>days every 28 days for 6 cycles (24 weeks).
Adverse events
NCI Common Terminology Criteria for Adverse Events (v2), with clearly defined protocol for modifications and delays.
Quality of Life
Assessed using EORTC QLQ-C30 (version 3) and ESPAC-32 patient questionnaires at baseline, 3 and 6 months, and yearly until 5 years.
Statistical analyses
All analyses ITT, two-sided significance level P<0.05</td>
<td>DFS at 2 years by arm: 28% vs 31% [from Valle 2014]
DFS at 5 years by arm: 14% vs 14% [from Valle 2014]
Adverse events
patients experiencing treatment-related serious adverse events: 40/537 vs 77/551
Grade 3 or 4 toxicities
<table>
<tr><th></th><th>Gemcitabine (n=537)</th><th>5FU+FA (n=551)</th><th>P value</th></tr>
<tr><td>White Blood Cell count</td><td>53</td><td>32</td><td>p=0.01</td></tr>
<tr><td>Neutrophils</td><td>119</td><td>121</td><td>p=0.94</td></tr>
<tr><td>Platelets</td><td>8</td><td>0</td><td>p=0.003</td></tr>
<tr><td>Nausea</td><td>13</td><td>19</td><td>p=0.37</td></tr>
<tr><td>Vomiting</td><td>11</td><td>17</td><td>p=0.34</td></tr>
<tr><td>Stomatitis</td><td>1</td><td>54</td><td>p<0.001</td></tr>
<tr><td>Alopecia</td><td>1</td><td>1</td><td>p>0.99.</td></tr>
<tr><td>Tiredness</td><td>32</td><td>45</td><td>p=0.16</td></tr>
<tr><td>Diarrhoea</td><td>12</td><td>72</td><td>p<0.001</td></tr>
<tr><td>Other</td><td>43</td><td>67</td><td>p=0.03</td></tr>
</table>
</td>
<td>risk (Reasons for missing outcome data unlikely to be related to true outcome)
Selective reporting: Low risk (Study protocol available and all outcomes of interest fully reported)
Other sources of bias: Low risk (Study appears free of other sources of bias)</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Centre at the Royal Marsden Hospital.				Quality of life (n=565; arm 1=285, arm 2=280) Global QoL score by arm: 46.6 (19.7) vs 43.6 (20.1), p=0.08	
Full Citation Neoptolemnos, J.P., Palmer, D.H., Ghaneh, P., Psarelli, E.E., Valle, J.W., Büchler, M.W. et al. for the European Study Group for Pancreatic Cancer. (2017). Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients withj resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. The Lancet Country/ies where the study was carried out: ESPAC-4 (6 European Countries: England, Scotland, Wales, Germany, France, Sweden). Study type: Multicentre phase 3 open-label RCT Aim of the study:	N= 732 resected PC patients 2 patients (1 fromjeach arm) excluded from ITT analysis due to withdrawal of consent before start of treatment Arm 1=366 Arm 2=364 Inclusion aged 18 years or older undergone complete macroscopic resection for ductal adenocarcinoma of the pancreas (R0 or R1 resection) with histological confirmation and with no evidence of malignant ascites, liver or peritoneal metastasis, or	Arm 1: Gemcitabine Arm 2: Gemcitabine + capecitabine	Randomisation Patients were randomly assigned (1:1) to receive gemcitabine or gemcitabine plus capecitabine within 12 weeks of surgery by trained authorised staff within the Liverpool Clinical and Cancer Trials Unit. Randomisation was based on a minimisation routine with a random element of 20% including the resection margin (negative or positive) and country was used as a stratification factor. Participants and study investigators were not masked to treatment allocation. Treatment Patients were reviewed every 3 months after surgery for 5 years if alive at this point. The specific method of follow-up (haematology, clinical chemistry, and use of a tumour marker) at each clinic visit was determined by each site because of wide	Overall survival Relapse-free survival/#Disease relapse Adverse events Quality of life Chemotherapy-1 vs chemotherapy-2 Note: All data gemcitabine vs gemcitabine+capecitabine unless otherwise stated Overall survival (gemcitabine+capecitabine vs gemcitabine) HR 0.82 (95%CI 0.68-0.98), p=0.032 # of deaths: 219/364 vs 239/366 Median survival (months) [gem vs gem+cap]: 25.5 (22.7-27.9) vs 28 (23.5-31.5) Estimated OS at 12 months: 80·5% (95% CI 76·0–84·3) v 84·1% (95%CI 79·9–87·5) Estimated OS at 24 months: 52·1% (46·7–57·2) vs 53·8% (95%CI 48·4–58·8) Estimated OS at 5 years: 16.3 (95%CI 10.2-23.7) vs 28.8 (95%CI 22.9-35.2) # patients relapsed or died: 286/366 vs 271/364 # patients relapsed: 243/366 vs 236/364 Relapse-free survival:	Overall high risk of bias. Random sequence generation: low risk (minimisation method) Allocation concealment: High risk (participants/investigators not masked to group allocation) Blinding of participants and personnel assessments: Low risk (not blinded but unlikely to affect outcome) Blinding of outcome assessment: Low risk (not blinded but unlikely to affect outcome asssessment) Incomplete outcome data: Low risk (missing data balanced across

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
To determine the efficacy and safety of gemcitabine and capecitabine compared with gemcitabine monotherapy for resected pancreatic cancer. Study dates: November 2008 to September 2014 Source of funding: Funded by Cancer Research UK (grant number C245/A8968/A15957) and sponsored by the Royal Liverpool and Broadgreen University Hospitals NHS Trust, Liverpool, UK. DC is funded by the National Institute for Health Research Biomedical Research Centre at the Royal Marsden. TM is funded by the National Institute for Health Research Biomedical Research Centre at University College London Hospital.	spread to other distant abdominal, or extra-abdominal organs A clear CT scan of the chest, abdomen, and pelvis was required within 3 months before randomisation. Full recovery from surgery WHO performance score of two or less creatinine clearance of at least 50 mL/min life expectancy of more than 3 months Exclusion Previous neo-adjuvant chemotherapy or other concomitant chemotherapy Previous pancreatic lymphoma		variations in routine clinical practice. Arm 1: Gemcitabine was delivered as a 1000 mg/m² intravenous infusion administered once a week for three of every 4 weeks (one cycle) for six cycles (24 weeks). Arm 2: Gemcitabine procedure same as arm 1; Capecitabine was administered orally for 21 days followed by 7 days rest (one cycle) for six cycles (24 weeks) at a daily dose of 1660 mg/m². Adverse events NCI Common Toxicity Criteria, v4.03 Quality of life EORTC QLQ C-30, v3 Statistical analyses ITT analysis, two-sided p<0.05 Protocol available at https://www.lctu.org.uk/Public/SSES4_PROTOCOL.9-ESPAC-4_Protocol.pdf	Median relapse-free survival (months): 13.1 (95%CI 11.6-15.3) vs 13.9 (95%CI 12.1-16.6). RFS (Gem+Cap vs gem):HR 0.86 (95%CI 0.73-1.02), p=0.082 3-year RFS 20.9% (95%CI 16.5-25.7) vs 23.8% (95%CI 19.2-28.6) 5-year RFS 11.9 (95%CI 7.8-16.9) vs 18.6 (95%CI 13.8-24) Adverse events # patients with treatment-related serious adverse events: 94/366 vs 86/359 # patients with grade 3-4 adverse events: 196/366 vs 226/359 Grade 3 or 4 toxicities Gemcitabine (n=366) / Gem+Capecitabine (n=359) / p-value Anaemia: 14 / 8 / 0.279 Diarrhoea: 6 / 19 / 0.008 Fatigue: 19 / 20 / 0.87 Fever: 6 / 6 / 1.0 Infection +infestations/other: 24 / 9 / 0.012 Decreased Lympho: 11 / 9 / 0.821	groups and for similar reasons) Selective reporting: Low risk for survival outcomes/adverse events; High risk for QoL outcomes (incomplete reporting) Other sources of bias: High risk (method of follow up determined by each site due to wide variations in practice; relapsed patients received additional chemotherapy, chemoradiotherapy, surgery and other treatment as appropriate)

Study details	Participants	Interventions	Methods	Outcomes and Results				Limitation (risk of bias)
	Previous macroscopically remaining tumours (R2 resection) TNM stage IV disease			cyte count				
				Neutropenia	89	137	0.0001	
				Hand-foot syndrome	0	26	<0.000	
				Platelets	7	8	0.8	
				Thromboembolic events	9	8	1.0	
				White blood cell count decreased	28	37	0.242	
				Acute kidney injury	2	0	0.499	
				Multi-organ failure	0	0	NA	
				Cardiac disorders	1	0	1.0	
				Benign, malignant and unspecified neoplasms (inc.	0	1	0.495	

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
				cysts/polyps).other Grade 5 toxicities Gemcitabine (n=366) / Gem+Capcitabine (n=359) Infection+infestations/other: 0 / 1 Multi-organ failure: 1 / 0 Cardiac disorders: 1 / 0 Benign, malignant and unspecified neoplasms (inc. cysts/polyps).other: 3 / 0 Quality of life data not reported correctly	
Full Citation 1. Oettle, H., Post, S., Neuhaus, P., Gellert, K., Langrehr, J., Ridwelski, K., Gutberlet, K. et al. (2007). Adjuvant chemotherapy with gemcitabine vs observation in patients	N= 368 resected PC patients from 88 centres in 2 countries Arm 1=186 (randomized; 179 ITT/survival analysis)	Arm 1: Chemotherapy (Gemcitabine) Arm 2: No adjuvant therapy	CONK0-001 trial Randomisation Patients were assigned on 1:1 basis to gemcitabine or no adjuvant therapy, using a central randomisation procedure with stratification for resection status (R0 vs	Overall survival Disease-free survival Adverse events Quality of life All data from Oettle 2013 unless otherwise stated Chemotherapy vs No adjuvant therapy Overall survival	Overall high risk of bias. Random sequence generation: Low risk (Majority of participants randomised using computer-

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. Jama, 297(3), 267-277. 2. Oettle, H., Neuhaus, P., Hochhaus, A., Hartmann, J. T., Gellert, K., Ridwelski, K., Sinn, M. et al. (2013). Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. Jama, 310(14), 1473-1481. Country/ies where the study was carried out: Germany and Austria Study type: Phase 3 open-label multicentre RCT Aim of the study: To test the hypothesis that adjuvant chemotherapy with gemcitabine administered after complete resection of pancreatic cancer improves disease-free survival by 6 months or more.	Arm2=182 (randomized; 175 ITT/survival analysis) Inclusion Patients with histologically-verified pancreatic cancer who had macroscopic complete resection and no prior radiation or neoadjuvant chemotherapy Patients required to have T1-4 N0-1 M0 disease prior to surgery Aged >18 years old Karnofsky performance status≥50% Adequate bone marrow function Patient availability, and adherence to long-term follow-up > 2 years after surgery. Exclusion		R1), T status (T1-2 vs T3-4), and nodal status (N– vs N+) according to the TNM classification standards. Randomisation using sealed envelopes was conducted in the first 73 patients by a statistician at the German Cancer Research Center (Deutsches Krebsforschungszentrum, Heidelberg, Germany), while randomisation for the remaining patients was performed at coordinating centre of the trial using computer-generated procedure. Treatment Median follow up=136 (IQR 104-144) months. Mortality at end of FU period: 156/179 vs 160/175 Start of adjuvant CT recommended between day 10 and day 42 following surgery or after wound healing. Arm 1: 6 cycles adjuvant CT every 4 weeks. Each cycle was 3 weekly intravenous infusions of gemcitabine 1000 mg/m2 during 30 min period, followed by 1-week pause. Adverse events	All patients Median OS by arm: 22.8 (95% CI, 18.5-27.2) vs 20.2 (95% CI, 17.7-22.8) months, HR=0.76 (95% CI, 0.61-0.95, log rank p=0.01 Observed deaths: 156/179 vs 160/175 Survival rate at 5 years: 20.7 (95%CI, 14.7-26.6) vs 10.4 (95%CI, 5.9-15) Survival rate at 10 years: 12.2 (95%CI, 7.3-17.2) vs 7.7 (95%CI, 3.6-11.8) Disease-free survival All patients Median DFS by arm: 13.4 (95% CI, 11.6-15.3) vs 6.7 (95% CI, 6.0-7.5), HR=0.55 (95% CI, 0.44-0.69) (p<0.001) 5 year DFS by arm: 6.6% (95%CI, 11.0%-22.2%) vs 7.0% (95%CI, 3.2%-10.8%) 10 year DFS by arm: 14.3% (95%CI, 8.9%-19.8%) vs 5.8% (95%CI, 2.3%-9.3%) All patients Recurrence of disease: 133/179 vs 161/175 (Data from Oettle 2007) Adverse events in CT group (n=186) (from Oettle 2007) Gemcitabine was well tolerated with infrequent Grade 3+ toxicity reports. No increase in hematologic or non-haematologic toxicity observed gemcitabine group. Total of 62 serious adverse events reported in 41 patients (26 patients in	generated procedure) Allocation concealment: Low risk (Central allocation) Blinding of participants and personnel assessments: Low risk for survival data (Not blinded but unlikely that outcome would be influenced by blinding) Blinding of outcome assessment: Low risk (Not blinded but unlikely that outcome measurement would be influenced by blinding) Incomplete outcome data: Low risk (Reasons for missing outcome data unlikely to be related to true outcome) Selective reporting: High risk (One or more

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Study dates: July 1998 to December 2004; follow up to September 2012 Source of funding: Supported in part by grant from Lilly Deutschland, Bad Homburg, Germany	Active infection, impaired coagulation (international normalized ratio and/or activated partial thromboplastin time ≥1.5 times the upper limit of normal). Transaminases > 3 times the upper limit of normal. Serum creatinine > 1.5 times the upper limit of normal Postoperative tumour markers (carcinoembryonic antigen/cancer antigen [CEA/CA19-9]) > 2.5 times the upper limit of normal History of another malignant disease other than carcinoma in situ of the uterine cervix or adequately treated basal cell		Assessed according to the WHO criteria. Quality of life Assessed using Karnofsky performance status and Spitzer QoL index Other Original protocol amended 4 months into trial, from requiring R0 patients only to also allowing R1 resection patients, after recruitment of 9 patients. Analyses ITT survival analysis; subgroup analysis stratified by resection, tumour and nodal status. Qualified survival analysis (>1 complete CT cycle in CT group; no adjuvant cytotoxic/radiation therapy in no adjuvant therapy group; patients with minor violations of entry criteria also excluded). Safety analysis included all gemcitabine patients for which toxicity data available.	the gemcitabine group and 15 patients in the control group) during study. In 5 out of 26 patients experiencing serious adverse event in gemcitabine group were considered treatment-related. Neither of the 2 fatal events occurring in the study (1 anastomotic ulceration, 1 hemorrhagic shock, both occurring in the gemcitabine group) were considered gemcitabine-related. Nausea/vomiting (21.2%), diarrhoea (9%) and edema (8.9) most common non-haematological toxicities reported in gemcitabine group. Quality of life (from Oettle 2007) Median Karnofsky performance status increased from 80% at baseline to 90% at 6 months in both groups. Although mean Spitzer score improved similarly in both groups, from 1.4 prior to cycle 1, to 1.8 prior to cycle 6, there were no significant differences between groups at any time point. Changes over time in Spitzer score also largely paralleled mean Spitzer scores, again with no significant differences between groups.	outcomes of interest are reported incompletely) Other sources of bias: High risk (Kaplan-Meier curves for overall survival cross, proportional hazards not satisfied)

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
	carcinoma of the skin. Pregnant or breastfeeding women (non-pregnant women of childbearing age were required to be using reliable contraceptive methods for the duration of the study > 3 months after its termination).				
Full Citation 1. Regine, W. F., Winter, K. A., Abrams, R. A., Safran, H., Hoffman, J. P., Konski, A., Haddock, M. G. et al. (2008). Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: a randomized controlled trial. Jama, 299(9), 1019-1026. 2. Regine, W. F., Winter, K. A., Abrams, R., Safran, H., Hoffman, J.	N=451 resected PC patients from 164 institutions Arm 1=221 (ITT) Arm2=230 (ITT) Inclusion Histologically confirmed adenocarcinoma of the pancreas and gross total tumour resection, confirmed by central review of operative and pathology reports Postoperative computed tomographic (CT) imaging within 3	Arm 1: Chemotherapy-1 (Gemcitabine) + chemoradiotherapy then chemotherapy (gemcitabine) Arm 2: Chemotherapy-2 (5-FU) + chemoradiotherapy then	RTOG 9704 trial Study protocol available at clinicaltrials.gov, NCT00003216 Randomisation Patients were stratified by nodal status (uninvolved vs involved), tumour diameter (<3 cm vs ≥3 cm), and surgical margin status (negative vs positive vs unknown). The permuted block randomization method was used with patient factors balanced according to the permuted block randomization method. Randomisation performed 3 to 8 week after surgery.	Overall survival Adverse events Data from Regine 2011 unless otherwise stated Overall survival All patients Arm 1 vs Arm 2, HR=0.933 (95%CI, 0.76-1.145), log rank p=0.51 Observed events 180/221 vs 188/230 Patients with pancreatic head tumour only (arm 1=187, arm 2=201) Median OS (months) by arm=20.5 vs 17.1, HR=0.838 (95%CI, 0.671-1.045), log rank p=0.12 Adjusted HR=0.82 (95%CI, 0.65-1.02, log rank p=0.08 Estimated OS at 3 years by arm: 31% vs 22% (Regine 2008) Estimated OS at 5 years=22% vs 18%	Overall unclear risk of bias. Random sequence generation: Unclear risk (permuted block randomisation with stratification but no further information about method) Allocation concealment: Unclear risk (Insufficient information) Blinding of participants and personnel assessments: Low risk (Not blinded

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
P., Konski, A., Willett, C. G. et al. (2011). Fluorouracil-based chemoradiation with either gemcitabine or fluorouracil chemotherapy after resection of pancreatic adenocarcinoma: 5-year analysis of the US Intergroup/RTOG 9704 phase III trial. Annals of surgical oncology, 18(5), 1319-1326. Country/ies where the study was carried out: RTOC 9704 USA and Canada Study type: Phase III RCT Aim of the study: To report long-term follow up data of phase III trial examining addition of gemcitabine to 5-fluorouracil (5-FU) chemoradiation (CRT) in resected pancreatic adenocarcinoma Study dates: July 1998 to July 2002, with FU to August 2006. Source of funding: The National Cancer Institute supported the	weeks of randomisation to exclude patients who had evidence of persistent or recurrent local disease or developed metastatic disease prior to therapy Stages T1 to T4, N0 to N1, and M0 according to the 1997 staging criteria of the American Joint Commission on Cancer Karnofsky performance status ≥60 Adequate hematologic, renal, and hepatic function Submission of CA19-9 serum tumour marker required Written informed consent Exclusion No identifiable lymph nodes	chemotherapy-2 (5-FU)	Treatment Median follow up (years)=1.48 (range 0.1-9.1) Median follow up for alive patients=6.98 (range 0.3-9.1) Arm 1: 30-minute infusion 1000 mg/m2 gemcitabine once weekly for 3 weeks. Between 1 and 2 weeks after completion of chemotherapy, 50.4 Gy with a continuous infusion of 250 mg/m2 fluorouracil daily throughout radiation therapy. RT delivered in 28 fractions, 5 days per week to tumour bed and regional nodes. Post-CRT CT consisted of 3 months continuous infusion gemcitabine (3 weeks on, 1 week off). Arm 2: continuous infusion 250 mg/m2 fluorouracil per day for 3 weeks. Between 1 and 2 weeks after completion of chemotherapy, 50.4 Gy with a continuous infusion of 250 mg/m2 fluorouracil daily throughout radiation therapy. RT delivered in 28 fractions, 5 days per week to tumour bed and regional nodes. Post-CRT CT consisted of 3 months continuous infusion	Local relapse by arm: 25% vs 30% Regional relapse by arm: 7% vs 8% Distant relapse by arm: 76% vs 70% Adverse events Grade 3 or higher (From Regine 2008) One Grade 5 event in gemcitabine group due to non-neutropenic infection Worst haematologic: 129/221 vs 22/230, p<0.001 Grade 4: 32/221 vs 3/230, p<0.001 Worst non-haematologic: 129/221 vs 137/230, p=0.9 Worst overall: 175/221 vs 143/230, p=0.001 | | # of patients | | | Grade 3 or higher toxicities | CRT+gemcitabine | CRT+fluoroacil | | Diarrhoea | 33 | 44 | | Stomatitis | 22 | 35 | | Nausea/vomiting | 22 | 25 | Late Grade 2 or higher (From Regine 2011) Worst haematologic: 7/221 vs 10/230, two-sided p=0.5179 Worst nonhaematologic: 42/221 vs 39/230, two-sided p=0.5152 Worst overall: 46/221 vs 43/230, two-sided p=0.5301	but unlikely that outcome would be influenced by blinding) Blinding of outcome assessment: Low risk (Not reported but unlikely that outcome measurement would be influenced by blinding) Incomplete outcome data: Low risk for data (Missing outcome data unlikely to be related to true outcome) Selective reporting: Low risk (Study protocol available and all outcomes full reported) Other sources of bias: Low risk (Study appears free from other sources of bias)

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
cooperative clinical trials groups, which participated in this study, including the Radiation Therapy Oncology Group (RTOG), the Eastern Cooperative Oncology Group, and the Southwest Oncology group via grants U10 CA21661, U10 CA37422, and U10CA32115. Eli Lilly, the makers of gemcitabine, provided financial support to RTOG Headquarters and the statistical center.	within the resection specimen Prior radiotherapy to any site or chemotherapy Prior malignancy other than nonmelanoma of the skin or in situ of the cervix.		5FU (4 weeks on [7 days a week], 2 weeks off). Adverse events Routinely monitored by RTOG Data Monitoring Committee, which functions independently of the RTOG		
Full Citation Reni, M., Balzano, G., Aprile, G., Cereda, S., Passoni, P., Zerbi, A., Fugazza, C. et al. (2012). Adjuvant pefg (cisplatin, epirubicin, 5-fluorouracil, gemcitabine) or gemcitabine followed by chemoradiation in pancreatic cancer: A randomized phase ii trial. Annals of surgical oncology, 19(7), 2256-2263.	N= 102 resected PC patients from 5 institutions Arm 1=51 Arm2=51 Inclusion Chemotherapy- and radiotherapy-naive patients who had R0 or R1 resection of a stage IB–III pancreatic ductal adenocarcinoma	Arm 1: Chemotherapy-1 (Gemcitabine) + chemoradiotherapy then chemotherapy (gemcitabine) Arm 2: Chemotherapy-2 (PEFG	PACT-7 Protocol available at clinicaltrials.gov, NCT00960284 Randomisation Patients were registered at an independent contract research organization (CRO) that randomly assigned them on a 1:1 basis to either arm A or B by a random-allocation sequence that had been generated previously by use of a computer-generated random code. Patients were stratified	Overall survival Disease-free survival Adverse events Overall survival Median OS by arm (months): 26.2 (IQR 17.4-37.4) vs 31.6 (IQR 17.6-42.2) Median OS from randomisation by arm (months): 24.8 vs 29.7 Disease-free survival Median DFS by arm (months): 11.7 (IQR 7-20.5) vs 15.2 (95%CI, IQR 10.3-25.7) # disease-free patients at 1 year: 25/51 (95%CI, 35%-65%) vs 34/51 (95%CI, 56%-83%)	Overall high risk of bias. Random sequence generation: Low risk (1:1 computer-generated random code with stratification) Allocation concealment: Low risk (central allocation) Blinding of participants and personnel assessments: Low

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Country/ies where the study was carried out: Italy Study type: Open Phase II RCT Aim of the study To examine whether PEFG combination improves overall survival compared to standard gemcitabine treatment. Study dates: August 2003 to August 2008 Source of funding: Supported in part by a grant from the non-profit organization ‘‘Per la Vita’’ (‘‘For Life’’), which was used for costs of conducting study.	Aged 18–70 years old and Karnofsky Performance Status (KPS)>60; or 71–75 years old and KPS>80 Treatment started within 2 months of resection Exclusion Ampullary tumours Other histological variants of pancreatic carcinoma Pregnant or breast feeding Concurrent treatment with other experimental drugs Previous or concurrent malignancies at other sites apart from surgically cured carcinoma in situ of the cervix Basal, or squamous cell carcinoma of the	[Cisplatin + Epirubicin + Gemcitabine + 5-FU]) + chemoradiotherapy then chemotherapy-2 (5-FU)	according to institution and surgical margins. Treatment Protocol was amended in January 2008, when oral capecitabine was shown to be equally effective as 5-FU in oesophagogastric cancer, to allow substitution of continuous infusion 5-FU by 625 mg/m2 oral CAP at a twice daily dose Radiotherapy delivered to tumour bed as defined by preoperative CT scan, with an isocentric 3- or 4-field technique using photon beam energies of at least 6 MV. Doses were limited to 45 Gy for the spinal cord, 20 Gy for the kidney, and less than one-third of hepatic volume receiving 30 Gy. Arm 1: 1000 mg/m2 gemcitabine weekly every 4 weeks for 3 months. Chemoradiotherapy initiated between 2-4 weeks after completion of CT, consisting of 54–60 Gy in 27–30 fractions with a concurrent continuous infusion of 250mg/m2 5-Fluororacil daily or 625 mg/m2 capecitabine twice daily.	Estimated HR: 1.33 (0.86-2.06) (calculated using Kaplan-Meier curve and Tierney 2007 method 11) Adverse events Grade 3-4 neutropenia and thrombocytopenia sig more frequent in PEFG arm, two sided p<0.0001. # patients with Grade 3 toxicity per cycle (worst ever by patient) Toxicity / Gemcitabine / PEFG arm Granulocytes 22 (12) 51 (18) Platelets 0 (0) 13 (8) Haemoglobin 1 (1) 2 (2) Stomatitis 0 (0) 9 (2) Nausea 0 (0) 1 (1) Diarrhoea 2 (2) 4 (3) Fatigue 1 (1) 0 (0) Liver 1 (1) 6 (2) Fever 0 (0) 1 (1) Febrile neutropenia 4 (4) 3 (3) Non-neutropenic infection 1 (1) 0 (0) # patients with Grade 4 toxicity per cycle (worst ever by patient) Toxicity / Gemcitabine arm / PEFG arm	risk (Not blinded but unlikely that outcome would be influenced by blinding) Blinding of outcome assessment: Low risk (Not reported but unlikely that outcome measurement would be influenced by blinding) Incomplete outcome data: Low risk for data (Missing outcome data unlikely to be related to true outcome) Selective reporting: High risk (Primary outcomes not fully reported) Other sources of bias: Low risk (Study appears free of other sources of bias).

Study details	Participants	Interventions	Methods	Outcomes and Results			Limitation (risk of bias)
	skin and other neoplasms without evidence of disease at least from 5 years		Arm 2: PEFG regimen (40 mg/m2 cisplatin and epirubicin on day 1, 600 mg/m2 gemcitabine on days 1 and 8, and 200 mg/m2 5-Fluororacil daily on days 1–28) every 4 weeks for 3 months. Chemoradiotherapy initiated between 2-4 weeks after completion of CT, consisting of 54–60 Gy in 27–30 fractions with a concurrent continuous infusion of 250mg/m2 5-Fluororacil daily or 625 mg/m2 capecitabine twice daily. Adverse events NCI Common Toxicity Criteria, v2. Statistical analyses ITT analysis for all outcomes except safety analysis for toxicity	Granulocytes Platelets Liver	3 (3) 0 (0) 0 (0)	25 (23) 3 (3) 2 (1)	
Full Citation Schmidt, J., Abel, U., Debus, J., Harig, S., Hoffmann, K., Herrmann, T., Capussotti, L. et al. (2012). Open-label, multicenter, randomized phase III trial of adjuvant chemoradiation plus interferon Alfa-2b versus	N= 132 resected PC patients (unclear # of centres/countries) Arm 1=64 (ITT) Arm 2=68 (ITT) Inclusion Histologically proven resected	Arm 1: Chemotherapy (Folinic Acid + 5-FU) Arm 2: Chemotherapy (5-FU) + chemoradio immunother	CapRI study Study protocol available, Knaebel et al (2005), BMC Cancer, 5(37), ISRCTN62866759 Randomisation (From protocol) A block-randomisation-list generated via computer system. Sealed	Overall survival Disease-free survival Adverse events Quality of life Chemotherapy vs chemoradioimmunotherapy Overall survival Median follow up (months; ITT)=42.7			Overall high risk of bias. Random sequence generation: Low risk (computer-generated 1:1 blocked randomisation list) Allocation concealment: Low

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
fluorouracil and folinic acid for patients with resected pancreatic adenocarcinoma. Journal of Clinical Oncology, 30(33), 4077-4083. Country/ies where the study was carried out Germany, Italy [not clear whether other countries] Study type Phase III open-label RCT Aim of the study To compare adjuvant chemotherapy (5-FU) + chemoradiotherapy (5-FU + Cisplatin + interferon alpha-2b) with 5-FU plus folinic acid in a randomized, controlled, prospective, multicenter phase III trial Study dates: August 2004 to July 2006 Source of funding: Supported by a grant from the Manfred Lautenschlager Foundation.	(R0 or R1) pancreatic adenocarcinoma Karnofsky performance score≥70 within 12 weeks of operation Written and oral informed consent Exclusion Known hypersensitivity to IFN α-2b, autoimmune disease or depression	apy (RT+5-FU + Cisplatin + interferon α-2b)	randomisation list stored in investigator file. Patients randomised using sealed opaque envelopes in the independent study centre at the Department of Surgery until informed consent attained and diagnostic procedures ruled out any contra-indication for participation in this trial. Treatment Arm 1: bolus injections of 20 mg/m2 folinic acid and 425 mg/m2 fluororacil given on 5 consecutive days every 28 days for six cycles Arm 2: Continuous infusion 200 mg/m2 fluororacil per day, 30 mg/m2 cisplatin per week, and 3 million units of interferon α-2b three times a week for 5.5 weeks combined with external beam radiation (50.4 Gy in 28 fractions) followed by two cycles of continuous fluororacil (days 64 to 101 and days 120 to 161). Patients treated in arm 2 were challenged 4 to 6 days before therapy with a single dose of IFN α-2b. Nonsteroidal anti-inflammatory drugs and corticosteroids were avoided	Median OS (arm 2 vs 1) HR=1.04 (95%CI, 0.66-1.53), log rank p=0.99) Median OS from date of resection (arm 1 vs arm 2; months; ITT): 28.5 (95%CI, 20.4-38.6) vs 26.5 (95%CI, 21.6-39.5) Median follow up (months; PPA)=45.9 Median OS from date of resection (arm 1 vs arm 2; PPA): 28.5 (95%CI, 19.5-38.6) vs 32.1 (95%CI, 22.8-42.2) Treatment effect unadjusted for covariates (arm 2 vs arm 1), log rank p=0.49 (HR not provided) Treatment effect adjusted for covariates (using Cox proportional hazards model) (arm 2 vs arm 1): HR=1.2 (95%CI, 0.49-2.95). Age, type of surgery, log(carcinoembryonic antigen), and log(CA19-9) were retained as possible confounders in final model Disease-free survival Median DFS (months; PPA): 11.5 (95%CI, 9.8-17.6) vs 15.2 (95%CI, 10.3-24.8) Time from recurrence to death (months; PPA): 12.3 (95%CI, 9.3-14.4) vs 10.2 (95%CI, 7.6-13) Adverse events No adverse events resulting in death # of patients having total Grade 3 or 4 toxicities (PPA): 9/53 (16%) vs 45/57 (85%) # of Grade 3 and 4 toxicities	risk (Central allocation procedure) Blinding of participants and personnel assessments: Low risk for survival data (Not reported but unlikely that outcome would be influenced by blinding); High risk for QoL data (Not blinded and outcome likely to be influenced by this) Blinding of outcome assessment: Low risk (Not reported but unlikely that outcome measurement would be influenced by blinding) Incomplete outcome data: Low risk (Reasons for missing outcome data unlikely to be related to true outcome)

Study details	Participants	Interventions	Methods	Outcomes and Results					Limitation (risk of bias)
			if possible during IFN α-2b treatment. Because major combined electrolyte deficiency was observed in some patients, an intensive electrolyte monitoring and prophylactic substitution treatment was performed. Adverse events Common Toxicity Criteria Quality of life Assessed using EORTC Quality of Life Questionnaire (QLQ) C30, EORTC QLQ-PAN26 assessing pancreatic cancer-specific symptoms; Centre for Epidemiologic Studies Depression Scale Statistical analyses ITT analysis for overall survival PPA for DFS, adverse events, and QoL	Toxicities	Arm 1 (n=57)	Arm 2 Cycle 1 (n=53)	Arm 2 Cycle 2 (n=51)	Arm 2 Cycle 3 (n=57)	Selective reporting: High risk (One or more outcomes of interest are reported incompletely) Other sources of bias: High risk (Kaplan-Meier curves for overall and disease-free survival cross, proportional hazards not satisfied)
				Neutropenia	0	52	2	0	
				Hypovolemia/electrolyte disturbance	1	10	0	0	
				Nausea/vomiting	1	8	0	0	
				Anaemia	0	3	0	0	
				Diarrhoea	10	4	0	0	
				Thrombocytopenia	0	2	0	0	
				Other	1	14	0	2	
				# of Grade 4 toxicities					

Study details	Participants	Interventions	Methods	Outcomes and Results			Limitation (risk of bias)
				Toxicities	Arm 1 (n=57)	Arm 2 Cycle 1 (n=53)	
				Acute renal insufficiency	0	1	
				Neutropenia	0	7	
				Hypovolemia/electrolyte disturbance	0	1	
				Hand-foot syndrome	0	1	
				Nausea/vomiting	0	1	
				Diarrhoea	1	0	
				Quality of life (arm 1=35, arm 2=50, unless otherwise noted) EORTC QLQ-30 scores Dyspnea: 18.2 (range 0-93.4) vs 24.3 (range 0-70.1), p=0.53 Role functioning: 69.5 (22.5) vs 55.6 (22.6), p=0.08 [higher score worse] Social functioning: 74.5 (19.4) vs 64.5 (24), p=0.061 Global Health Status (arm 1=36): 62.8 (14.6) vs 55.5 (16.4), p=0.024			

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
				Nausea/vomiting (arm 1=36): 8.2 (13.3) vs 15.9 (15.1), p=0.01 [higher score worse] Appetite loss (arm 1=36): 18.2 (range 0-71.3; 25th percentile=0; 75th percentile=31) vs 29.8 (range 0-90.5; 25th percentile 10.8; 75th percentile=41), p=0.04 [higher score worse] Constipation (arm 1=36): 9.2 (range 0-50) vs 13.6 (range 0-64.9), p=0.055 [higher score worse] EORTC QLQ-PAN26 No significant differences on any parameter (data not provided) CES Depression scale Box plots but no data provided	
Full Citation Takada, T., Amano, H., Yasuda, H., Nimura, Y., Matsushiro, T., Kato, H., Nakayama, T. et al. (2002). Is postoperative adjuvant chemotherapy useful for gallbladder carcinoma? Cancer, 95(8), 1685-1695. Country/ies where the study was carried out: Japan Study type: RCT Aim of the study:	N= 173 resected PC patients from 31 institutions Arm 1=89 Arm2=84 Inclusion Histologically confirmed, preoperative diagnosis of carcinoma of the pancreas, gallbladder, bile duct, or ampulla of Vater Stage II–IV disease	Arm 1: Chemotherapy (5-FU + mitomycin C) Arm 2: No adjuvant therapy	Data only for pancreatic cancer group only Randomisation Participants allocated on day of surgery into the postoperative adjuvant chemotherapy group (MF regimen arm) or the surgery alone group (control arm). A randomized design, stratified according to institution and disease, was used. Treatment Arm 1: intravenous infusion 6 mg/m2 mitomycin C on day of surgery, then slow intravenous infusion 310 mg/m2 5-fluororacil in 2	Overall survival Disease-free survival Quality of life Chemotherapy vs No adjuvant therapy Overall survival OS at 5 years: 11.5% vs 18%, n.s. Observed events (death) at 5 years: 70/89 vs 69/84 5-year survival rate in curative resection patients (n=92) by arm: 8/45 vs 13/47 (17.8% vs 26.6%), log rank p=0.4544 Observed events (death) at 5 years in curative: 37/45 vs 34/47 5-year survival rate in non-curative resection patients (n=66) by arm: 3.1% vs 3.7%, log rank p=0.4544	Overall high risk of bias. Random sequence generation: Unclear risk (Insufficient information about randomisation method) Allocation concealment: Unclear risk (Insufficient information) Blinding of participants and personnel assessments: Low

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
To evaluate the effect of postoperative adjuvant therapy with mitomycin C (MMC) and 5-fluorouracil (5-FU) (MF arm) versus surgery alone (control arm) on survival and disease-free survival (DFS) for each specific disease comprising resected pancreaticobiliary carcinoma (pancreatic, gallbladder, bile duct, or ampulla of Vater carcinoma) separately. Study dates: April 1986 to June 1992 Source of funding: Not reported	Confirmed resection of the primary lesion Aged < 75 years Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–3 No previous surgery, radiotherapy or chemotherapy No serious concomitant disease No concurrent or non-concurrent multicentric tumour or double tumour At the start of treatment, a leukocyte count ≥ 4000/mm3, a platelet count ≥ 100,000/mm3, liver enzymes (aspartate aminotransferase and alanine aminotransferase) ≤ 100 U, and		courses of treatment for 5 consecutive days (each during 1 and 3 weeks after resection), then daily oral 100 mg/m2 5-FU from 5th week after resection. Quality of life Assessed by Eastern Cooperative Oncology Group Performance Status Statistical analysis PPA for each disease examined ITT analysis as reference data	Observed events (death) at 5 years in non-curative: 35/36 vs 29/30 Disease-free survival DFS at 5 years by arm (n=158): 8.6% vs 7.8%, log rank p=0.8372 Observed events (recurrence) by arm: 74/81 vs 71/77 DFS at 5 years in curative resection patients (n=92) by arm: 13.3% vs 12.8, log rank p=0.2872 DFS at 5 years in non-curative resection patients (n=66) by arm: 2.8% vs 0%, p=0.5482 No significant difference in 5-year DFS between chemotherapy and no adjuvant therapy groups (data not reported). Recurrence of pancreatic carcinoma in 132/145 patients during 5-year follow up period. Quality of life # patients that had performance score of 1-3 pre-resection who improved by one grade or more on ECOG PS: 41/58 vs 39/55 Adverse events No data for pancreatic cancer group provided	risk for survival data (Not blinded but unlikely that outcome would be influenced by blinding); High risk for QoL data (Not blinded and outcome likely to be influenced by this) Blinding of outcome assessment: Low risk (Not blinded but unlikely that outcome measurements would be influenced by blinding) Incomplete outcome data: Low risk (Reasons for missing outcome data unlikely to be related to true outcome) Selective reporting: High risk (One or more outcomes of interest reported incompletely) Other sources of bias: High risk (No

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
	negative urinary protein. Exclusion Extended right or left hepatic lobectomy				Kaplan-Meier curve provided for disease-free survival, not clear whether proportional hazards satisfied).
Full Citation Ueno, H., Kosuge, T., Matsuyama, Y., Yamamoto, J., Nakao, A., Egawa, S., Shimada, M. et al. (2009). A randomised phase III trial comparing gemcitabine with surgery-only in patients with resected pancreatic cancer: Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer. British journal of cancer, 101(6), 908-915. Country/ies where the study was carried out: Japan Study type Phase 3 open-label RCT Aim of the study: To determine whether adjuvant chemotherapy with gemcitabine improves the outcomes of patients with resected pancreatic cancer	N= 118 curatively resected PC patients from 10 centres. Arm 1=58 (ITT) Arm2=60 (ITT) Inclusion Patients who underwent macroscopically curative resection of pancreatic cancer Histologically-proven invasive ductal carcinoma of the pancreas No history of earlier chemotherapy or radiotherapy for pancreatic cancer except intraoperative radiotherapy Age 20–74 years old	Arm 1: Chemotherapy (Gemcitabine) Arm 2: No adjuvant therapy	JSAP-02 trial Randomisation Patients enrolled within 10 weeks after surgery, through fax by the staff at the data centre. Patients were randomly assigned at a 1:1 ratio to either gemcitabine group or the surgery-only group using the minimisation method stratified by resection status (R0 versus R1), pathological stage (I–II versus III–IV) and enrolment centre. Stage classification and the evaluation of resected specimens were performed in accordance with the fifth edition of the tumour–node–metastasis classification system of the International Union Against Cancer. Treatment Arm 1: Gemcitabine 1000 mg/m2 over 30 mins on days 1, 8 and 15 every 4 weeks, repeated for 3 cycles.	Overall survival Disease-free survival Adverse events Chemotherapy vs No adjuvant therapy Overall survival (median, months) All patients Median OS by arm: 22.3 (95% CI, 16.1-30.7) vs 18.4 (95% CI, 15.1-25.3), HR=0.77 (95% CI, 0.51-1.14) (p=0.19) Observed deaths: 45/58 vs 53/60 Estimated OS at 6 months: 94.8% vs 85% Estimated OS at 12 months: 77.6% vs 75% Estimated OS at 18 months: 58.6% vs 53.3% Estimated OS at 24 months: 48.3% vs 40% Estimated OS at 60 months: 23.9% vs 10.6% Recurrence of disease: 44/58 vs 53/60 Disease-free survival (median, months) All patients Median DFS: 11.4 (95% CI, 8-14.5) vs 5 (95% CI, 3.7-8.9), HR=0.6 (95% CI, 0.4-0.89) (p=0.01)	Overall low risk of bias. Random sequence generation: Low risk (1:1 using minimisation method) Allocation concealment: Low risk (Central allocation) Blinding of participants and personnel assessments: Low risk (Not blinded but unlikely that outcome would be influenced by blinding) Blinding of outcome assessment: Low risk (Not blinded but unlikely that outcome measurements would be

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Study dates: April 2002 to March 2005 Source of funding: Supported by funding from the Health and Labour Sciences Research Grant for Clinical Cancer Research from the Ministry of Health, Labour and Welfare, Japan	Karnofsky performance status≥50 Adequate organ function Exclusion Pulmonary fibrosis or interstitial pneumonia Clinically significant pleural effusions Presence of distant metastasis (except distant lymph node metastasis confirmed by resected specimen) Other concomitant malignant disease Active infection History of serious complications related to surgery Active gastrointestinal ulcers History of myocardial		Median dose 667 mgm-2 per week; median relative dose intensity 89%. Patients in the gemcitabine group had laboratory tests and assessment of clinical symptoms every week during the treatment period and every 3 months after completing adjuvant chemotherapy. Arm 2: Patients received no anticancer treatment after surgery, unless there was a confirmed relapse. Patients in this group underwent similar examinations as gemcitabine group every 3 months. Adverse events Assessed with NCI Common Terminology Criteria for Adverse Events, v2. Gemcitabine administration was stopped until recovery if patients developed leukocyte counts of <2000mm-3 or >12,000mm-3, or platelet counts of <75,000mm-3 during chemotherapy. Analyses ITT efficacy analysis; subgroup analysis stratified	Observed recurrence: 44/58 vs 53/60 Estimated DFS at 6 months: 70.7% vs 43.4% Estimated DFS at 12 months: 49% vs 26.7% Estimated DFS at 24 months: 27.2% vs 16.7%. Adverse events in gemcitabine group (n=57) Most common Grade 3 haematological adverse events (AEs) were neutropenia (56%) and leukopenia (23%); Grade 4 were neutropenia (14%) and leukopenia (2%) Grade 3 non-haematological AEs were alanine aminotransferase (ALT) (7%) and aspartate aminotransferase (AST) (5%); Grade 4 were abscess, nausea and anorexia (all 2%). # of patients with Grade 3 or 4 haematological toxicities in gemcitabine group (n=57) Haematological toxicity / Grade 3 / Grade 4 Leukopenia / 13 / 1 Neutropenia / 32 / 8 Anaemia / 2 / 0 Thrombocytopenia / 1 / 0 # of patients with Grade 3 or 4 non-haematological toxicities in gemcitabine group (n=57)	influenced by blinding) Incomplete outcome data: Low risk (Reasons for missing outcome data unlikely to be related to true outcome) Selective reporting: Low risk (Study protocol not available but all expected outcomes fully reported) Other sources of bias: Low risk (Study appears free of other sources of bias)

Study details	Participants	Interventions	Methods	Outcomes and Results			Limitation (risk of bias)
	infarction within 3 months Severe mental disorder Pregnant or lactating women Other serious concomitant systemic disorders incompatible with the trial in the investigator's judgment.		by resection and tumour status Safety analysis included all adjuvant gemcitabine patients.	Non-haematological toxicity Diarrhoea Fever Nausea Anorexia Fatigue AST ALT Abscess	Grade 3 1 1 0 1 1 3 4 0	Grade 4 0 0 1 1 0 0 0 1	
Full Citation Uesaka, K., Boku, N., Fukutomi, A., Okamura, Y., Konishi, M., Matsumoto, I., Morinaga, S. et al. (2016). Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). The Lancet. Country/ies where the study was carried out: Japan Study type: Phase 3 open-label RCT Aim of the study:	N= 375 curatively resected PC patients from 33 hospitals Arm 1=193 (ITT; 190 PPA) Arm 2=192 (ITT; 187 PPA) Inclusion Histologically-proven invasive ductal carcinoma of the pancreas (excluding cystadenocarcinoma, according to the General Rules for the Study of Pancreatic Cancer)	Arm 1: Chemotherapy-1 (Gemcitabine) Arm 2: Chemotherapy-2 (S-1)	JASPAC 01 trial Study protocol in English available at http://www.fuji-pvc.jp/center/jaspac/01/nojoin.aspx?j=1 Randomisation All required sections of a case report form were sent via fax to the CSPOR (Comprehensive Support Project for Oncology Research) data centre by investigators in each hospital. Patients were randomly assigned to either the gemcitabine group or the S-1 group (in a 1:1 ratio) at the data centre by a modified minimisation method, balancing	Overall survival Relapse-free survival Adverse events Quality of life Chemotherapy-1 vs chemotherapy-2 Overall survival (median, month) Per protocol analysis Median OS: 25.5 (95% CI, 22.5-29.6) vs 46.5 (95%CI, 37.8-63.7), HR (arm 2 vs arm 1)=0.57 (95% CI, 0.44-0.72) (non-inferiority p<0.0001; superiority p<0.0001) Observed events: 153/193 vs 114/192 Estimated OS at 3 years: 38.8% (95% CI, 31.9-45.7) vs 59.7% (95% CI, 52.3–66.3) Estimated OS at 5 years: 24.4% (95% CI, 18.6–30.8) vs 44.1% (95% CI, 36.9–51.1) Relapse-free survival (median, months)		Overall low risk of bias. Random sequence generation: Low risk (1:1 using modified minimisation method) Allocation concealment: Low risk (Central allocation) Blinding of participants and personnel assessments: Low risk for survival data (Not blinded but unlikely that outcome would be influenced by blinding); High risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
To investigate the non-inferiority of S-1 to gemcitabine as adjuvant chemotherapy for pancreatic cancer in terms of overall survival Study dates: April 2007 to June 2010, follow up to Jan 2016 Source of funding: Funding from Pharma-Valley Center, Shizuoka Industrial Foundation, and Taiho Pharmaceutical	Pathologically-documented stage I, II, or stage III with combined resection of the coeliac artery (according to the TNM Classification of Malignant Tumours, using the methods recommended in the General Rules for the Study of Pancreatic Cancer) No local residual tumour (R0) or microscopic residual tumour (R1) No cancer cells in intraoperative peritoneal lavage fluid cytological examination No distant metastasis or malignant ascites Possibility of adequate oral intake		adjustment factors of residual tumour status (R0 or R1), nodal status (no regional lymph node metastasis or regional lymph node metastasis), and study site. The algorithm was created at the Japan Clinical Research Support Unit (JCRSU), and to which the investigators were masked. Investigators were not masked to patients' allocated treatment. Patients were aware of their group assignment. Treatment Arm 1: intravenous gemcitabine 1000 mg/m² over 30 min on days 1, 8, and 15 (once every week), followed by a week rest period. This cycle was repeated every 4 weeks for up to six cycles. Mean dose=594 mg/m2 (SD=137); median dose=632 mg/m2 (IQR 509-711). Median relative dose intensity=84% (IQR 68-95). Treatment started only if adequate bone marrow, liver, and kidney function in measurements (see inclusion criteria for details); no inadequately-controlled	Per protocol analysis Median DFS: 11.3 (95% CI, 9.7–13.6) vs 22.9 (95%CI, 17.4–30.6), (arm 2 vs arm 1) HR=0.60 (95% CI 0.47–0.76) (p<0.0001) Recurrence of disease: 149/190 vs 123/187 patients Estimated DFS at 3 years: 22.6% (95% CI, 17.0–28.8) vs 39.2% (95% CI, 32.2–46.2) Estimated DFS at 5 years: 16.8% (95% CI, 11.9–22.5) vs 33.3% (95% CI, 26.7–40.1) Most frequent site of recurrence in gemcitabine group was liver (29%) and local recurrence (26%); in S-1 group, local recurrence (19%) and liver (19%) Adverse events (gemcitabine, n=190; S-1, n=187) Two grade 5 infections (cholangitis in one patient; pneumonia in other) reported in gemcitabine group. Grade 3 Grade 4 Toxicities: Gemcitabine / S-1 / Gemcitabine / S-1 / p value Gr e 3 or Leucocytes/WBC: 61 / 7 / 13 / 9 / <0 00	for QoL data (Not blinded and outcome likely to be influenced by this) Blinding of outcome assessment: Low risk (Not blinded but unlikely that outcome measurement would be influenced by blinding) Incomplete outcome data: Low risk (Reasons for missing outcome data unlikely to be related to true outcome) Selective reporting: Low risk (Study protocol available and all outcomes fully reported) Other sources of bias: Low risk (Study appears free of other sources of bias)

Study details	Participants	Interventions	Methods	Outcomes and Results					Limitation (risk of bias)
	Aged 20 years or older Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 No history of chemotherapy or radiotherapy within the past 3 years Enrolment within 10 weeks after resection of pancreatic cancer Adequate bone marrow, liver, and kidney function in measurements taken within 7 days before registration Written informed consent. Exclusion Previous treatment with gemcitabine or S-1 Confirmed recurrence of		diarrhoea; no other Grade 2+ non-haematological AEs as judged by investigator. Arm 2: oral dose of S-1 40 mg for body-surface area < 1.25 m², 50 mg for body-surface area of ≥1.25 m² and <1.5 m², or 60 mg for body-surface area ≥1.5 m², twice per day for 28 consecutive days followed by a 14-day rest (one cycle). This cycle was repeated every 6 weeks for up to four cycles. Mean dose 301 mg/m2 (SD=64); median dose 317 mg/m2 (IQR 288-342). Median relative dose intensity=89% (IQR 85-100). Treatment started only if same criteria for gemcitabine group satisfied; additionally, serum creatinine concentrations of ≤1.5 mg/dL. Adverse events NCI Common Terminology Criteria for Adverse Events, v3. Analyses Per protocol survival analysis ITT sensitivity analysis	Neutrophils	86	21	52	4	<0.000	
				Haemoglobin	18	16	15	10	0.369	
				Platelets	4	0	14	9	0.097	
				Aspartate aminotransferase	10	2	0	0	0.011	
				Alanine aminotransferase	8	1	0	0	0.0	
				Bilirubin	0	2	1	0	0.502	
				Creatinine	0	1	1	0	0.98	
				Fatigue	9	9	0	1	0.766	
				Stomatitis	0	5	0	0	0.035	
				Anorexia	10	15	1	0	0.331	

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
	disease before registration Moderate or more severe pleural effusion or ascites on chest radiograph and abdominal CT Pulmonary fibrosis or interstitial pneumonia clearly observed in chest radiograph Inadequately controlled watery diarrhoea or diabetes Heart failure of class III or IV (according to New York Heart Association functional classification) Myocardial infarction in 6 months before registration. Active infectious disease (e.g. pyrexia of 38°C or higher;			Nausea 3 7 2 0 0.592 Vomiting 1 3 1 0 0.601 Diarrhoea 0 8 0 1 0.022 Fever 1 5 0 0 0.062 Febrile neutropenia 3 1 0 0 0.331 Infection 6 2 2 0 0.081 Two grade 5 infections (cholangitis in one patient; pneumonia in other) reported in gemcitabine group. Quality of life EQ-5D score treatment x type interaction: p=0.0598. Difference in EuroQoL-5 dimensional questionnaire (EQ-5D) since randomisation: At 3 months: p=0.2 At 6 months: p=0.22 At 12 months: p=0.0016 At 24 months: p=0.0082	

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
	excluding viral hepatitis) Blood transfusion in 2 weeks before trial registration Other serious complications (e.g. heart failure, kidney failure, or liver failure) Complicating psychiatric disorder or psychological symptoms Serious drug allergy Active multiple primary cancers Receiving flucytosine, phenytoin, or warfarin potassium Pregnant or breastfeeding women, or who are of childbearing potential, or were willing to bear or conceive children				

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
	Men who were willing to conceive a child If investigator judged participation to be incompatible with the safety of the study.				
Full Citation Van Laethem, J. L., Hammel, P., Mornex, F., Azria, D., Van Tienhoven, G., Vergauwe, P.,Collette, Let al. (2010). Adjuvant gemcitabine alone versus gemcitabine-based chemoradiotherapy after curative resection for pancreatic cancer: a randomized EORTC-40013-22012/FFCD-9203/GERCOR phase II study. Journal of clinical oncology, 28(29), 4450-4456. Country/ies where the study was carried out: Various European countries (EORTC + ROG) Study type: Phase II RCT	N= 90 curative resection patients from 29 centres Arm 1=45 Arm 2=45 Inclusion Histologically confirmed pancreatic head adenocarcinoma with R0 duodenopancrea-tectomy (Whipple procedure or pylorus-preserving procedure), documented histologic examination of surgical margins (including retroperitoneal margins), and documented	Arm 1: Chemotherapy (Gemcitabine) Arm 2: Gemcitabine-based chemoradiotherapy	Randomisation Initial trial design compared CRT with no adjuvant therapy. Major amendment to the protocol on September 7, 2004, when the control arm was changed to gemcitabine alone. After this date, patients were randomly assigned (1:1) to gemcitabine alone for four cycles of 4 weeks (control arm) and gemcitabine for two cycles followed by gemcitabine weekly and concurrent radiation therapy (experimental arm). Patients were stratified by institution, WHO performance status (PS), and nodal status. Treatment Arm 1: Four cycles of 1000 mg/m2 gemcitabine by 30-minute infusion during 3 consecutive weeks followed by 1 week of rest.	Overall survival Disease-free survival Adverse events Chemotherapy vs CRT Overall survival Median OS by arm (months): 24.4 (95%CI, 21.5- infinity) vs 24.3 (95%CI, 20.5-infinity) Observed events (death) by arm=26/45 vs 25/45 Estimated OS at 2 years (ITT): 50.2% (95%CI, 34.8-63.8) vs 50.6% (95%CI, 34.3-64.8) Estimated OS at 2 years (treated population): 53.8% (95%CI, 37.6-67.6) vs 53.8% (95%CI, 35.4-69.1) Disease-free survival Median DFS by arm (months; ITT): 10.9 (95%CI, 8.3-16) vs 11.8 (95%CI, 10.1-19.3) Median DFS by arm (treated population): 10.9 (95%CI, 8.3-16.7) vs 12.4 (95%CI, 10.1-19.3) Observed events (recurrence) by arm: 37/45 vs 34/45	Overall high risk of bias. Random sequence generation: Unclear risk (1:1 but insufficient information about randomisation method) Allocation concealment: Unclear risk (Insufficient information) Blinding of participants and personnel assessments: Low risk (Not reported but unlikely that outcome would be influenced by blinding) Blinding of outcome assessment: Low risk (Not reported

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
Aim of the study: To evaluate the feasibility and tolerability of a gemcitabine-based CRT regimen after R0 resection of pancreatic head cancer. Study dates: September 2004 to January 2007 Source of funding: Supported in part by an educational grant from Eli Lilly, by Grants No. 5U10CA11488-30 through 5U10CA011488-40 from the National Cancer Institute, and by a donation from the Federation Belge Contre le Cancer through EORTC trust. Study drugs provided by Eli Lilly.	lymph node examination (<10 v ≥10; International Union Against Cancer [UICC] TNM classification 2006) Completely recovered from surgery within 8 weeks. Completed abdominal spiral computed tomography (CT) scan maximum 8 weeks before random assignment to exclude manifest distant metastases. Aged > 18 years old WHO PS 0 to 2 Adequate bone marrow, liver, and renal functions Written informed consent. Exclusion		Arm 2: two cycles of 1000 mg/m2 gemcitabine 30-minute infusion during 3 consecutive weeks followed by 1 week of rest. Cycle 1 treatment was given on days 1, 8, and 15; cycle 2 treatment was given on days 29, 36, and 43. After the 1-week rest, CRT was started on day 57: 300 mg/m2 gemcitabine by 30-minute infusion once per week, given 4 hours before radiation (50.4 Gy in 28 fractions, 1.8 Gy per fraction) for 5 to 6 weeks. Adverse events NCI Common Terminology Criteria for Adverse Events, v2 Statistical analyses ITT analysis Dose delays not considered treatment failures Sensitivity analysis excluding those who did not start treatment or those who did not have RT.	Adverse events Grade 4 WBC, platelet, haemoglobin, vomiting or diarrhoea toxicities (Predefined coprimary toxicity end point): 0/42 vs 2/43 Grade 3-related late toxicities: 0/42 vs 3/43 (one had anorexia and gastritis; one had epigastric pain; one had insulin requirement) Grade 3 / Grade 4 Toxicity: Gemcitabine (n=42) / CRT (n=43) / Gemcitabine (n=42) / CRT (n=43) White blood cell count: 6 / 7 / 0 / 0 Neutrophils: 15 / 12 / 3 / 2 Platelets: 0 / 1 / 0 / 0 Haemoglobin: 0 / 2 / 0 / 1 Serum glutamicpyruvi: 5 / 5 / 0 / 0	but unlikely that outcome measurement would be influenced by blinding) Incomplete outcome data: Low risk (Reasons for missing outcome data unlikely to be related to true outcome) Selective reporting: High risk (One or more outcomes of interest reported incompletely) Other sources of bias: High risk (Kaplan-Meier curves for overall survival cross, proportional hazards not satisfied)

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
	Previous chemotherapy or radiotherapy Previous or coexistent malignant disease (except basal cell carcinoma or carcinoma in situ of the cervix) Periampullary, neuroendocrine, intraductal papillary, or mucinous tumours Incomplete resection			c transaminase Fatigue 2 3 0 0 Fever 0 3 0 0 Weight loss 0 1 0 0 Anorexia 0 1 0 1 Nausea 0 1 0 0 Vomiting 0 0 0 1 Gastritis 0 1 0 1 Diarrhoea 0 0 0 1 Haemorrhage 1 0 0 1 Other GI toxicity 0 0 0 1 Other 2 7 1 1	
Full Citation Yoshitomi, H., Togawa, A., Kimura, F., Ito, H., Shimizu, H., Yoshidome,	N= 99 resected PC patients from 19 institutions Arm 1=49	Arm 1: Chemotherapy-1	Randomisation Patients were registered within 10 weeks of surgery and were then randomly	Overall survival Disease-free survival Adverse events	Overall high risk of bias. Random sequence generation: Low

Study details	Participants	Interventions	Methods	Outcomes and Results	Limitation (risk of bias)
H., Miyazaki, M. et al. (2008). A randomized phase II trial of adjuvant chemotherapy with uracil/tegafur and gemcitabine versus gemcitabine alone in patients with resected pancreatic cancer. Cancer, 113(9), 2448-2456. Country/ies where the study was carried out: Japan Study type: Phase II RCT Aim of the study: To estimate the possible efficacy of a UFT combination with gemcitabine, compared with gemcitabine alone, for adjuvant chemotherapy in patients with resected pancreatic cancer Study dates: May 2002 to December 2005 Source of funding: Partially supported by a grant from the Ministry of Education, Culture,	Arm 2=50 Inclusion Pancreatic cancer histologically verified as invasive ductal carcinoma and who had undergone macroscopic complete resection Aged ≥ 20 years old and ≤79 years old at time of registration Absence of active infection, significant cardiac disease, brain disease, and/or active malignancies other than pancreatic cancer Adequate hematologic, renal, and hepatologic function Exclusion Patients with prior radiation or neoadjuvant	(Gemcitabine) Arm 2: Chemotherapy-2 (Gemcitabine + UFT [tegafur/uracil])	assigned to 1 of 2 groups: adjuvant chemotherapy with a gemcitabine only group and a gemcitabine + UFT group. Treatment Patients who received 4 cycles of treatment were considered completers. Patients were allowed to continue same therapy after 4 cycles Arm 1: at least 4 cycles of gemcitabine every 4 weeks. Each chemotherapy cycle consisted of 3 weekly intravenous infusion of 1000 mg/m2 gemcitabine during a 30-minute period, followed by a 1-week pause. Arm 2: same as arm 1 plus 200 mg/day UFT continuously. Adverse events Toxicity assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events v2 and v3.	Chemotherapy-1 vs chemotherapy-2 Overall survival Median OS by arm (months): 29.8 vs 21.2, log rank p=0.28 Observed events (death): 26/49 vs 31/50 Estimated OS at 1 year: 85.7% vs 80% Estimated OS at 3 years: 46.9% vs 30.4% Disease-free survival Median DFS by arm: 12 vs 12.3, log rank p=0.67 Estimated DFS at 1 year: 49% vs 50% Estimated DFS at 3 years: 21.6% vs 17.7% Observed events (recurrence): 36/49 vs 39/50 Local recurrence: 13/49 vs 17/50 Most frequent primary site of distant metastasis was liver (12/49 vs 13/50). Adverse events No Grade 4 or higher toxicities recorded. All toxicities reversible and resolved with conservative treatment only. Grade 3 Toxicities: Gemcitabine (n=49) / Gemcitabine +UFT (n=50) Total: 15 / 12 Leukocytes (WBC): 11 / 9 Haemoglobin: 4 / 2	risk (computer-generated procedure) Allocation concealment: Low risk (Central allocation) Blinding of participants and personnel assessments: Low risk (Not blinded but unlikely that outcome measurement would be influenced by blinding) Blinding of outcome assessment: Low risk (Not blinded but unlikely that outcome measurement would be influenced by blinding) Incomplete outcome data: Low risk (Reasons for missing data unlikely to be related to true outcome)

Study details	Participants	Interventions	Methods	Outcomes and Results			Limitation (risk of bias)
Science, Sports, and Technology of Japan.	chemotherapy or with distant metastasis (except minimal para-aortic lymph node metastasis) Patients with carcinoma in situ			Platelets Anorexia Aspartate aminotransferase/alanine aminotransferase Glucose intolerance	3 1 0 0	0 1 1 1	Selective reporting: Low risk (Study protocol not reported but all expected outcomes reported) Other sources of bias: High risk (Kaplan-Meier curves for overall survival and disease-free survival cross, proportional hazards not satisfied)

1

2

F.153 Follow-up for people with resected pancreatic cancer

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Reeder-Hayes, K. E., Freburger, J., Feaganes, J., Peacock Hinton, S., Henderson, L. M., Massing, M., Schenck, A. P., Stearns, S. C., Carpenter, W. R.,	Sample size n = 6691 (n= 4652 analysed, 7 excluded as diagnosed with lymphoma, 2021 excluded as died within 45 days of diagnosis) Characteristics	Interventions Follow-up imaging: PET (reference standard) vs. CT/MRI only or	Details Sample Individuals who did not have stage IV disease were classified as "surgical" if their first treatment after	Results Association of imaging use and adjusted treatment duration In adjusted negative binomial	Limitations Newcastle-Ottawa Quality Assessment Scale: Cohort Studies Selection 1) Representative of the exposed

Covariate	Overall: n (%)	PET (n= 578)	CT/MRI (n=2409): n (%)	Never imaged (n=1665): n (%)	P value

Study details	Participants						Interventions	Methods	Outcomes and Results	Comments
Chen, R. C., Khandani, A. H. Comparative effectiveness of follow-up imaging approaches in pancreatic cancer, Journal of Comparative Effectiveness ResearchJ, 3, 491-502, 2014 Ref ID 482253 Country/ies where the study was carried out: USA Study type: Retrospective cohort study Aim of the study: To describe current patterns of PET use in follow-up, determine whether exposure to PET compared with CT/MRI alone is associated with use of radiation and chemotherapy and determine			: n (%)				None	diagnosis was surgery within 60 days, and "borderline" if they did not receive surgery within 60 days. The remaining patients were classified as "metastatic" if they had stage IV disease or "unknown" if they had unknown stage in the registry data. These groups were intended to mirror categories used in the clinical management of pancreatic cancer, in which clearly resectable patients generally proceed to initial surgery while borderline resectable	models (data not shown), survival adjusted chemotherapy treatment duration for patients receiving CT/MRI or never imaged was lower than that of patients receiving PET (HR: 0.82; 95% CI: 0.72-0.93 and HR: 0.26; 95% CI: 0.22-0.31, respectively) Radiation treatment duration for patients receiving CT/MRI was not significantly different from that for patients receiving PET (HR:	cohort - Somewhat representative of surgically resected pancreatic cancer cohort, limitations in the categorisation of patients as surgical, borderline or metastatic is imperfect, as it relies on registry and claims data alone to approximate clinical intent. Thus, some patients included in the borderline category may not have been treated with curative intent * 2) Selection of the non exposed cohort - drawn from the same SEER and CDC-funded cancer
	Age (mean = 77, range = 66-103)					<0.0001				
	66-69	792 (17)	138 (24)	470 (19)	184 (11)					
	70-74	1057 (23)	152 (26)	619 (26)	286 (17)					
	75-79	1105 (24)	166 (29)	577 (24)	362 (22)					
	80+	1698 (36)	122 (21)	743 (31)	833 (50)					
	Race					0.1139				
	white	3674 (79)	475 (82)	1885 (78)	1314 (79)					
	non-white	978 (21)	103 (18)	524 (22)	351 (21)					
	Sex					0.0068				
	Male	2003 (43)	266 (46)	1070 (44)	667 (40)					
	%uninsured					0.0405				

Study details	Participants						Interventions	Methods	Outcomes and Results	Comments
whether exposure to PET compared with CT/MRI alone is associated with mortality. Study dates: Retrospective cohort design to examine individuals with newly diagnosed pancreatic adenocarcinoma in 2003-2007 Registry data were linked with Medicare claims data (2002-2008) Source of funding: Supported by the agency for healthcare research and quality (AHRQ), US department of health and human services (HHS) as part of the developing evidence to inform decisions about	Lower (<20%)	3336 (72)	398 (69)	1701 (71)	1237 (74)			patients are often treated initially with non-surgical modalities with the goal of downstaging disease to permit surgery. The treatment-pathway groups rather than disease stage alone were used to classify patients based on the hypothesis that follow-up strategies would be determined by initial treatment as well as stage. Definition of study variables The primary exposure was imaging modality (PET, traditional imaging including CT and MRI, or never imaged)	0.96; 95% CI: 0.85-1.08), but adjusted duration for patients with no follow-up imaging was significantly lower (HR; 0.59; 95% CI: 0.48-0.73) Effect of follow-up imaging on mortality using a time-varying exposure model (n= 3923) Follow-up imaging Overall HR (95% CI): PET (reference) 1.00; CT/MRI 0.86 (0.77-0.95); None 0.88 (0.77-1.00) Surgical group HR (95% CI):	registries as exposed cohort * 3) Ascertainment of exposure - secure medicare analytical files for inpatient, outpatient, carrier and durable medical equipment. The area resource files were used to obtain country-level socio-demographic information as well as measures of healthcare supply * 4) Demonstration that outcome of interest was not present at start of study - yes, individuals with a new, single primary cancer diagnosis of pancreatic malignancy
	Higher (>20%)	1316 (28)	180 (31)	708 (29)	428 (26)					
	Comorbidity index					0.0063				
	0	1965 (42)	273 (47)	1033 (43)	659 (40)					
	1	1438 (31)	174 (30)	761 (32)	503 (31)					
	2+	1198 (26)	129 (22)	599 (25)	470 (29)					
	Region of USA					<0.0001				
	CA	3018 (65)	426 (74)	1555 (65)	1037 (62)					
	UT	217 (5)	12 (2)	108 (4)	96 (6)					
	NC	1417 (30)	139 (24)	746 (31)	532 (32)					
	Year of diagnosis					<0.0001				
	2003	864 (18)	47 (8)	476 (20)	341 (20)					

Study details	Participants						Interventions	Methods	Outcomes and Results	Comments
effectiveness program. Lead author supported by National Research Service Award training grant from AHRQ, US department of HHS and by a building interdisciplinary careers in womens health career development grant from the NIH.	2004	963 (21)	93 (16)	502 (21)	368 (22)			during follow-up, defined as any imaging that occurred 45 days or more after the cancer registry diagnosis date. Imaging use was determined from procedure codes in the Medicare claims data. For registries that only included diagnosis month, the 15th day was designated as the diagnosis date. Within this article, "PET imaging" refers to claims for PET with or without concurrently aquired CT. The vast majority (97%) of PETs included concurrently	PET (reference) 1.00; CT/MRI 0.66 (0.52-0.83); None 0.17 (0.10-0.28) Borderline group HR (95% CI): PET (reference) 1.00; CT/MRI 0.95 (0.81-1.13); None 1.02 (0.84-1.24) Metastatic group HR (95% CI): PET (reference) 1.00; CT/MRI 0.90 (0.76-1.08); None 0.99 (0.81-1.22) Effect of early follow-up imaging on survival beyond 180 days (n= 2010)	(ICD-O-2 codes C250-C259) were identified in the registries * (4 stars) - Low risk of bias Comparability 1) Comparability of cohorts on the basis of the design or analysis - study controls for treatment duration, misattribution of survival time, and immortal time bias. However, no control over specific confounders between patient groups, other than potential covariates (not specified), a table of characteristics between interventions and associated p-values.
	2005	923 (20)	122 (21)	492 (20)	309 (19)					
	2006	974 (21)	155 (27)	471 (20)	348 (21)					
	2007	928 (20)	161 (28)	468 (19)	299 (18)					
	Initial treatment pathway					0.0147				
	Surgery	500 (11)	162 (28)	310 (13)	28 (2)					
	Borderline	1477 (32)	201 (35)	768 (32)	508 (31)					
	Metastatic	1946 (42)	180 (31)	993 (41)	773 (46)					
	Unknown	729 (16)	35 (6)	338 (14)	356 (21)					
	Staging modality at diagnosis					<0.0001				
	PET + other staging	551 (12)	134 (23)	285 (12)	132 (8)					

Study details	Participants						Interventions	Methods	Outcomes and Results	Comments
	CT/MRI only	3760 (81)	417 (72)	1943 (81)	1400 (84)			acquired CT, which is a limited CT study routinely performed alongside a PET scan and used clinically for anatomic localisation of PET findings only. Such studies can be distinguished in claims because they are billed with the PET in a single claim on a single day. Concurrently aquired CTs were not counted as distinct CT exposures for the purposes of this analysis. Outcome variables included survival-adjusted chemotherapy treatment duration,	Follow-up imaging Overall HR HR (95% CI): PET (reference) 1.00; CT/MRI 0.98 (0.84-1.16); None 0.94 (0.78-1.14) Surgical group HR (95% CI): PET (reference) 1.00; CT/MRI 0.80 (0.57-1.14); None 0.56 (0.37-0.85) Borderline group HR (95% CI): PET (reference) 1.00; CT/MRI 1.04 (0.82-1.33); None 0.90 (0.69-1.19) Metastatic group HR (95% CI): PET (reference)	(0 stars) - Unclear risk of bias Outcome 1) Assessment of outcome - record linkage, categorisation of patients as surgical, borderline, or metastatic is imperfect, as it relies on registry claims data alone to approximate clinical intent. Thus, some patients included in the borderline category may not have been treated with curative intent. 2) Was follow-up long enough for outcomes to occur -Not specified in protocol, but given the progressive and aggressive nature of the
	CT/MRI only	3760 (81)	417 (72)	1943 (81)	1400 (84)					
	No scan	341 (7)	27 (5)	181 (7)	133 (8)					
	Received curative intent surgery	1073 (23)	233 (40)	434 (18)	38 (2)					
	Follow-up imaging									
	Included PET	578 (12)								
	Included CT/MRI only	2409 (52)								
	No follow-up imaging	1665 (36)								
	Area of residence					0.0007				
	Metro area	3914 (84)	517 (89)	2018 (84)	1379 (83)					
	Nonmetro area	738 (16)	61 (11)	391 (16)	286 (17)					
	Hospitals with oncology services in county					0.006				

Study details	Participants						Interventions	Methods	Outcomes and Results	Comments
	Yes	4146 (89)	536 (93)	2146 (89)	1464 (88)			survival-adjusted radiation treatment duration and all-cause mortality. For chemotherapy treatment duration, we calculated the number of days receiving chemotherapy as the time between the first and last claims for chemotherapy infusion. If a gap of >30 days was present, the prior course of chemotherapy was considered ended and the next subsequent chemotherapy claim marked the beginning of a new course. The number of days on	1.00; CT/MRI 1.01 (0.76-1.38); None 1.29 (0.92-1.83)	disease analyses for survival beyond 45 and 180 days seems appropriate * 3) Adequacy of follow up of cohorts - follow-up rate differs for different analyses, main unadjusted analysis - drop out 31%, but all accounted for, time-varying exposure model and early follow-up model included more drop outs and did not explain their nature (1 star) - High risk of bias Other information
	No	506 (11)	42 (7)	263 (11)	201 (12)					
	Outcomes									
	Median overall survival (days)	177	489	236	86					
	Received chemotherapy	2984 (64)	510 (88)	1830 (76)	644 (39)	<0.0001				
	Number of days chemotherapy (mean)	97.5	171.5	104.1	20.3					
	Received radiation	1049 (23)	258 (45)	693 (29)	98 (6)	<0.0001				
	Number of days radiation (mean)	8.7	9.5	8.9	5					
	Inclusion criteria Individuals with a new, single primary cancer diagnosis of pancreatic malignancy (ICD-O-2 codes C250-C259) between 2007-2007 were identified in the registries. Individuals included were >66 years at diagnosis (to allow 1-year look back for comorbidity assessment) and continuously enrolled in Medicare									

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	part A and B for 1 year prior to diagnosis and from diagnosis forward to death or end of the study perios. Exclusion criteria Medicare health maintenance organisation (HMO) patients were excluded due to incomplete claims. Individuals with in-situ cancer or lymphoma (who have distinct management pathways) and who have died within 45 days of diagnosis (who have minimal opportunity for follow-up imaging)Fol		chemotherapy was adjusted for days surviving from diagnosis, to account for the fact that patients with longer survival have greater opportunity to receive treatment. To examine radiation treatment duration, we counted the number of days during follow-up on whihc the patient had a claim for radiation services and adjusted for number of days surviving. Potential covariates were chosen based on known prognostic factors in pancreatic		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			cancer and factors influencing access to care. Demographic variables included age, sex, race, marital status and medicaid coverage, comorbidities were determined from the medicare data using the klabunde modification of the charlston comorbidity index. County-level data on education, income, urban/rural designation and percent uninsured were obtained from the ARF. The ARF was also used to obtain data on the number of hospitals with		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			CT, MRI and PET scanners and oncologic services. To account for possible stage migration due to the increased sensitivity of PET in detecting metastases at diagnosis, we controlled for type of diagnostic imaging, defined as a claim for PET, CT or MRI within 45 days before or after diagnosis date. Analytic approach To examine the association between PET exposure and receipt of chemotherapy and radiation treatment, we conducted cross-sectional		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			analyses using negative binomial models. To examine the association between PET exposure and mortality we used two analytic approaches: a time-varying exposure model and an early-exposure model. Considering our sample size and to develop parismonious models, we selected covariates by first conducting univariate analyses to identify variables associated with either the exposure or the outcome of interest. These variables were		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			included in the initial model. Final models were fitted in which the variables were reduced on the basis of statistical significance and clinical concern for potential confounding. The effect of treatment on outcomes was examined by preplanned stratification of models by treatment pathway (surgical, borderline or metastatic). All analyses for this paper were generated using SAS/STAT software, version 9.2 of the SAS system for windows on		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			the XP_PRO platform. Models for adjusted treatment duration outcome Negative binomial models - relationship between PET exposure and chemotherapy or radiation duration adjusted for days surviving. Time-varying exposure model for mortality Time varying exposure model approach - misattribution of survival time to PET scans that occurred after a significant portion of the survival time had already accured.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			Early-exposure model for mortality outcome Cox proportional hazard models		
Full citation Vaccaro, V., Fleming, J. B., Wolff, R. A., Evans, D. B., Tamm, E. P., Crane, C. H., Javle, M. M., Abbruzzese, J. L., Lee, J. E., Varadhachary, G. R. Role of surveillance CT scans in resected PC: Correlation with CA19-9 and symptoms, Journal of Clinical Oncology. Conference, 28, 2010 Ref ID 482434	Sample size n= 476 (n= 461, n= 15 lost to follow up, data for analysis only n = 296 available, no details) Characteristics 308 patients pancreatic cancer recurred 156 patients were without pancreatic cancer recurrence, of which 117 were alive or 39 died of other causes. Inclusion criteria Pancreatic cancer patients who underwent potentially curative surgery (abstract) Exclusion criteria None specified (abstract)	Interventions Follow-up Intervention CT scans (every 4-6 months) Control Ca 19-9 and/ or clinical symptoms	Details A retrospective review to assess the value of surveillance CT scans (every 4-6 months) compared to clinical symptoms and CA 19-9 levels. Data on patients with PC who underwent potentially curative surgery from Feb 1998 to December 2008.	Results Disease Recurrence post resected PC In 15% of the population (n= 296), cancer recurrence was noted only on body CT scan in the sbsence of symptoms and/ or elevation of CA 19-9. In 85% of patients, symptoms and/ or CA 19-9 elevation preceeds or accompanies	Limitations Newcastle-Ottawa Quality Assessment Scale: Cohort Studies Selection 1) Representative of the exposed cohort - no details 2) Selection of the non exposed cohort -no details 3) Ascertainment of exposure - no details 4) Demonstration that outcome of interest was not present at start

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out: USA Study type: Retrospective cohort study Aim of the study: Assess the value of surveillance CT scans (every 4-6 months) compared to clinical symptoms and CA 19-9 levels. Study dates: Feburary 1998 - December 2008 Source of funding: None declared				disease recurrence. Median overall survival (OS) in months from time of recurrence (FR) and from time of surgery (FS) Symptomatic patients (n= 161) Overall survival FR Elevated CA 19.9: 5 months vs Normal CA 19.9: 10 months Overall survival FS Elevated CA 19.9: 17 months vs Normal CA 19.9: 23 months Asymptomatic patients (n= 135)	of study - yes, surgically resected pancreatic cancer* (1 star) - Unclear risk of bias Comparability 1) Comparability of cohorts on the basis of the design or analysis - no details (0 stars) - Unclear risk of bias Outcome 1) Assessment of outcome - no details 2) Was follow-up long enough for outcomes to occur -yes, in line with progression of the disease 3) Adequacy of follow up of cohorts - follow-up rate differs for different analyses, main

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Overall survival FR Elevated CA 19.9: 10 months vs Normal CA 19.9: 18 months Overall survival FS Elevated CA 19.9: 23 months vs Normal CA 19.9: 35 months	unadjusted analysis - drop out 38%, majority not accounted for. (1 star) - High risk of bias Other information

F.161 Management of locally advanced pancreatic cancer

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Full citation Cantore M, Fiorentini G, Luppi G, Rosati G, Caudana R, et al. Gemcitabine versus FLEC regimen given intra-arterially to patients with unresectable pancreatic cancer: a prospective, randomized phase III trial of the Italian Society for Integrated Locoregional Therapy in Oncology. J Chemother. 2004	Sample size N= 175 patients with LAPC Characteristics M/F (n): 45/26 (G1); 47/20 (G2) Median age (range): 61(38-76) years (G1); 64(37-79) years (G2) Primary tumour site within pancreas: Head(n): 42 (G1); 40 (G2)	Interventions G1: CT [FLEC -based] (n=71) - FLEC at 3 week intervals through an angiographic catheter via femoral artery to the celiac axis. Leucovorin at 100mg/m2 5-FU at 1000mg/m2 Carboplatin 300mg/m2 Epirubicin at 60mg/m2 Antiemetic and H2 receptor antagonist	Details Design: Phase III RCT Randomization method: A pre-randomised list of treatment allocation was computer generated and kept by an independent data manager. Blinding: unclear	Objective Response* Progression Free Survival* Overall Survival* Adverse Events * Covered in the NMA (not included in the pairwise analyses)	Limitations Random sequence generation: Unclear risk –pre-randomised list of treatment allocation was generated but no details of methods reported. Allocation concealment: Unclear risk - Not reported Blinding of participants and

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Dec;16(6):589-94. PubMed PMID: 15700852. Ref ID Cantore et al. 2005 Country/ies where the study was carried out: Italy Study type: Phase III RCT Aim of the study: To assess the real efficacy of the FLEC regimen (5-fluoruracil + leucovorin + epirubicin + carboplatin) compared with the gold standard CT (weekly gemcitabine or 5-5-FU (5-FU) + leucovorin) in patients with LAPC Study dates: Data collection-patients enrolment: June 1997-June 2001 Publication year: 2005 Source of funding: n.r.	Body(n): 19 (G1); 19 (G2) Tail(n): 10 (G1); 8 (G2) Multicentre(n): 0 (G1); 0 (G2) Inclusion criteria Histologically proven adenocarcinoma of the pancreas that was not suitable for resection Karnofsky performance status of ≥50 Adequate baseline bone marrow reserve Adequate baseline hepatic function Adequate renal function Exclusion criteria Peritonela metastases Previous CT or radiotherapy or combination of both Previous myocardial infarction Severe coagulopathy Second malignancy (except skin cancer and in-situ carcinoma of the cervix) Pregnancy	Haematological growth factor G2: CT [GEM-based] (n=67) – Gemcitabine at 1000mg/m3 IV once a week for up to seven weeks and once weekly for 3 consecutive weeks out of four thereafter. G3: CT [5FU-based] (randomisation to this arm was stopped due to reluctance of patients and practitioners to randomise to this treatment)	Duration/last follow-up: every 2 months until patients' death		personnel Assessments: Unclear risk (Not reported but recruitment to a third arm was halted due to reluctance on the part of patients and practitioners) Blinding of outcome assessment: Unclear risk (Not reported) Incomplete outcome data: Low Risk: Selective reporting: unclear risk (no study protocol available). Other sources of bias: High Risk (sample size calculation reported requiring 103 participants per arm) Overall risk of bias: Very serious Other information
Full citation Cantore M, Girelli R, Mambrini A, Frigerio I, Boz G, Salvia R, Giardino A, Orlandi M, Auriemma A,	Sample size N= 107 patients with LAPC Characteristics	Interventions G1: RFA as primary treatment (n=47) G2: RFA after other primary treatment	Details Design: Prospective cohort study. Randomization method: N/A	Overall Survival	Limitations Representativeness of the exposed cohort: low risk

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Bassi C. Combined modality treatment for patients with locally advanced pancreatic adenocarcinoma. Br J Surg. 2012 Aug;99(8):1083-8. doi: 10.1002/bjs.8789. Ref ID Cantore et al. 2012 Country/ies where the study was carried out: Italy Study type: Prospective cohort study. Aim of the study: To examine the effect of adding radiofrequency ablation (RFA) to radioCT (RCT) on survival, and to find the most appropriate timing of RFA in relation to multimodal treatment in patients with LAPC. Study dates: Data collection-patients enrolment: February 2007-May 2010 Publication year: 2012 Source of funding: None reported.	M/F (n): 26/21 (G1); 34/26 (G2) Median age (range): 68.9(53.0-83.0) years (G1); 60.3(44.7-77.5) years (G2) ECOG PS: 0(n): 8 (G1); 27 (G2) 1(n): 39 (G1); 33 (G2) 2+(n): 0 (G1); 0 (G2) Primary tumour site within pancreas: Head(n):31 (G1); 43 (G2) Body/tail(n):16 (G1); 17 (G2) Multicentre(n):0 (G1); 0 (G2) Inclusion criteria aged between 18 and 80 years; preoperative staging (ultrasonography, abdominal computed tomography (CT) or magnetic resonance imaging) indicative of an unresectable solid mass in the pancreatic head, body or tail; pretreatment cytology positive for pancreatic carcinoma; absence of distant metastases;	(systemic CT and/or radiochiamotherapy and/or intra-arterial CT combined with systemic CT [IASC]. (n=60) Radiotherapy was delivered as external beam radiation at a dose of 54·0–59·4 Gy. CT involved the use of gemcitabine administered weekly at a daily dose of 40 mg/m2 throughout the entire course of radiotherapy. IASC consisted of epirubicin (35 mg/m2) and cisplatin (42 mg/m2) via the coeliac axis, by bolus injection through a catheter inserted in the femoral artery, on day 1. Gemcitabine was administered on day 2 of each cycle (1000 mg/m2intravenously over 30 min). Capecitabine was given orally (650 mg/m2 twice a day) on days 2–15. Cycles were repeated every 28 days until progression of disease, unacceptable toxicity or withdrawal of patient consent. Gemcitabine	Blinding: Unblinded Duration/last follow-up: after 30 days and every 3 months – until 1 July 2011		Selection of the non-exposed cohort: low risk Ascertainment of exposure: low risk Demonstration that outcome of interest was not present at start of study: low risk Comparability of cohorts on the basis of the design or analysis: low risk Assessment of outcome: unclear risk Was follow-up long enough for outcomes to occur: unclear risk Adequacy of follow up of cohorts: unclear risk Overall risk of bias: Low Other information

Study details	Participants	Interventions	Methods	Outcomes*	Comments
	ECOG PS 0 or 1. Exclusion criteria contraindications to surgery presence of multiple pancreatic lesions	and capecitabine doses were reduced by 25 per cent if either grade 2 neutropenia or thrombocytopenia occurred.			
Full citation Chauffert B, Mornex F, Bonnetain F, Rougier P, Mariette C, et al. Phase III trial comparing intensive induction CRT (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer Definitive results of the 2000-01 FFCD/SFRO study. Ann Oncol. 2008 Sep;19(9):1592-9. Ref ID Chauffert et al. 2008 Country/ies where the study was carried out: France Study type: Phase III RCT Aim of the study: To compare an intensified induction phase with CHRT combining infusion FU and	Sample size N= 119 patients with LAPC Characteristics M/F (n): 31/28 (G1); 34/26 (G2) Median age (range): 60(41-79) years (G1); 62(38-80) years (G2) WHO PS: 0/1 (n): 54 (G1); 46 (G2) 2 (n): 5 (G1); 14 (G2) Primary tumour site within pancreas: Head(n): 46 (G1); 40(G2) Other(n): 13 (G1); 20 (G2) Inclusion criteria adenocarcinoma of the pancreas No distant metastases at CT scan 0-2 WHO performance status Unresectable tumours due to extension to	Interventions G1: CRT (n=59) - 60Gy in 2 Gy fractions, five fractions per week. Concomitant 5-FU as continuous IV at 300mg/m2/day administered from days 1-5 of each week through irradiation and cisplatin in a short IV infusion with hydration at 20mg/m2/day from days 1 to 5 during weeks 1 and 5. G2: CT [GEM-based] (n=52) - Gemcitabine at 1000mg/m2 given weekly in 30 mins for seven weeks Both Arms: Maintenance Gemcitabine at 1000mg/m2 weekly in 30 min for 3 weeks every 4 weeks until disease progression or excessive toxicity	Details Design: Phase III RCT Randomization method: Randomised 1:1 using a minimisation technique with stratification according to the centre, the WHO performance status, prior exploratory surgery and/or biliary drainage Blinding: unclear Duration/last follow-up: Median follow-up was 31 months in the CRT arm and 33 months in the GEM arm.	Objective Response* Progression Free Survival* Overall Survival* Adverse Events * Covered in the NMA (not included in the pairwise analyses)	Limitations Random sequence generation: Low risk – randomisation 1:1 using minimisation technique Allocation concealment: Unclear risk (Not reported) Blinding of participants and personnel Assessments: Unclear risk (Not likely that patients and treatment administrators are blinded due to differences in treatments) Blinding of outcome assessment: Unclear risk (Not reported) Incomplete outcome data: High Risk: Study was stopped before completion of recruitment

Study details	Participants	Interventions	Methods	Outcomes*	Comments
cisplatin, followed by maintenance gemcitabine with gemcitabine alone in histologically or cytologically proven LAPC Study dates: Data collection-patients enrolment: March 2000-July 2005 Publication year: 2008 Source of funding: Ligue Nationale Contre le Cancer; Lilly Laboratories.	regional lymph nodes and/or vascular structures such as the superior mesecteric artery or the celiac trunk or the existence of a portal or superior mesenteric-portal venous confluent thrombosis. Adequate organ function Exclusion criteria Not reported	Analysis was intention to treat Unplanned interim analysis was requested due to low recruitment Study was stopped before the completion of recruitment due to a lower survival among patients in the CHRT arm.			Selective reporting: unclear risk (no study protocol available). Other sources of bias: High Risk (sample size calculation not reported) Overall risk of bias: Very serious Other information
Full citation Chung HW, Bang SM, Park SW, Chung JB, Kang JK, et al. A prospective randomized study of gemcitabine with doxifluridine versus paclitaxel with doxifluridine in concurrent CRT for locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys. 2004 Dec 1;60(5):1494-501. Ref ID Chung et al. 2004 Country/ies where the study was carried out: South Korea Study type: Phase III RCT Aim of the study:	Sample size N= 46 patients with LAPC Characteristics M/F (n): 13/9 (G1); 10/14 (G2) Median age (range): 62(51-74) years (G1); 61.5(39-74) years (G2) Primary tumour site within pancreas: Head(n):16 (G1); 18 (G2) Body/ tail (n):6 (G1); 6 (G2) Inclusion criteria Histologically proven pancreatic adenocarcinoma 18-75 years of age Karnofsky performance score ≥60	Interventions G1: CRT [GEM-based] (n=22) Gemcitabine at 1000mg/m2 per week IV Doxifluridine 600mg/m2 per day orally Radiotherapy daily as a single course of 4500 cGy in 25 fractions over 5 weeks G2: CRT [Paclitaxel-based] (n=24) Paclitaxel 50mg/m2 per week IV Doxifluridine 600mg/m2 per day orally Radiotherapy daily as a single course of 4500 cGy in 25 fractions over 5 weeks	Details Design: Phase III RCT Randomization method: Randomisation was by a computer driven procedure. No other details reported Blinding: unclear Duration/last follow-up: every 3 months until patients death	Objective Response Overall Survival Adverse Events	Limitations Random sequence generation: Unclear risk –randomisation was by computer but no details of methods reported. Allocation concealment: Unclear risk - Not reported Blinding of participants and personnel Assessments: Unclear risk (Not reported) Blinding of outcome assessment: Unclear risk (Not reported) Incomplete outcome data: Low Risk

Study details	Participants	Interventions	Methods	Outcomes*	Comments
To compare the efficacy and toxicity of gemcitabine based concurrent CRT (CCRT) with paclitaxel-CCRT in patients with locally advanced pancreatic cancer Study dates: Data collection-patients enrolment: January 1997-July 2002 Publication year: 2004 Source of funding: None reported.	Absolute granulocyte count ≥1500/mm3 Platelet count ≥100,00/mm3 Serum creatinine <2mg/dL Aspartateor alanine aminotransferase<5 times the upper limit of normal No prior CT or radiotherapy No other malignancy No active ulcer in the gastrointestinal tract No other serious medical conditions Exclusion criteria Not reported				Selective reporting: unclear risk (no study protocol available). Other sources of bias: High Risk (sample size calculation not reported requiring 24 participants per arm) Overall risk of bias: Very serious Other information Unresectability was defined as: Involving the superior mesenteric arteries or the celiac axis Occlusion of the portal or superior mesenteric vein
Full citation Cohen SJ, Dobelbower R Jr, Lipsitz S, Catalano PJ, Sischy B, et al. A randomized phase III study of radiotherapy alone or with 5-5-FU and mitomycin-C in patients with locally advanced adenocarcinoma of the pancreas: Eastern Cooperative Oncology Group study E8282. Int J Radiat Oncol Biol Phys. 2005 Aug 1;62(5):1345-50. Ref ID Cohen et al. 2005	Sample size N= 114 patients with LAPC Characteristics M/F (n): 67/33 (G1);55/45 (G2) Median age (range): 42(44-76) years (G1); 64(39-77) years (G2) ECOG PS: 0(n): 29 (G1); 29 (G2) 1(n): 53 (G1); 50 (G2) 1+(n): 18 (G1); 22 (G2) Inclusion criteria Not reported	Interventions G1: CRT (n=55) 59.4Gy external beam radiotherapy in 1.8Gy fractions. 5-FU at 1,000mg/m2 as a continuous infusion on days 2-5 and 28-31 of radiation therapy (maximum 1,800mg/day) and mytomycin C as a one-time bolus of 10mg/m2 on day 2 G2: Radiotherapy (n=49)	Details Design: Open label Phase III RCT Randomization method: Randomisation was performed centrally after verification of eligibility and stratification by stage and by whether pancreatic lesion was outlined by clips Blinding: open label trial	Objective Response* Progression Free Survival* Overall Survival* Adverse Events * Covered in the NMA (not included in the pairwise analyses)	Limitations Random sequence generation: unclear risk Allocation concealment: low risk Blinding of participants and personnel Assessments: high risk (Not likely that patients and treatment administrators are blinded due to

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Country/ies where the study was carried out: USA Study type: Phase III RCT Aim of the study: To determine whether the addition of 5 5-FU and mytomycin C to radiation therapy improves outcomes in patients with LAPC Study dates: Data collection-patients enrolment: 1983-1989 Publication year: 2005 Source of funding: supported in part by Public Health Service Grants CA23318, CA21115, CA66636, CA27525, CA11083, CA07190, CA15488 and from the National Cancer Institute, National Institutes of Health, and the Department of Health and Human Services.	Exclusion criteria Prior systemic therapy or abdominal radiotherapy Any concurrent malignancy excluding skin cancer Ongoing infection or post-surgical complications Tumour ≥15cm	59.4Gy external beam radiotherapy in 1.8Gy fractions	Duration/last follow-up: unclear		differences in treatments) Blinding of outcome assessment: High risk (open label) Incomplete outcome data: Low Risk: Selective reporting: unclear risk (no study protocol available). Other sources of bias: High Risk (sample size calculation not reported) Overall risk of bias: Very serious Other information
Full citation Hammel P, Huguet F, van Laethem JL, Goldstein D, Glimelius B, et al. Effect of CRT vs CT on Survival in Patients With Locally Advanced Pancreatic	Sample size N= 269 patients with LAPC Characteristics RANDOMISATION 1: M/F (n): 111/108 (G1); 117/106 (G2)	Interventions RANDOMISATION 1: G1: CT [GEM-based] (n=223) - Gemcitabine IV at 1000mg/m2/week for 3 weeks followed by 1 week rest	Details Design: Multicentre, open label, phase III RCT Randomization method: 1:1 randomisation using	Progression Free Survival*^ Overall Survival*^ Adverse Events * Covered in the NMA (not included in the pairwise analyses -	Limitations Random sequence generation: Low risk – randomisation using a minimisation technique with stratification

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Cancer Controlled After 4 Months of Gemcitabine With or Without Erlotinib: The LAP07 Randomized Clinical Trial. JAMA. 2016 May 3;315(17):1844-53. Ref ID Hammel et al. 2016 Country/ies where the study was carried out: France Study type: Phase III RCT Aim of the study: To assess whether CRT in patients with LAPC controlled after 4 months of gemcitabine based induction CT may improve survival compared with CT alone. Study dates: Data collection-patients enrolment: February 2008–December 2011 Publication year: 2016 Source of funding: This trial was supported by Roche and French National Institute of Cancer (INCa).	Median age (range): 63 (58-71) years (G1); 64 (57.0-70.0) years (G2) WHO PS: 0/1(n): 200 (G1); 200 (G2) 1+(n): 19 (G1); 23 (G2) RANDOMISATION 2: M/F (n): 58/75 (G1); 76/60 (G2) Median age (range): 62 (55-70) years (G1); 63(58-71) years (G2) WHO PS: 0/1(n): 124 (G1); 124 (G2) 1+(n): 9 (G1); 12 (G2) Inclusion criteria ≥18 years old Histologically or cytologically confirmed stage III locally advanced pancreatic cancer according to the International Union against Cancer staging system Measurable or evaluable disease as assessed according to the RECIST criteria WHO performance status of ≤2 No prior CT or radiotherapy	G2: CT [GEM+ERLONITIB] (n=219) - Gemcitabine IV at 1000mg/m2/week for 3 weeks followed by 1 week rest. Erlotinib orally at 100mg/day Maintenance Daily dose of erlotinib was increased to 150mg. Patients with stable disease or objective response and who had a WHO performance status of 2 or less after completion of induction CT were randomised to stage 2. RANDOMISATION 2: G1: CT [GEM+ERLONITIB] (n=135) G2: CRT (n=133) - Radiotherapy 54 Gy in 30 daily fraction over 6 weeks Concurrent capecitabine at 800mg/m2 twice daily on days of radiation therapy.	a minimisation technique with stratification for centre and performance status. Randomisation was carried out at the study coordination centre and was a 2 stage process. Blinding: open label Duration/last follow-up: until patients' death	1ST RANDOMIZATION) ^ included in the pairwise analyses (2ND RANDOMIZATION)	Allocation concealment: Unclear risk - Not reported trial Blinding: Unclear risk – open label trial Blinding of participants and personnel Assessments: High risk (open label – participants/treatment administrators not blinded) Blinding of outcome assessment: Unclear risk (Not reported) Incomplete outcome data: Low Risk: Selective reporting: low risk Other sources of bias: Low Risk Overall risk of bias: Low risk Other information

Study details	Participants	Interventions	Methods	Outcomes*	Comments
	Exclusion criteria Not reported				
Full citation Heinemann V, Ebert MP, Laubender RP, Bevan P, Mala C, et al. Phase II randomised proof-of-concept study of the urokinase inhibitor upmostat (WX-671) in combination with gemcitabine compared with gemcitabine alone in patients with non-resectable, LAPC. Br J Cancer. 2013 Mar 5;108(4):766-70. Ref Id Heinemann et al. 2013 Country/ies where the study was carried out: Germany Study type: Phase II RCT Aim of the study: To evaluate the efficacy and safety of an uPA inhibitor for patients with LAPC Study dates: Data collection-patients enrolment: June 2007-August 2008 (recruitment)|December	Sample size N= 95 patients with LAPC Characteristics M/F (n): 20/11 (G1); 12/21 (G2); 14/77(G3) Median age (range): 67(48-81) years (G1); 62(39-82) years (G2); 59(48-71) years (G3) ECOG PS: 0(n): 4 (G1); 8 (G2); 5 (G3) 1(n): 27 (G1); 25 (G2); 26 (G3) Primary tumour site within pancreas: Head (n): 28 (G1); 28 (G2); 25 (G3) Body (n): 4 (G1); 4 (G2); 5 (G3) Tail (n): 0 (G1); 0 (G2); 0 (G3) Others (n):0 (G1); 0 (G2); 1 (G3) Inclusion criteria Patients with locally advanced, unresectable, non-metastatic, histologically or cytologically proven pancreatic adenocarcinoma	Interventions G1: Gemcitabine + 200mg upmostat (n=31) - As arm 3 with the addition of a daily oral dose of 200mg upmostat. G2: Gemcitabine + 400mg upmostat (n=33) – As arm 3 with the addition of a daily oral dose of 400mg upmostat G3: CT [GEM-based] (n=31) - Gemcitabine 1000mg/m2 IV over 30 min weekly for 7 weeks in the first 8 weeks, followed by weekly gemcitabine for 3 weeks of a 4 week cycle	Details Design: Open label, proof of concept, phase II RCT Randomization method: Randomisation was performed centrally on a 1:1:1 ratio Blinding: open label Duration/last follow-up: every 8 weeks until patients death	Objective Response* Progression Free Survival* Overall Survival* Adverse Events * Covered in the NMA (not included in the pairwise analyses)	Limitations Random sequence generation: Unclear Risk – no details were provided on the randomisation method other than randomisation was performed centrally Allocation concealment: Low risk Blinding: High Risk – Open label study Blinding of participants and personnel Assessments: High risk – Open Label Study Blinding of outcome assessment: High risk – Open Label Study Incomplete outcome data: Low Risk Selective reporting: Low risk Other sources of bias: Low Risk Overall risk of bias: Serious risk Other information

Study details	Participants	Interventions	Methods	Outcomes*	Comments
2009 (data collection ended) Publication year: 2013 Source of funding: None reported.	(locoregional lymph nodes were not considered metastases) Age 18 years or older No prior (or concomitant) CT or radiotherapy ECOG performance status 0-1 Adequate bone marrow, liver and renal function Exclusion criteria Not reported				
Full citation Herman JM, Wild AT, Wang H, Tran PT, Chang KJ, et al. Randomized phase III multi-institutional study of TNFerade biologic with 5-FU and radiotherapy for locally advanced pancreatic cancer: final results. J Clin Oncol. 2013 Mar 1;31(7):886-94. Ref ID Herman et al. 2013 Country/ies where the study was carried out: USA Study type: Phase III RCT Aim of the study: To test gene transfer against LAPC Study dates:	Sample size N= 304 patients with LAPC Characteristics M/F (n): 112/75 (G1); 48/42 (G2) Median age (range): 64(31-86) years (G1); 65(29-85) years (G2) Inclusion criteria Biopsy confirmed, unresectable LAPC defined by extension to the superior mesenteric artery and or/celiac axis with no fat plane separating the tumour and these arterial structures or obstruction of the superior mesenteric-portal vein confluence.	Interventions G1: CRT (standard of care) + TNFerade (n=187) - TNFerade (4x104 PU) delivered via intratumoral injection plus standard of care TNFerade was delivered by percutaneous transabdominal approach or an endoscopic ultrasound guided transgastric/transduodenal approach G2: Standard of care (n=90) - Continuous infusion 5-FU 200mg/m2/day Radiotherapy 45Gy delivered in 25 fractions of 1.8Gy followed by boost to the tumour plus	Details Design: Open label phase III RCT Randomization method: Patients randomised 2:1, stratified by centre and KPS. Blinding: Open label trial Duration/last follow-up: “Median follow-up was 9.1 months”	Objective Response* Progression Free Survival* Overall Survival* Adverse Events * Covered in the NMA (not included in the pairwise analyses)	Limitations Random sequence generation: Unclear risk –randomisation was on a 2:1 basis and stratified by centre and KPS but no information on randomisation method. Allocation concealment: Unclear risk - Not reported Blinding: Unclear risk – details not reported Blinding of participants and personnel Assessments: Unclear risk (Not reported but unlikely that participants and treatment

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Data collection-patients enrolment: April 2005-March 2010 Publication year: 2013 Source of funding: Kenneth J. Chang, GenVec	Karnofsky performance status ≥70% Life expectancy more than 3 months Adequate hepatic, hematologic, immune and renal function Patients with technically resectable tumours were also considered unresectable because of medical comorbidities or refusal of surgery Exclusion criteria Evidence of metastatic disease Previous pancreatic cancer therapy Previous target field irradiation Clinically significant ascites Bulky coeliac adenopathy (≥2.5cm) Nonadenocarcinoma histology	a 1cm margin consisting of 5.4Gy in 3x1.8Gy fractions. Gemcitabine or Gemcitabine+ Erlotinib maintenance therapy at investigator discretion.			administrators were blinded.) Blinding of outcome assessment: Low risk (An independent blinded central reading laboratory reviewed CT scans and MRI scan assess for progression and tumour response according to RECIST).) Incomplete outcome data: Low Risk Selective reporting: low risk Other sources of bias: High Risk (sample size sample size calculated but required 330 patients to be randomised) Overall risk of bias: Serious risk Other information
Full citation Hurt CN, Mukherjee S, Bridgewater J, Falk S, Crosby T, et al. Health-Related Quality of Life in SCALOP, a Randomized Phase 2 Trial Comparing Chemoradiation Therapy Regimens in Locally	Sample size N= 114 patients with LAPC were registered and underwent induction CT (N=78 patients were randomly allocated) Characteristics M/F (n): 24/14 (G1); 17/19 (G2)	Interventions G1: CRT [GEM-based] (n=38) G2: CRT [Capecitabine-based] (n=36) Research nurses who recruited patients phone the Wales Clinical Trials Unit where	Details Design: Multi-centre, open label, Phase II RCT Randomization method: Randomisation on 1:1 ratio after 3 cycles of induction	Objective Response Resection rate Progression Free Survival (local, distant) Overall Survival Adverse Events Health Related Quality of Life	Limitations Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Advanced Pancreatic Cancer. Int J Radiat Oncol Biol Phys. 2015 Nov 15;93(4):810-8. Ref ID Hurt et al. 2015 Country/ies where the study was carried out: UK Study type: Phase II RCT Aim of the study: 1) To assess the activity, safety and feasibility of gemcitabine based and capecitabine based CRT after induction CT for patients with locally advanced pancreatic cancer; 2) To describe generic, disease and treatment specific health related quality of life during and after treatment with CRT Study dates: Data collection-patients enrolment: December 2009-October 2011 Publication year: 2015 Source of funding: Cancer Research UK (CR UK 07/040) and CRUK core funding at Wales Cancer Trials Unit. S.M. is partly	Median age (range): 63.1(56-70) years (G1); 66.0(58-70) years (G2) ECOG PS: 0(n): 20 (G1); 20 (G2) 1(n): 17 (G1); 14 (G2) 1+(n): 1 (G1); 2 (G2) Primary tumour site within pancreas: Head(n):32 (G1); 31 (G2) Body(n):6 (G1); 5 (G2) Inclusion criteria Aged 18 years or older Histologically or cytologically proven, locally advanced, non-metastatic and inoperable (or operable but unfit for surgery) pancreatic cancer Tumour diameter of less than 7cm WHO performance status 0-2 Adequate haematological, liver and renal function Exclusion criteria Not reported	randomisation was done by a trial or data manager Study was open label so treatment was not masked from patients or investigators Induction Chemotherapy 3 Cycles of gemcitabine IV for 1hour on days 1,8 and 15 of a 28 day cycle and capecitabine orally, twice daily on days 1-21 of a 28 day cycle Eligible patients were randomised to receive a further cycle of gemcitabine and capecitabine CT followed by radiotherapy in combination with either gemcitabine or capecitabine Health related quality of life was assessed using the HQRL generic instrument: EORTC QLQ-C-30 which assesses global quality of life, functional domains and symptoms that commonly occur in people with cancer. Disease specific measure: EORTC QLQ-PAN26 relates to pancreatic disease	CT by use of minimisation with a random element (80:20) Randomisation was stratified by recruiting hospital, WHO performance status, and disease location Blinding: open label trial Duration/last follow-up: “All patients were followed until progression, death, or 12-month follow-up assessment”	Pain control Patient experience & PROMS	Assessments: High risk (trial was open label) Blinding of outcome assessment: High risk (trial was open label) Incomplete outcome data: Low Risk Selective reporting: Low risk Other sources of bias: Unclear Risk (A Fleming’s single-stage design was assigned to each treatment group to show worthwhile efficacy in each group separately. The study was not formally powered to compare progression free survival between each) Overall risk of bias: Serious risk Other information See Mukherjee 2013

Study details	Participants	Interventions	Methods	Outcomes*	Comments
funded by National Institute for Health Research Oxford Biomedical Research Centre and the CRUK Experimental Cancer Medicines Centre, Oxford. J.B. is partly supported by the UCLH/UCL University College London/University College London Hospital NHS Trust Biomedical Research Center. J.M.B. is partly supported by the MRC ConDuCT-II Hub for Trials Methodology Research.		symptoms, treatment side effects and emotional issues			
Full citation Khan K, Cunningham D, Peckitt C, Barton S, Tait D, et al. miR-21 expression and clinical outcome in locally advanced pancreatic cancer: exploratory analysis of the pancreatic cancer Erbitux, radiotherapy and UFT (PERU) trial. Oncotarget. 2016 Mar 15;7(11):12672-81. Ref ID Khan et al. 2016 Country/ies where the study was carried out: UK Study type: Phase II RCT Aim of the study:	Sample size N= 17 patients with LAPC Characteristics Not reported Inclusion criteria Histologically confirmed unresectable LAPC Had a World Health Organisation performance status (PS) of 0-2. Exclusion criteria prior CT CT scan-evidence of metastatic disease were not allowed	Interventions G1: CRT + cetuximab after induction CT (n=6) G2: CRT alone after induction CT (n=6) Following, neo-adjuvant CT, Capecitabine 1600mg/m2/day was given concomitantly with RT alone in arm A (G1) or with i.v. Cetuximab (400mg/m2 on day 1 and 250mg/m2 subsequently, weekly for 5 weeks) in arm B (G2)	Details Design: Phase II RCT Randomization method: no details given Blinding: unclear Duration/last follow-up: median follow-up of 61.2 months	Objective Response Overall Survival Adverse Events	Limitations Random sequence generation: Unclear risk (No details given in the text) Allocation concealment: Unclear risk (No details given in the text) Blinding of participants and personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: Unclear risk (No details given in the text)

Study details	Participants	Interventions	Methods	Outcomes*	Comments
1) To evaluate the safety and the efficacy CRT (CRT) +/− cetuximab, following induction CT and 2) the prognostic role of miR-21 in patients with locally advanced pancreatic cancer (LAPC) treated with a multimodality approach. Study dates: Data collection-patients enrolment: The PERU trial was closed in June 2013. Publication year: 2016 Source of funding: This work was supported by the National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) at the Royal Marsden NHS Foundation Trust and Institute of Cancer Research, from the Research Innovation Fund from Pancreatic Cancer UK and Career Integration Grant from European Union (C.B), and the Robert McAlpine Charity (K.K.).					Incomplete outcome data: low risk Selective reporting: low risk Other sources of bias: High Risk (sample size not achieved the trial was closed pre-maturely, following emergent data from LAP-07) Overall risk of bias: Very Serious Other information
Full citation Li CP, Chao Y, Chi KH, Chan WK, Teng HC, et al. Concurrent CRT treatment of locally advanced pancreatic cancer:	Sample size N= 34 patients with LAPC Characteristics M/F (n): 13/5 (G1); 12/4 (G2)	Interventions G1: CRT [GEM-based] (n=16) - Cemcitabine at 600mg/m3 IV weekly for 6 weeks during radiotherapy	Details Design: Open label phase III RCT Randomization method: Open label randomised trial no	Objective Response* Progression Free Survival* Overall Survival* Adverse Events Pain control	Limitations Random sequence generation: Unclear risk –no details of randomisation methods

Study details	Participants	Interventions	Methods	Outcomes*	Comments
gemcitabine versus 5-5-FU,a randomized controlled study. Int J Radiat Oncol Biol Phys. 2003 Sep 1;57(1):98-104. Ref ID Li et al. 2003 Country/ies where the study was carried out: Taiwan Study type: Phase III RCT Aim of the study: To determine the efficacy and tolerability of gemcitabine-concurrent CRT versus 5-fluourouracil Study dates: Data collection-patients enrolment: January 1998–December 2001 Publication year: 2003 Source of funding: Supported by Grant VGH 91-196 from Taipei Veterans General Hospital, Taiwan.	Median age (range): 68.5(45-83) years (G1); 69(31-77) years (G2) Primary tumour site within pancreas: Head (n):11 (G1); 12 (G2) Body n):7 (G1); 2 (G2) Tail (n):0 (G1); 2 (G2) Inclusion criteria Patients with histologically confirmed locally advanced pancreatic cancer AJCC stage IVA disease Unresectable according to the NCCN guidelines for pancreatic cancer Karnofsky performance ≥50 Absolute granulocyte count ≥1500/mm3 Platelet count ≥ 100,000/mm3 Serum creatinine <2mg/dL Aspartate aminotransferase or alanine aminotransferase <5 times the upper limit of normal No prior CT or radiotherapy	Radiotherapy total dose of 50.4-61.2GY in 1.8Gy daily fractions Maintenance Gemcitabine at 1000mg/m3 once weekly for 3 weeks repeated every 4 weeks after chemoradiotherapy G2: CRT [5FU-based] (n=18) - 5FU at 500mg/m2 IV for the first 3 days during radiotherapy and repeated every 2 weeks for 6 weeks during the radiotherapy course. Radiotherapy total dose of 50.4-61.2GY in 1.8Gy daily fractions Maintenance Gemcitabine at 1000mg/m3 once weekly for 3 weeks repeated every 4 weeks after chemoradiotherapy	details reporting the method of randomisation Blinding: Open label Duration/last follow-up: until patients' death	HQRL: Average monthly Karnofsky performance score * Covered in the NMA (not included in the pairwise analyses)	Allocation concealment: Unclear risk - Not reported Blinding of participants and personnel Assessments: Unclear risk (Open label trial) Blinding of outcome assessment: Unclear risk (Not reported) Incomplete outcome data: Low Risk: Selective reporting: unclear risk (no study protocol available). Other sources of bias: Low Risk (sample size calculated and required 34 patients which the study recruited however they recruited 18 to one arm and 16 to the second arm) Overall risk of bias: Very Serious Other information

Study details	Participants	Interventions	Methods	Outcomes*	Comments
	No other malignancy apart from carcinoma in situ of the cervix No serious medical or psychological issues Exclusion criteria Not reported				
Full citation Loehrer PJ Sr, Feng Y, Cardenes H, Wagner L, Brell JM, et al. Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: an Eastern Cooperative Oncology Group trial. J Clin Oncol. 2011;29(31):4105-12. Ref ID Loehrer et al. 2011 Country/ies where the study was carried out: USA Study type: Phase III RCT Aim of the study: To determine whether radiation improves survival or provides additional benefit compared with gemcitabine alone in patients with LAPC Study dates:	Sample size N= 71 patients with LAPC Characteristics M/F (n): 19/15 (G1); 16/21 (G2) Median age (range): 66(47-84) years (G1); 69(50-84) years (G2) ECOG PS: 0(n): 8 (G1); 9 (G2) 1(n): 26 (G1); 28 (G2) Primary tumour site within pancreas: Head(n): 25 (G1); 20 (G2) Body(n): 3 (G1); 6 (G2) Tail(n): 2 (G1); 3 (G2) Other(n): 7 (G1); 5 (G2) Inclusion criteria Histologically or cytologically proven locally unresectable adenocarcinoma of the pancreas 18 years or older	Interventions G1: CRT (n=34) - Gemcitabine at 600mg/m2 IV beginning on the first day of radiotherapy and weekly thereafter during radiotherapy. Radiotherapy at 1.8Gy per daily fraction, 5 days/week for a total dose of 50.4Gy administered in 28 fractions over 5.5 weeks G2: CT (n=37) - Gemcitabine at 1000mg/m2 IV weekly for six weeks followed by 1 week rest then weekly for 3 weeks followed by 1 week rest for five additional 4 week cycles	Details Design: Phase III RCT Randomization method: No details on randomisation method though patients were stratified by performance status and prior weight loss within previous 6 months. Blinding: unclear Duration/last follow-up: FACT-Hep questionnaire to assess health related quality of life. Administered at baseline, week 6, week 15/16 and 9 months post baseline	Objective Response* Progression Free Survival* Overall Survival* Adverse Events Health Related Quality of Life * Covered in the NMA (not included in the pairwise analyses)	Limitations Random sequence generation: Unclear risk –no details of randomisation methods Allocation concealment: Unclear risk - Not reported Blinding of participants and personnel Assessments: Unclear risk (Not reported but unlikely that participants and treatment administrators were blinded.) Blinding of outcome assessment: Unclear risk (Not reported) Incomplete outcome data: High Risk: (quality of life data should be taken with caution due to high rate of attrition from baseline)

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Data collection-patients enrolment: April 2003-December 2005 Publication year: 2011 Source of funding: Eli Lilly	ECOG performance score of 0-2 No prior CT or radiotherapy Absolute granulocyte count of 2.0x109/µl or greater Platelet count greater than 100,000/µl Total bilirubin of less than 3mg/dL (unless secondary to biliary obstruction or cholangitis) AST less than 5x upper limit of normal Albumin greater than 2.5 g/dl Serum creatinine 1.5x or less than upper limit of normal Exclusion criteria Patients with small cell carcinoma, mucinous cystadenocarcinoma or islet cell or papillary cystic neoplasm History of active collagen vascular disease or signs of recent peptic or duodenal ulver Serious concomitant systemic disorders or active infections Pregnancy				Selective reporting: unclear risk (no study protocol available). Other sources of bias: High Risk Sample size calculation required a sample size of 316 patients however recruitment was stopped early due to poor accrual rates 46% of patients in Arm A and 21% of patients in Arm B did not have CT scans performed at adequate intervals to appropriately assess duration of treatment response Comparison of progression was compromised as precise tumour measurement was difficult in many patients due to margins being obscured by local inflammatory processes Overall risk of bias: Very serious Other information

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Full citation Mukherjee S, Hurt CN, Bridgewater J, Falk S, Cummins S, et al. Gemcitabine-or capecitabine-CRT for locally advanced pancreatic cancer (SCALOP): a multicentre, randomised, phase 2 trial. Lancet Oncol. 2013 Apr;14(4):317-26. Ref ID Mukherjee et al. 2013 Country/ies where the study was carried out: UK Study type: Multi-centre, open label, Phase II RCT Aim of the study: 1) To assess the activity, safety and feasibility of gemcitabine based and capecitabine based CRT after induction CT for patients with locally advanced pancreatic cancer; 2) To describe generic, disease and treatment specific health related quality of life during and after treatment with CRT Study dates: Data collection-patients enrolment:	Sample size N= 114 patients with LAPC were registered and underwent induction CT (N=78 patients were randomly allocated) Characteristics M/F (n): 24/14 (G1); 17/19 (G2) Median age (range): 63.1(56-70) years (G1); 66.0(58-70) years (G2) ECOG PS: 0(n): 20 (G1); 20 (G2) 1(n): 17 (G1); 14 (G2) 1+(n): 1 (G1); 2 (G2) Primary tumour site within pancreas: Head(n):32 (G1); 31 (G2) Body(n):6 (G1); 5 (G2) Inclusion criteria Aged 18 years or older Histologically or cytologically proven, locally advanced, non-metastatic and inoperable (or operable but unfit for surgery) pancreatic cancer Tumour diameter of less than 7cm WHO performance status 0-2	Interventions G1: CRT [GEM-based] (n=38) G2: CRT [Capecitabine-based] (n=36) Research nurses who recruited patients phone the Wales Clinical Trials Unit where randomisation was done by a trial or data manager Study was open label so treatment was not masked from patients or investigators Induction Chemotherapy 3 Cycles of gemcitabine IV for 1hour on days 1,8 and 15 of a 28 day cycle and capecitabine orally, twice daily on days 1-21 of a 28 day cycle Eligible patients were randomised to receive a further cycle of gemcitabine and capecitabine CT followed by radiotherapy in combination with either gemcitabine or capecitabine Health related quality of life was assessed using the HQRL generic instrument: EORTC	Details Design: Multi-centre, open label, Phase II RCT Randomization method: Randomisation on 1:1 ratio after 3 cycles of induction CT by use of minimisation with a random element (80:20) Randomisation was stratified by recruiting hospital, WHO performance status, and disease location Blinding: open label trial Duration/last follow-up: “All patients were followed until progression, death, or 12-month follow-up assessment”	Objective Response Progression Free Survival Overall Survival Adverse Events	Limitations Random sequence generation: Low risk Allocation concealment: Low risk Blinding: High risk – Trial was open label – patients and investigators were not blinded. Blinding of participants and personnel Assessments: High risk (trial was open label) Blinding of outcome assessment: High risk (trial was open label) Incomplete outcome data: Low Risk Selective reporting: Low risk Other sources of bias: Unclear Risk (A Fleming’s single-stage design was assigned to each treatment group to show worthwhile efficacy in each group separately. The study was not formally powered to compare progression free

Study details	Participants	Interventions	Methods	Outcomes*	Comments
December 2009-October 2011 Publication year: 2013 Source of funding: Cancer Research UK (CR UK 07/040) and CRUK core funding at Wales Cancer Trials Unit. S.M. is partly funded by National Institute for Health Research Oxford Biomedical Research Centre and the CRUK Experimental Cancer Medicines Centre, Oxford. J.B. is partly supported by the UCLH/UCL University College London/University College London Hospital NHS Trust Biomedical Research Center. J.M.B. is partly supported by the MRC ConDuCT-II Hub for Trials Methodology Research.	Adequate haematological, liver and renal function Exclusion criteria Not reported	QLQ-C-30 which assesses global quality of life, functional domains and symptoms that commonly occur in people with cancer. Disease specific measure: EORTC QLQ-PAN26 relates to pancreatic disease symptoms, treatment side effects and emotional issues			survival between each) Overall risk of bias: Serious risk Other information See Hurt 2015
Full citation Rich TA, Winter K, Safran H, Hoffman JP, Erickson B, et al. Weekly paclitaxel, gemcitabine, and external irradiation followed by randomized farnesyl transferase inhibitor R115777 for locally advanced pancreatic cancer. Onco Targets Ther. 2012;5:161-70.	Sample size N=195 patients from 71 institutions enrolled with 185 analysable Characteristics M/F (n): 52/42 (G1); 54/37 (G2) Median age (range): 60(43-82) years (G1); 62(40-82) years (G2) Inclusion criteria	Interventions G1: CRT + R115777 (n=94) - As arm 2 plus maintenance R115777 at 300mg twice a day for 21 days every 28 days until disease progression or unacceptable toxicity. G2: CRT alone (n=91) - 50.4GY in 1.4Gy doses plus Gemcitabine at	Details Design: Phase II RCT Randomization method: No details regarding the method of randomisation Blinding: unclear Duration/last follow-up: unclear	Overall Survival Adverse Events	Limitations Random sequence generation: Unclear Risk – no details were provided on the randomisation method other than randomisation was performed centrally Allocation concealment: Unclear risk - No details

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Ref ID Rich et al. 2012 Country/ies where the study was carried out: USA Study type: Phase II RCT Aim of the study: To evaluate the addition of weekly low dose gemcitabine with paclitaxel and concurrent radiation (RT) and to evaluate the safety and efficacy of the farnesyl transferase inhibitor R115777 following chemoradiation Study dates: Data collection-patients enrolment: October 2001-December 2003 Publication year: 2012 Source of funding: None reported.	Pathologically confirmed unresectable, nonmetastatic adenocarcinoma of the pancreas deemed unresectable by extra-pancreatic involvement, extensive peripancreatic lymphatic involvement, nodal involvement beyond the peripancreatic tissue or encasement or direct invasion of the superior mesenteric vein, artery, inferior vena cava, aorta or celiac plexus. Zubrod performance status of 0 or 1 Radiographically assessable disease No significant infection Exclusion criteria Biliary or gastroduodenal obstruction with drainage prior to chemoradiation Malignancy with the past 2 years except for non-melanoma skin cancer or carcinoma in situ of the cervix, uterus or bladder Co-existent uncontrolled medical condition	75mg/m2 and paclitaxel at 40mg/m2 for 6 weeks			Blinding: High Risk – Unclear risk - No details Blinding of participants and personnel Assessments: Unclear risk - No details Blinding of outcome assessment: Unclear risk - No details Incomplete outcome data: Low Risk Selective reporting: Low risk Other sources of bias: Low Risk Overall risk of bias: Serious Other information

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Full citation Shinchi H, Takao S, Noma H, Matsuo Y, Mataki Y, et al. Length and quality of survival after external-beam radiotherapy with concurrent continuous 5-5-FU infusion for locally unresectable pancreatic cancer. Int J Radiat Oncol Biol Phys. 2002;53(1):146-50. Ref ID Shinchi et al. 2002 Country/ies where the study was carried out: Japan Study type: Phase III RCT Aim of the study: To evaluate whether external beam radiotherapy with concurrent 5-FU infusion affect the length and quality of survival in patients with LAPC Study dates: Data collection-patients enrolment: January 1997-June 2000 Publication year: 2002 Source of funding: None reported.	Sample size N= 31 patients with LAPC Characteristics M/F (%): 33/67 (G1); 64/36 (G2) Mean age (SD): 63(2.8) years (G1); 64.6(4) years (G2) Primary tumour site within pancreas: Head (%):44 (G1); 67 (G2) Body/ Tail (%):56 (G1); 33 (G2) Inclusion criteria Histologically or cytologically confirmed locally advanced and unresectable pancreatic cancer without distant metastases Adequate biliary drainage Normal excretion from both kidneys Karnofsky performance status or 60 or higher Exclusion criteria Not reported	Interventions G1: CRT (n=16) - Radiotherapy in fractions of 1.8-2.0Gy/day, 5 days/week with an average total dose of 50.8Gy (range: 25.2-60Gy) over 3-7 weeks. 5-FU at 200mg/m2/day IV for the duration of radiotherapy Maintenance 5-FU at 500mg/m2 weekly by bolus injection until disease progression or unacceptable toxicity. G2: BSC (n=15) – no intervention [no details given]	Details Design: Phase III RCT Randomization method: No details on the randomisation methods Blinding: unclear Duration/last follow-up: monthly from the start of therapy until patients date	Objective Response* Progression Free Survival* Overall Survival* Health Related Quality of Life * Covered in the NMA (not included in the pairwise analyses)	Limitations Random sequence generation: Unclear risk –no details of randomisation methods Allocation concealment: Unclear risk - Not reported Blinding of participants and personnel Assessments: Unclear risk (Not reported but unlikely that participants and treatment administrators were blinded.) Blinding of outcome assessment: Unclear risk (Not reported) Incomplete outcome data: Low Risk Selective reporting: unclear risk (no study protocol available). Other sources of bias: high Risk (no sample size calculations) Overall risk of bias: Very serious Other information
Full citation	Sample size	Interventions	Details	Objective Response Overall Survival	Limitations

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Sunamura M, Karasawa K, Okamoto A, Ogata Y, Nemoto K, Hosotani R, Nishimura Y, Matsui K, Matsuno S; PR-350 study group.. Phase III trial of radiosensitizer PR-350 combined with intraoperative radiotherapy for the treatment of locally advanced pancreatic cancer. Pancreas. 2004 Apr;28(3):330-4. Ref ID Sunamura et al. 2004 Country/ies where the study was carried out: Japan Study type: Phase III RCT Aim of the study: To examine the effects of novel radiosensitizer, PR-350, accompanied by intraoperative radiology (IOR) on LAPC Study dates: Data collection-patients enrolment: July 1999-March 2002 Publication year: 2004 Source of funding: None reported.	N= 48 patients with LAPC Characteristics M/F (n): 15/7 (G1); 20/5 (G2) Median age (range): 61.1 (50-74) years (G1); 61.3 (45-74) years (G2) ECOG PS: Not reported Primary tumour site within pancreas: Not reported Inclusion criteria Age 20-75 years Performance status of 0-2 Life expectancy of >3 months Unresectable tumours due to invasion to the arterial system and/or peripancreatic nerve plexus Maximal diameters of tumours must be less than that required for radiotherapy An absence of liver metastases, other organ metastases and peritoneal seeding. Exclusion criteria	G1: PR-350 + radiotherapy (n=25) - PR-350 IV at 2000mg/m2 for ~25 minutes before intraoperative radiotherapy IOR at 25Gy 10-40 minutes are placebo infusion External Beam Radiotherapy two weeks after surgery at 40Gy delivered in 20x2Gy fractions, 5 fractions per week G2: Placebo + radiotherapy (n=22) - Placebo IV for ~25 minutes before intraoperative radiotherapy IOR at 25Gy 10-40 minutes are placebo infusion External Beam Radiotherapy two weeks after surgery at 40Gy delivered in 20x2Gy fractions, 5 fractions per week	Design: Double-blind phase III RCT Randomization method: no details of randomisation method used. Blinding: Double-blind (no details are provided) Duration/last follow-up: 6 months		Random sequence generation: Unclear risk –no details of randomisation methods Allocation concealment: Unclear risk - Not reported Blinding: Unclear risk – No methodology reported though in the discussion it states that this was a double blind trial Blinding of participants and personnel Assessments: Unclear risk (Discussion states this is a double blind trial but nothing in the methodology) Blinding of outcome assessment: Unclear risk (Discussion states this is a double blind trial but nothing in the methodology) Incomplete outcome data: Low Risk Selective reporting: unclear risk (no study protocol available). Other sources of bias: High Risk (no sample size calculations)

Study details	Participants	Interventions	Methods	Outcomes*	Comments
	Previous radiation therapy or chemotherapy Idiosyncrasy to drugs, including contrast media Presence of serious cardiovascular, pulmonary, renal or hepatic disease Coexistence of an active neoplasm Any conditions the physician believe may preclude the trial				Overall risk of bias: Very serious Other information
Full citation Wilkowski R, Boeck S, Ostermaier S, Sauer R, Herbst M, et al. CRT with concurrent gemcitabine and cisplatin with or without sequential CT with gemcitabine/cisplatin vs CRT with concurrent 5-5-FU in patients with locally advanced pancreatic cancer--a multi-centre randomised phase II study. Br J Cancer. 2009 Dec 1;101(11):1853-9. Ref ID Wilkowski et al. 2009 Country/ies where the study was carried out: Germany Study type:	Sample size N= 95 patients with LAPC Characteristics M/F (n): 16/16 (G1); 15/16 (G2); 20/11 (G3) Median age (range): 63(40-75) years (G1); 63(42-74) years (G2); 65(41-75) years (G3) ECOG PS: Not reported Primary tumour site within pancreas: Head(n):22 (G1); 25 (G2); 20 (G3) Body(n):6 (G1); 6 (G2); 6 (G3) Tail(n):1 (G1); - (G2); 2 (G3)	Interventions G1: CRT [GEM/Cisplatin] (n=32) - 300mg/m2 Gemcitabine and 30mg/m2 Cisplatin administered IV on days 1, 8, 22 and 29, 1hour before the start of radiotherapy G2: CRT [5-FU] (n=30) – Concurrent 5FU as a 24hr continuous infusion of 350mg/m2/day on each day of radiotherapy G3: CRT [GEM/Cisplatin] followed by Gemcitabine/Cisplatin-CT (n=31): 300mg/m2 Gemcitabine and 30mg/m2 Cisplatin	Details Design: Multi-centre phase II RCT Randomization method: Randomisation was 1:1:1 and stratified according to performance status and centre Blinding: unclear Duration/last follow-up: until patients' death	Objective Response* Progression Free Survival* Overall Survival* Adverse Events * Covered in the NMA (not included in the pairwise analyses)	Limitations Random sequence generation: Unclear Risk – no details were provided on the randomisation method Allocation concealment: Unclear risk - Not clear if this was an open label study Blinding: Unclear risk – No details provided. Blinding of participants and personnel Assessments: Unclear risk – No details provided

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Phase II RCT Aim of the study: To compare three different CRT regimens in terms of efficacy and tolerance in the treatment of patients with LAPC Study dates: Data collection-patients enrolment: February 2002-July 2005 Publication year: 2009 Source of funding:None reported.	Multicentre(n):3 (G1); -(G2); 3 (G3) Inclusion criteria Histologically confirmed, non-resectable pancreatic cancer (stages III and IVA) Exclusion criteria Distant metastases Previous Radiotherapy of the abdominal region Pregnant or lactating patients Women of childbearing age who lack a reliable method of contraception Patients with KPS <70% Insufficient renal function Active infections Patients who participated in another trial within 6 weeks of the start of treatment	administered IV on days 1, 8, 22 and 29, 1hour before the start of radiotherapy Patients without disease progression received 1000mg/m2 over 30 mins and 50mg/m2 every two weeks until disease progression, resectability of the tumour or unacceptable toxicity			Blinding of outcome assessment: Unclear risk – No details provided Incomplete outcome data: Low Risk Selective reporting: Low risk Other sources of bias: High Risk (No sample size calculations were provided) Overall risk of bias: Very serious Other information
*(please see Forest plots and Evidence grade profiles for full detail about study's findings)					

F.171 Management of metastatic pancreatic cancer

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Full citation Aigner KR, Gailhofer S, Kopp S. Regional versus systemic chemotherapy for advanced pancreatic cancer: a randomized	Sample size N= 14 patients with locally advanced/metastatic PC (mixed population) Characteristics	Interventions G1: Regional Intra-Arterial Chemotherapy (n=9) - Celiac axis infusion regional chemotherapy with	Details Design: Multicentre Phase 3 RCT Randomization method: not reported	Overall response rate (CR + PR)	Limitations - Cochrane Collaboration's 'Risk of bias' tool. Random sequence generation: Unclear

Study details	Participants	Interventions	Methods	Outcomes*	Comments
study. Hepatogastroenterology. 1998;45(22):1125-9. Ref ID Aigner et al., 1998 Country/ies where the study was carried out: Germany Study type: Multicentre Phase 3 RCT Aim of the study: To compare regional chemotherapy with systemic chemotherapy in advanced/metastatic pancreatic cancer Study dates: Data collection-patients enrolment: not reported Publication year: 1998 Source of funding: Not reported	M/F (n): 1/8 (G1); 2/3 (G2) Median age (range): 56(n.r.) years (G1); 59 (n.r.) years (G2) Clinical stage: Stage III: 2 (G1); 1 (G2) Stage IV: 7 (G1); 4 (G2) Primary tumour site within pancreas: Head: 7 (G1); 3 (G2) Body: 1 (G1); 1 (G2) Tail: 1 (G1); 1 (G2) Multicentre: 0 (G1); 0 (G2) Inclusion criteria Not reported Exclusion criteria Not reported	SpherexR microembolization. G2: Systemic Chemotherapy (n=5) - including mitomycin, mitoxanthrone and cisplatin (5pts.)	Blinding: unclear Duration/last follow-up: unclear		risk (No details given in the text) Allocation concealment: Unclear risk (No details given in the text) Blinding of participants and personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: Unclear risk (No details given in the text) Selective reporting: Low risk Overall risk of bias: very serious Other information
Full citation Azmy A, Abdelwahab S, Yassen M. Oxaliplatin and Bolus-Modulated 5-FU as a Second-Line Treatment for Advanced Pancreatic Cancer: Can Bolus Regimens Replace FOLFOX When Considered	Sample size N= 48 patients with locally advanced/metastatic PC (mixed population) Characteristics M/F (n): 16/8 (G1); 17/7 (G2) Median age (range): 56(44–69) years (G1); 54 (41–68) years (G2)	Interventions G1: Oxaliplatin + 5-FU as second line chemotherapy (n=24) - FU 500 mg/m(2) IV bolus weekly x6 weeks + leucovorin 500mg/m(2) IV weekly for 6 weeks during each 8-week	Details Design: Phase 3 RCT Randomization method: “Patients were randomly assigned to one of the treatment	Overall response rate (CR + PR) Progression Free Survival* Overall Survival* Adverse Events (Grade 3/4	Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool. Random sequence generation: Low risk Allocation concealment: Unclear

Study details	Participants	Interventions	Methods	Outcomes*	Comments
for Second Line?. ISRN Oncol. 2013;2013:358538. Ref ID Azmy et al., 2013 Country/ies where the study was carried out: Egypt Study type: Unblinded Phase 3 RCT Aim of the study: To compare the activity of 2 regimens combining oxaliplatin to bolus modulated 5-FU as second line treatment in advanced/metastatic pancreatic cancer pretreated with Gemcitabine -containing schedule. Study dates: Data collection-patients enrolment: 2008-2011 Publication year: 2013 Source of funding: Not reported	Clinical stage: LA: 15 (G1); 14 (G2) Metastatic: 9 (G1); 10 (G2) Site of metastases: Liver: 5 (G1); 6 (G2) Lung: 1 (G1); 1 (G2) LN: 2 (G1); 2 (G2) Peritoneal: 1 (G1); 1 (G2) Inclusion criteria Patients with histologically or cytologically proven LA or metastatic pancreatic adenocarcinoma, with at least 1 bidimensionally measurable lesion (World Health Organization (WHO) criteria); Eastern Cooperative Oncology Group (ECOG) PS of 1-2; (IV) tumor progression after first line GEM (whether GEM pretreated or GEM resistance); absence of severe uncontrolled cardiovascular, metabolic, infectious, or neurological diseases; adequate bone marrow reserve (neutrophil count > 1.5 × 109/L, platelet count > 100.000/mm3 and Hb > 10 g/dL); (VII) adequate liver function (serum bilirubin < 1.5 mg/dL, serum transaminases < 2x the upper limit of normal);	cycle + oxaliplatin 85mg/m(2) IV on weeks 1, 3, and 5 of each 8-week (FLOX) G2: Bolus leucovorin + bolus 5-FU as second line chemotherapy (n=24) -intravenous infusions of oxaliplatin 40mg/m(2), 5-FU 500 mg/m(2), and leucovorin 250mg/m(2) (3 weeks on, 1 week off)	regimens (block randomization at 4)” Blinding: open-label Duration/last follow-up: until patients' death	toxicities: Nausea/vomiting, Diarrhoea, Stomatitis, and haematological [including Neutropenia, Anaemia , Thrombocytopenia)	risk (No details given in the text) Blinding of participants and personnel Assessments: High risk Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: serious Other information * Not analytical data on results are reported (narrative reporting)

Study details	Participants	Interventions	Methods	Outcomes*	Comments
	adequate renal function (serum creatinine < 1.5 mg/dL); age between 18 and 75 years. Exclusion criteria Patients with: Histologic types other than adenocarcinoma. Neuropathy ≥ CTCAE grade 1. Ototoxicity > CTCAE grade 2. Serious, active comorbidity,				
Full citation Bernhard J, Dietrich D, Scheithauer W, Gerber D, Bodoky G, et al. Clinical benefit and quality of life in patients with advanced pancreatic cancer receiving Gemcitabine + capecitabine versus Gemcitabine single-agent : a randomized multicenter phase III clinical trial--SAKK 44/00-CECOG/PAN13001. J Clin Oncol. 2008;26(22):3695-701. Ref ID Bernhard et al., 2008 Country/ies where the study was carried out: Multicentre (Switzerland, Italy, Austria, Germany) Study type: Multicentre unblinded Phase 3 RCT	Sample size N= 319 patients with locally advanced/metastatic PC (mixed population) Characteristics M/F (n): 86/74 (G1); 85/74 (G2) Median age (range): 62(27-83) years (G1); 62 (36-84) years (G2) Clinical stage: LA: 32 (G1); 34 (G2) Metastatic: 128 (G1); 125 (G2) Inclusion criteria histologic/cytologic proof of primary inoperable/metastatic pancreatic adenocarcinoma; age more than 18 years; Karnofsky performance score (KPS) ≥ 60; no prior chemotherapy; and adequate bone marrow reserve Exclusion criteria known CNS metastases	Interventions G1: GEM + capecitabine (n=160) - oral Cap 650 mg/m2 twice daily on days 1 through 14 + Gem 1,000 mg/m2 in a 30-minute infusion on days 1 and 8 every 3 weeks G2: GEM single-agent (n=159) - 1,000 mg/m2 in a 30-minute infusion weekly for 7 weeks, followed by a 1-week break, and then weekly for 3 weeks every 4 weeks	Details Design: Multicentre Phase 3 RCT Randomization method: not reported Blinding: open-label Duration/last follow-up: 24 weeks	Response rate Overall Survival Adverse Events Health Related Quality of Life	Limitations - Cochrane Collaboration's 'Risk of bias' tool. Random sequence generation: Unclear risk (No details given in the text) Allocation concealment: Unclear risk (No details given in the text) Blinding of participants and personnel Assessments: High risk Blinding of outcome assessment: Low risk Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: serious

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Aim of the study: To compare clinical benefit response and quality of life in patients receiving Gemcitabine (Gem) + capecitabine versus single-agent Gem in advanced/metastatic pancreatic cancer Study dates: Data collection-patients enrolment: 2001-2004 Publication year: 2008 Source of funding: The trial was sponsored by the Swiss Group for Clinical Cancer Research, and the Central European Cooperative Oncology Group played a supportive role in Austria.	history of other primary malignancy within 5 years except for adequately treated cervical carcinoma in situ or basal cell skin carcinoma insufficient liver function creatinine clearance less than 30 mL/min active infection; breast feeding/pregnancy; reproductive potential without using effective contraception; serious concomitant systemic disorder incompatible with the trial in the investigator's judgment; known hypersensitivity or anticipated severe reaction to fluoropyrimidines; concomitant treatment with sorivudine or related analogs; grade 2 nausea or grade 1 vomiting				Other information
Full citation Bukowski RM, Balcerzak SP, O'Bryan RM, Bonnet JD, Chen TT. Randomized trial of 5-FU and mitomycin C with or without streptozotocin for advanced pancreatic cancer A Southwest Oncology Group study. Cancer. 1983;52(9):1577-82. Ref ID Bukowski et al., 1983	Sample size N= 181 patients with locally advanced/metastatic PC (mixed population) Characteristics Clinical stage: LA: 26 (G1); 22 (G2) Metastatic: 46 (G1); 51 (G2) All other population characteristics are reported unclearly. Inclusion criteria	Interventions G1: First line chemotherapy combination (n=70) streptozotocin, mitomycin C, and 5-FU (SMF) G2: First line chemotherapy combination (n=70) - mitomycin C and 5-FU (MF)	Details Design: Phase 3 RCT Randomization method: unclear “Patients were stratified according to risk status, and the presence of measurable or nonmeasurable disease, and randomized to	Overall response rate (CR + PR) Overall Survival* Adverse Events (Grade 3/4 toxicities: Nausea/vomiting, Diarrhoea, Leucopoenia Thrombocytopenia)	Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool. Random sequence generation: Unclear risk (No details given in the text) Allocation concealment: Unclear risk (No details given in the text)

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Country/ies where the study was carried out: USA Study type: Phase 3 RCT Aim of the study: To compare streptozotocin, mitomycin C, and 5-FU (SMF) with mitomycin C and 5-FU (MF) in advanced/metastatic pancreatic cancer Study dates: Data collection-patients enrolment: not reported Publication year: 1983 Source of funding Grant Support CA-04915/CA/NCI NIH HHS/United States; CA-04919/CA/NCI NIH HHS/United States; CA-04920/CA/NCI NIH HHS/United States;	histologic or cytologic confirmation of pancreatic adenocarcinoma; no previous chemotherapy or radiation therapy adequate renal function (BUN)l 25 mg% and creatinine 5 2.0 mg%). Exclusion criteria Patients with: not reported		receive either the MF or SMF regimens" Blinding: unclear Duration/last follow-up: unclear	Drug-related deaths	Blinding of participants and personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: very serious Other information * Not analytical data on results are reported (narrative reporting)
Full citation Burris HA 3rd, Moore MJ, Andersen J, Green MR, Rothenberg ML, et al. Improvements in survival and clinical benefit with Gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol. 1997;15(6):2403-13.	Sample size N= 160 patients with locally advanced/metastatic PC (mixed population) Characteristics M/F (n): 34/29 (G1); 34/29 (G2) Median age (range): 62(37-79) years (G1); 61 (36-77) years (G2) Clinical stage:	Interventions G1: 5-FU single-agent (n=63) - 600 mg/m2 once weekly G2: GEM single-agent (n=63) -1,000 mg/m2 weekly x 7 followed by 1 week of rest, then weekly x 3 every 4 weeks thereafter	Details Design: Phase 3 RCT Randomization method: unclear "Randomization of patients …... was performed at a central location."	Response rate Progression Free Survival Overall Survival Adverse Events	Limitations - Cochrane Collaboration's 'Risk of bias' tool. Random sequence generation: Unclear risk (No details given in the text) Allocation concealment: Low risk

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Ref ID Burris et al., 1997 Country/ies where the study was carried out: USA Study type: Single(patients)-blinded Phase 3 RCT Aim of the study: To compare single-agent 5-FU with Gemcitabine in advanced/metastatic pancreatic cancer Study dates: Data collection-patients enrolment: 1992-1994 Publication year: 1997 Source of funding: Supported by a grant from Eli Lilly and Company, Indianapolis, IN.	Stage II/III: 18 (G1); 15 (G2) Stage IV: 45 (G1); 48 (G2) Primary tumour site within pancreas: Not reported Inclusion criteria baseline Karnofsky performance status of less than 80; baseline analgesic consumption of - 10 morphine equivalent mg/d baseline pain intensity score of > 20 mm Exclusion criteria see inclusion criteria		Blinding: Single(patients)-blinded Duration/last follow-up: 24 weeks		Blinding of participants and personnel Assessments: Low risk Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: no serious Other information
Full citation Cantore M, Fiorentini G, Luppi G, Rosati G, Caudana R, Piazza E, Comella G, Ceravolo C, Miserocchi L, Mambrini A, Del Freo A, Zamagni D, Rabbi C, Marangolo. Gemcitabine versus FLEC regimen given intra-arterially to patients with nresectable pancreatic cancer: a prospective, randomized phase III trial	Sample size N= 138 patients with locally advanced/metastatic PC (mixed population) Characteristics M/F (n): 45/26 (G1); 47/20 (G2) Median age (range): 61 (38-76) years (G1); 64 (37-79) years (G2) Clinical stage: LA: 35 (G1); 32 (G2) Metastatic: 36 (G1); 35 (G2)	Interventions G1: FLEC (n=71) - 5-fluoruracil 1,000 mg/m2, leucovorin 100 mg/m2, epirubicin 60 mg/m2, carboplatin 300 mg/m2 infused bolus intra-arterially into celiac axis G2: GEM single-agent (n=67) - dose of 1,000 mg/m2 over 30 minutes intravenously weekly for 7 weeks, followed by 1 week of rest, then	Details Design: Phase 3 RCT Randomization method: not reported Blinding: unclear Duration/last follow-up: 12 months	Overall response rate (CR + PR) Overall Survival Adverse Events (Grade 3/4 toxicities: Nausea/vomiting, Diarrhoea, Leucopoenia Thrombocytopenia)	Limitations - Cochrane Collaboration's 'Risk of bias' tool. Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel Assessments: Unclear risk (No

Study details	Participants	Interventions	Methods	Outcomes*	Comments
of the Italian Society for Integrated Locoregional Therapy in Oncology. J Chemother. 2004;16(6):589-94. Ref ID Cantore et al., 2004 Country/ies where the study was carried out: Italy Study type: Phase 3 RCT Aim of the study: To compare FLEC (5-fluoruracil 1,000 mg/m2, leucovorin 100 mg/m2, epirubicin 60 mg/m2, carboplatin 300 mg/m2 infused bolus intra-arterially into celiac axis) with Gemcitabine in advanced/metastatic pancreatic cancer Study dates: Data collection-patients enrolment: 1998-2002 Publication year: 2004 Source of funding: Not reported	Primary tumour site within pancreas: Head: 42 (G1); 40 (G2) Body: 19 (G1); 19 (G2) Tail: 10 (G1); 8 (G2) Inclusion criteria histologically-proven adenocarcinoma of the pancreas not suitable for curative resection, baseline Karnofsky performance status of at least 50. adequate baseline bone marrow reserve, adequate baseline hepatic function adequate renal function .Exclusion criteria peritoneal metastases previous chemotherapy or radiotherapy or combination of both previous myocardial infarction, severe coagulopathy second malignancy (except cell skin cancer and in situ carcinoma of the cervix), pregnancy	weekly for 3 weeks every 4 weeks			details given in the text) Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: no serious Other information
Full citation Chao Y, Wu CY, Wang JP, Lee RC, Lee WP, Li CP. A randomized controlled trial of Gemcitabine + cisplatin versus Gemcitabine single-	Sample size N= 46 patients with metastatic PC Characteristics M/F (n): 17/4 (G1); 18/7 (G2)	Interventions G1: GEM + cisplatin (n=21) - 1,000 mg/m2 GEM and 25 mg/m2 cisplatin	Details Design: RCT Randomization method: not reported	Response rate Progression Free Survival Overall Survival Adverse Events	Limitations - Cochrane Collaboration's 'Risk of bias' tool. Random sequence generation: Unclear

Study details	Participants	Interventions	Methods	Outcomes*	Comments
agent in the treatment of metastatic pancreatic cancer. Cancer Chemother Pharmacol. 2013 Sep;72(3):637-42. Ref ID Chao et al., 2013 Country/ies where the study was carried out: Taiwan Study type: Unblinded RCT Aim of the study: To compare the efficacy and toxicity of single-agent Gemcitabine with Gemcitabine + cisplatin (G + C) in patients with metastatic pancreatic cancer Study dates: Data collection-patients enrolment: 2000-2002 Publication year: 2013 Source of funding: This work was supported by grants from Taipei Veterans General Hospital (V101C-178), National Science Council (NSC 98-2314-B-075-029), and National Research Program for Biopharmaceutics of Taiwan (100CT202).	Median age (range): 69 (47–81) years (G1); 69 (46–83) years (G2) Clinical stage: LA: 0 (G1); 0 (G2) Metastatic: 21 (G1); 25 (G2) Primary tumour site within pancreas: Head: 7 (G1); 7 (G2) Body: 7 (G1); 6 (G2) Tail: 7 (G1); 12 (G2) site of metastases: Liver: 13 (G1); 21 (G2) Lung: 7 (G1); 3 (G2) Bone: 1 (G1); 0 (G2) Inclusion criteria stage IV (metastatic) disease according to the Cancer Staging Manual of the American Joint Committee on Cancer Karnofsky performance score ≥50 absolute neutrophil count (ANC) ≥1,500 mm−3 platelet count ≥100,000 mm−3 serum creatinine level ≤1.5 mg dl−1 aspartate aminotransferase (AST) alanine aminotransferase (ALT) level <5 times the upper limit of normal measurable disease	G2: GEM single-agent (n=25) - 1,000 mg/m2	Blinding: open-label Duration/last follow-up: until patients' death	Health Related Quality of Life	risk (No details given in the text) Allocation concealment: Unclear risk (No details given in the text) Blinding of participants and personnel Assessments: High risk Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: very serious Other information

Study details	Participants	Interventions	Methods	Outcomes*	Comments
	no prior chemotherapy or radiotherapy no other malignancy and no serious medical or psychological illness that would preclude informed consent Exclusion criteria see Inclusion criteria				
Full citation Ciuleanu TE, Pavlovsky AV, Bodoky G, Garin AM, Langmuir VK, et al. A randomised Phase III trial of glufosfamide compared with best supportive care in metastatic pancreatic adenocarcinoma previously treated with Gemcitabine . Eur J Cancer. 2009;45(9):1589-96. Ref ID Ciuleanu et al., 2009 Country/ies where the study was carried out: Multicentre (Argentina, Brazil, Czech Republic, Hungary, India, Russia) Study type: Multicentre unblinded Phase 3 RCT Aim of the study: To compare the efficacy and safety of glufosfamide as compared with best supportive care (BSC) in	Sample size N= 303 patients with metastatic PC Characteristics M/F (n): 90/58 (G1); 90/65 (G2) Median age (range): 58(27–78) years (G1); 57 (29–80) years (G2) Clinical stage: LA: 0 (G1); 0 (G2) Metastatic: 148 (G1); 155 (G2) Sites of metastatic disease: Liver: 114 (G1); 120 (G2) Non-liver: 34 (G1); 35 (G2) Region: EU: 62 (G1); 63 (G2) Russia: 41 (G1); 39 (G2) South America: 26 (G1); 35 (G2) USA: 10 (G1); 11 (G2) India: 9 (G1); 7 (G2) Inclusion criteria at least 18 years of age at least one target or non-target lesion by RECIST	Interventions G1: Second line chemotherapy + best supportive care (n=148) - glufosfamide in patients previously treated with GEM. G2: Best supportive care (n=155) - BSC was defined as analgesics, antibiotics, transfusions, therapeutic haematopoietic colony-stimulating factors, erythropoietin and other appropriate supportive measures including concomitant medications that do not have anti-tumour effects.	Details Design: Multicentre Phase 3 RCT Randomization method: unclear “Randomisation was stratified by KPS (70 versus P80)” Blinding: open-label Duration/last follow-up: until patients' death	Progression Free Survival Overall Survival Adverse effects	Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool. Random sequence generation: Unclear risk (No details given in the text) Allocation concealment: Unclear risk (No details given in the text) Blinding of participants and personnel Assessments: High risk Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: high risk Selective reporting: Low risk Overall risk of bias: serious

Study details	Participants	Interventions	Methods	Outcomes*	Comments
patients with metastatic pancreatic cancer Study dates: Data collection-patients enrolment: 2004-2006 Publication year: 2009 Source of funding: This study was funded by Threshold Pharmaceuticals.	recovered from reversible toxicities of prior therapy adequate organ reserve including haematopoietic, hepatic and renal function (CrCL ⩾ 1.0 mL/s calculated by the Cockcroft-Gault formula) Karnofsky performance status (KPS) of at least 70. Exclusion criteria Patients were excluded if they had received more than one prior systemic therapy regimen for advanced disease				Other information
Full citation Cullinan S, Moertel CG, Wieand HS, Schutt AJ, Krook JE, Foley JF, Norris BD, Kardinal CG, Tschetter LK, Barlow JF. A phase III trial on the therapy of advanced pancreatic carcinoma. Evaluations of the Mallinson regimen and combined 5-FU, doxorubicin, and cisplatin. Cancer. 1990;65(10):2207-12. Ref ID Cullinan et al., 1990 Country/ies where the study was carried out: USA Study type: Phase 3 RCT	Sample size N= 187 patients with metastatic PC Characteristics M (%): 66 (G1); 56 (G2); 64 (G3) Median age (range): 60(35-80) years (G1); 62 (34-19) years (G2); 62 (27-76) years (G3) Clinical stage: LA: 0 (G1); 0 (G2); 0 (G3) Metastatic: 64 (G1); 61 (G2) ; 59 (G3) Extent of metastatic disease (%): Abdominal: 28 (G1); 30 (G2) ; 31 (G3) Hepatic: 59 (G1); 64 (G2) ; 59 (G3) Extra-abdominal: 13 (G1); 7 (G2) ; 10 (G3)	Interventions G1: Single-agent 5-FU alone chemotherapy (n=64) G2: Mallisom regimen (n=61) - combined and sequential 5-FU, cyclophosphamide, methotrexate, vincristine, and mitomycin C; G3: 5-FU combination chemotherapy (n=59) - 5-FU, doxorubicin, and cisplatin.	Details Design: Phase 3 RCT Randomization method: unclear "Patients were stratified according to the presence of measurable disease, the extent of metastasis (abdominal and/or retroperitoneal only, hepatic, or extra-abdominal), and ECOG performance status (0 or 1 versus 2 or 3)" Blinding: unclear Duration/last follow-up: until patients' death	Response rate Progression Free Survival Overall Survival Adverse Events	Limitations - Cochrane Collaboration's 'Risk of bias' tool. Random sequence generation: Unclear risk (No details given in the text) Allocation concealment: Unclear risk (No details given in the text) Blinding of participants and personnel Assessments: High risk Blinding of outcome assessment: Unclear risk (No details given in the text)

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Aim of the study: To compare the efficacy and toxicity of a combination chemotherapy regimen consisting of 5-FU (5-FU) alone, or the Mallinson regimen (combined and sequential 5-FU, cyclophosphamide, methotrexate, vincristine, and mitomycin C), or to combined 5-FU, doxorubicin, and cisplatinin patients with metastatic pancreatic cancer Study dates: Data collection-patients enrolment: not reported Publication year: 1990 Source of funding: Grant Support CA-31224/CA/NCI NIH HHS/United States CA-37404/CA/NCI NIH HHS/United States	Inclusion criteria histologic proof of ductal or undifferentiated adenocarcinoma consistent with a pancreatic primary and to have a pancreatic primary that could be reasonably established by surgical inspection, computed tomography (CT) scan, or sonography. ambulatory, maintaining an unassisted oral food intake of at least 1200 calories daily, and have a minimum of 3 weeks recovery from any major surgical procedure involving resection or bypass or 2 weeks recovery from exploration and biopsy only Exclusion criteria see inclusion criteria				Incomplete outcome data: Low risk Selective reporting: Unclear risk (No protocol published a-priori) Overall risk of bias: very serious Other information
Full citation Cullinan SA, Moertel CG, Fleming TR, Rubin JR, Krook JE, Everson LK, Windschitl HE, Twito DI, Marschke RF, Foley JF, et al. A comparison of three chemotherapeutic regimens in the treatment of advanced pancreatic and gastric carcinoma. 5-FU vs	Sample size N= 187 patients with metastatic PC Characteristics M (%): 68 (G1); 59 (G2); 64 (G3) Age 50-69 years (%): 70 (G1); 86 (G2); 76 (G3) Clinical stage (%): LA: 28 (G1); 36 (G2); 26 (G3)	Interventions G1: Single-agent 5-FU alone chemotherapy (n=50) G2/3: 2) 5-FU combination chemotherapy (n=44) 5-FU, 5-FU + doxorubicin; 3) 5-FU combination chemotherapy (n=50) 5-	Details Design: Multicentre Phase 3 RCT Randomization method: unclear "Patients were stratified according to the presence of measurable disease, the extent of metastasis	Response rate Progression Free Survival Overall Survival Adverse Events	Limitations - Cochrane Collaboration's 'Risk of bias' tool. Random sequence generation: Unclear risk (No details given in the text) Allocation concealment: Unclear

Study details	Participants	Interventions	Methods	Outcomes*	Comments
5-FU and doxorubicin vs 5-FU, doxorubicin, and mitomycin. JAMA. 1985;253(14):2061-7 Ref ID Cullinan et al., 1985 Country/ies where the study was carried out: USA Study type: Multicentre Phase 3 RCT Aim of the study: To compare single-agent 5-FU alone with 5-FU combination chemotherapy (a. 5-FU + doxorubicin, or b. 5-FU + doxorubicin + mitomycin) in advanced/metastatic pancreatic cancer Study dates: Data collection-patients enrolment: not reported Publication year: 1985 Source of funding: Grant Support CA 25224/CA/NCI NIH HHS/United States CA 31224/CA/NCI NIH HHS/United States CA 37404/CA/NCI NIH HHS/United States	Metastatic: not reported Extent of metastatic disease (%): Not reported Inclusion criteria histologic proof of ductal or undifferentiated adenocarcinoma ambulatory, maintaining an unassisted oral food intake of at least 1200 calories daily, have a minimum of 3 weeks recovery from any major surgical procedure involving resection or Exclusion criteria see inclusion criteria	FU + doxorubicin + mitomycin	(abdominal and/or retroperitoneal only, hepatic, or extra-abdominal), and ECOG performance status (0 or 1 versus 2 or 3)” Blinding: unclear Duration/last follow-up: unclear		risk (No details given in the text) Blinding of participants and personnel Assessments: High risk Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: Low risk Selective reporting: Unclear risk (No protocol published a-priori) Overall risk of bias: very serious Other information
Full citation Dahan L, Bonnetain F, Ychou M, Mitry E, Gasmi	Sample size N= 202 patients with metastatic PC	Interventions G1: Chemotherapy combination of 5-FU, FA	Details Design: Multicentre Phase 3 RCT	Overall response rate (CR + PR)	Limitations - Cochrane

Study details	Participants	Interventions	Methods	Outcomes*	Comments
M, et al. Combination 5-FU, folinic acid and cisplatin (LV5FU2-CDDP) followed by Gemcitabine or the reverse sequence in metastatic pancreatic cancer: final results of a randomised strategic phase III trial (FFCD 0301). Gut. 2010;59(11):1527-34. Ref ID Dahan et al., 2010 Country/ies where the study was carried out: France Study type: Multicentre Phase 3 RCT Aim of the study: To compare the combination of 5-FU (5FU), folinic acid and cisplatin (LV5FU2-CDDP) followed by Gemcitabine with Gemcitabine followed by LV5FU2-CDDP for patients with metastatic pancreatic adenocarcinoma Study dates: Data collection-patients enrolment: 2003-2006 Publication year: 2010 Source of funding: Not reported	Characteristics M/F (n): 65/37 (G1); 65/35 (G2) Median age (range): xx(xx-xx) years (G1); xx (xx-xx) years (G2) Clinical stage: LA: 0 (G1); 0 (G2) Metastatic: 102 (G1); 100 (G2) Primary tumour site within pancreas: Head: 57 (G1); 49 (G2) Other: 44 (G1); 50 (G2) Unknown: 1 (G1); 1 (G2) Site of metastases: Liver: 87 (G1); 90 (G2) Lung: 15 (G1); 12 (G2) Lymph nodes: 18 (G1); 24 (G2) Peritoneum: 11 (G1); 17 (G2) Other: 7 (G1); 8 (G2) Inclusion criteria proven metastatic pancreatic adenocarcinoma by histological or cytological biopsy at least one measurable metastasis ≥10 mm on CT or MRI or ≥20 mm with a conventional scan. The targeted metastasis should not have been treated by radiotherapy. Patients over 18, who had a WHO performance status (PS) ≤2 and a life expectancy of >2 months.	and cisplatin (LV5FU2-CDDP) followed by GEM after progression (n=102) - LV5FU2-CDDP included a 2 h infusion of leucovorin (LV) 200 mg/m2 followed by 5FU as a bolus 400 mg/m2 then a 46 h infusion of 2400 mg/m2 with cisplatin 50 mg/m2 as a 2 h infusion on day 1, every 2 weeks. GEM included 1000 mg/m2 as a 30 min weekly infusion for 7/8 weeks and then a weekly infusion for 3/4 weeks according to a classic Burris regimen G2: GEM followed by LV5FU2-CDDP after progression (n=100)	Randomization method: "Patients were randomised 1:1 through a minimisation program. Patients were stratified according to WHO PS (0, 1 versus 2), tumour localisation (head versus other) and participating institutions (centre)." Blinding: unclear Duration/last follow-up: until disease progression or death.	Progression free survival Overall Survival Adverse Events (Grade 3/4 toxicities: Nausea/ vomiting)	Collaboration's 'Risk of bias' tool. Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: no serious Other information

Study details	Participants	Interventions	Methods	Outcomes*	Comments
	adequate bone marrow, liver function , and renal function Exclusion criteria previous palliative or adjuvant chemotherapy prior radiotherapy <4 weeks brain metastases a medical history of malignant tumours, pregnant women or woman who were breast feeding, and LA cancer with no evidence of metastases.				
Full citation Deplanque G, Demarchi M, Hebbar M, Flynn P, Melichar B, et al. A randomized, placebo-controlled phase III trial of masitinib + Gemcitabine in the treatment of advanced pancreatic cancer. Ann Oncol. 2015;26(6):1194-200. Ref ID Deplanque et al., 2015 Country/ies where the study was carried out: Multicentre (France, Czech Republic, US) Study type: Multicentre double-blinded Phase 3 RCT Aim of the study: To compare masitinib combined with Gemcitabine	Sample size N= 348 patients with locally advanced/metastatic PC (mixed population) Characteristics M/F (n): 86/87 (G1); 102/73 (G2) Median age (range): 62.6 (36.0–84.0) years (G1); 61.7 (31.0–79.0) years (G2) Clinical stage: LA: 22 (G1); 24 (G2) Metastatic: 151 (G1); 151 (G2) Primary tumour site within pancreas: Head: 93 (G1); 94 (G2) Body: 50 (G1); 59 (G2) Tail: 54 (G1); 49 (G2) Inclusion criteria Histologically or cytologically confirmed adenocarcinoma of the pancreas	Interventions G1: GEM + masitinib (n=173) - Masitinib (9 mg/kg/day) was administered orally in two daily doses, while GEM (1000 mg/m2) was administered according to standard clinical practice. G2: GEM + placebo (n=175)	Details Design: Multicentre Phase 3 RCT Randomization method: "Patients were centrally randomized to treatments groups (1:1) using an Interactive Voice Response System (IVRS), with treatment allocated according to a modified minimization method. Stratification was done according to geographic region and disease status (LA versus metastatic)."	Progression Free Survival Overall Survival Adverse Events	Limitations - Cochrane Collaboration's 'Risk of bias' tool. Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel Assessments: Low risk Blinding of outcome assessment: Low risk Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: no serious Other information

Study details	Participants	Interventions	Methods	Outcomes*	Comments
with Gemcitabine single-agent in advanced/metastatic pancreatic cancer Study dates: Data collection-patients enrolment: 2008-2013 Publication year: 2015 Source of funding: This study was financially supported by AB Science, Paris, France (no grant number) and by Acobiom, Montpellier, France (no grant number)	Chemo naïve patients with advanced/metastatic disease Documented decision justifying non eligibility for surgical resection. The documentation of the non eligibility for surgical resection will be reviewed by an independent committee. Men and women, age >18 years Men and women of childbearing potential (entering the study after a confirmed menstrual period and who have a negative pregnancy test), must agree to use two methods (one for the patient and one for the partner) of medically acceptable forms of contraception during the study and for 3 months after the last treatment intake. Patient should be able and willing to comply with study visits and procedures as per protocol. Patient should understand, sign, and date the written voluntary informed consent form at the screening visit prior to any protocol-specific procedures performed. Exclusion criteria Patient treated for a cancer other than pancreatic cancer within 5 years before enrollment, with the exception		Blinding: double-blinded Duration/last follow-up: 26 months (median follow-up time)		

Study details	Participants	Interventions	Methods	Outcomes*	Comments
	of basal cell carcinoma or in situ cervical cancer Any condition that the physician judges could be detrimental to subjects participating in this study; including any clinically important deviations from normal clinical laboratory values or concurrent medical events Previous treatment Any anti-tumor therapy (any chemotherapy, radiotherapy, immunotherapy, biologic or hormonal therapy) within 6 months prior to baseline Treatment with any investigational agent within 4 weeks prior to baseline				
Full citation Ducreux M, Rougier P, Pignon JP, Douillard JY, Seitz JF, Bugat R, Bosset JF, Merouche Y, Raoul JL, Ychou M, Adenis A, Berthault-Cvitkovic F, Luboinski M; Groupe Digestif of the Fédération Nationale des Centres de Lutte Contre le Cancer Digestif. A randomised trial comparing 5-FU with 5-FU + cisplatin in advanced pancreatic carcinoma. Ann Oncol. 2002;13(8):1185-91. Ref ID Ducreux et al., 2002	Sample size N= 207 patients with metastatic PC Characteristics M/F (n): 67/36 (G1); 67/37 (G2) Mean age (SD): 59.9 (9) years (G1); 60.0 (9.1) years (G2) Clinical stage: LA: 0 (G1); 0 (G2) Metastatic: 103 (G1); 104 (G2) Site of metastases: Pancreas only: 12 (G1); 6 (G2) Liver: 75 (G1); 75 (G2) Lung: 9 (G1); 12 (G2) Lymph nodes: 16 (G1); 24 (G2) Peritoneum: 2 (G1); 6 (G2)	Interventions G1: 5-FU single-agent (n=103) 500 mg/m2/day for 5 days G2: 5-FU combination chemotherapy (n=104) - continuous 5-FU 1000 mg/m(2)/day for 5 days + cisplatin 100 mg/m(2) on day 1 or day 2	Details Design: Phase 3 RCT Randomization method: "Patients were stratified according to risk status, and the presence of measurable or nonmeasurable disease, using minimizzation." Blinding: unclear Duration/last follow-up: until patients' death	Overall response rate (CR + PR) Progression free survival Overall Survival Adverse Events (Grade 3/4 toxicities: Vomiting, Diarrhoea, Stomatits)	Limitations - Cochrane Collaboration's 'Risk of bias' tool. Random sequence generation: Low risk Allocation concealment: Unclear risk (No details given in the text) Blinding of participants and personnel Assessments: Unclear risk (No details given in the text)

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Country/ies where the study was carried out: France Study type: Phase 3 RCT Aim of the study: To compare 5-FU (5-FU) + cisplatin with 5-FU alone in patients with metastatic pancreatic adenocarcinoma Study dates: Data collection-patients enrolment: 1992-1998 Publication year: 2002 Source of funding: Not reported	Other: 7 (G1); 8 (G2) No PC: Ampulloma: 4 (G1); 5 (G2) Inclusion criteria Histological or cytological proof of ductal or undifferentiated adenocarcinoma of the pancreas. Disease was also to be either LA or metastatic, and lesions were to be measurable or evaluable. Patients with ampulloma were also deemed eligible. a life expectancy of at least 2 months, a WHO performance status (PS) of <3 age <75 years no previous chemotherapy, no hormonotherapy during the previous 3 months, and no radiotherapy treatment of indicator lesions. adequate hepatic, renal and bone marrow functions Exclusion criteria leucopoenia thrombocytopenia elevated serum creatinine (>110 µmol/l), hyperbilirubinemia active heart disease any known previous second primary malignant disease.				Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: serious Other information

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Full citation Eckhardt SG, De Porre P, Smith D, Maurel J, Steward WP, et al. Patient-reported outcomes as a component of the primary endpoint in a double-blind, placebo-controlled trial in advanced pancreatic cancer. J Pain Symptom Manage. 2009;37(2):135-43. Ref ID Eckhardt et al., 2009 Country/ies where the study was carried out: Multicentre (Australia, Austria, France, Germany, Portugal, Spain, Sweden, UK, US) Study type: Multicentre double-blinded Phase 3 RCT Aim of the study: To compare Gemcitabine + tipifarnib with Gemcitabine + placebo in advanced/metastatic pancreatic cancer Study dates: Data collection-patients enrolment: 2000-2001 Publication year: 2009 Source of funding: This study was supported by Johnson & Johnson	Sample size N= 244 patients with locally advanced/metastatic PC (mixed population) Characteristics F (n): 45 (G1); 49 (G2) Median age (range): 63 (35–81) years (G1); 60 (35–86) years (G2) Clinical stage: LA: 36 (G1); 33 (G2) Metastatic: 88 (G1); 87 (G2) Primary tumour site within pancreas: Not reported Inclusion criteria patients with pathologically confirmed, LA or metastatic, chemotherapy-naïve adenocarcinoma of the pancreas. ECOG-PS score of 0 to 2 adequate bone marrow, and adequate hepatic and renal function Exclusion criteria Patients with: See inclusion criteria	Interventions G1: GEM + tipifarnib (n=124) - The starting dose of Tipifarnib (placebo) was 200 mg twice daily in a continuous daily dosing schedule G2: GEM + placebo (n=120) - Starting GEM dose of 1000 mg/m2 intravenously weekly for seven weeks, followed by one week of rest, and then weekly for three weeks of each subsequent four-week period.	Details Design: Multicentre Phase 3 RCT Randomization method: "Patients were randomized centrally to the...through a dynamic randomization procedure, with stratification for the presence or absence of metastatic disease, ECOG-PS (0 versus 1 versus 2), and investigator site." Blinding: double-blinded Duration/last follow-up: until patients' death	Response rate Overall Survival Adverse Events	Limitations - Cochrane Collaboration's 'Risk of bias' tool. Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel Assessments: Low risk Blinding of outcome assessment: Low risk Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: no serious Other information

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Pharmaceutical Research & Development, LLC.					
Full citation Fuchs CS, Azevedo S, Okusaka T, Van Laethem JL, Lipton LR, et al. A phase 3 randomized, double-blind, placebo-controlled trial of ganitumab or placebo in combination with Gemcitabine as first-line therapy for metastatic adenocarcinoma of the pancreas: the GAMMA trial. Ann Oncol. 2015;26(5):921-7. Ref ID Fuchs et al., 2015 Country/ies where the study was carried out: Multicentre (Australia, Canada, Japan, Brazil, Czech Republic, Poland, Spain, UK, US) Study type: Multicentre double-blinded Phase 3 RCT Aim of the study: To compare ganitumab combined with Gemcitabine with Gemcitabine single-agent in patients with metastatic pancreatic adenocarcinoma Study dates:	Sample size N= 800 patients with metastatic PC Characteristics M/F (n): 188/134 (G1); 159/159 (G2) ; 85/75 (G3) Median age (range): 63 (36–83) years (G1); 62 (36–85) years (G2) ; 62 (31–81) years (G3) Clinical stage: LA: 0 (G1); 0 (G2); 0 (G3) Metastatic: 322 (G1); 318 (G2) ; 160 (G3) Primary tumour site within pancreas: Head: 115 (G1); 124 (G2) ; 159 (G3) Head & Body: 20 (G1); 21 (G2) ; 8 (G3) Head & Tail: 4 (G1); 1 (G2) ; 0 (G3) Head & Body & Tail : 2 (G1); 5 (G2) ; 2 (G3) Body: 71 (G1); 60 (G2) ; 30 (G3) Body & Tail: xx (G1); xx (G2) ; xx (G3) Tail: 44 (G1); 50 (G2) ; 33 (G3) No pancreas: 11 (G1); 12 (G2) ; 8 (G3) Site of metastases:	Interventions G1: GEM + placebo (n=322) - patients received GEM on days 1, 8, and 15, and placebo/ganitumab on days 1 and 15 of each 28-day cycle. G2: GEM + ganitumab 12 mg/kg (n=318) - GEM could be withheld or reduced depending on timing and toxicity severity; ganitumab was withheld until GEM was resumed. Ganitumab dose reductions up to 50% were allowed for toxicity; reductions were permanent. Ganitumab could be withheld or permanently discontinued for certain adverse events G3: GEM + ganitumab 20 mg/kg (n=160)	Details Design: Multicentre Phase 3 RCT Randomization method: "Patients were randomly assigned 2: 2: 1 to .... Randomization was stratified by ECOG PS (0 versus 1), liver metastases (yes versus no), and region (Australia, Western Europe, USA, and Canada versus rest of world)..." Blinding: double-blinded Duration/last follow-up: until patients' death	Response rate Progression Free Survival Overall Survival Adverse Events	Limitations - Cochrane Collaboration's 'Risk of bias' tool. Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel Assessments: Low risk Blinding of outcome assessment: Low risk Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: no serious Other information

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Data collection-patients enrolment: 2011-2012 Publication year: 2015 Source of funding: This study was supported by Amgen Inc. in collaboration with Takeda Global Research & Development Center, Inc.	Liver: 249 (G1); 255 (G2) ; 125 (G3) Lung: 76 (G1); 70 (G2) ; 37(G3) Lymph nodes: 97 (G1); 37 (G2) ; 8 (G3) Other: 104 (G1); 116 (G2) ; 51 (G3) Inclusion criteria Eligible patients (≥18 years) had previously untreated histologically or cytologically confirmed metastatic pancreatic adenocarcinoma; Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤1; and adequate hematologic, renal, hepatic, and cardiac function. Exclusion criteria histology other than pancreatic adenocarcinoma central nervous system metastases external biliary drain paracentesis or thoracentesis for malignant effusion within previous 14 days prior or synchronous malignancy major or minor surgery within previous 30 or 7 days				
Full citation Gill S, Ko YJ, et al. PANCREOX: A	Sample size	Interventions G1: Modified FOLFOX6 (infusion 5-FU,	Details Design: Multicentre Phase 3 RCT	Overall response rate (CR + PR)	Limitations - Cochrane

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Randomized Phase III Study of 5-Fluorouracil/Leucovorin With or Without Oxaliplatin for Second-Line Advanced Pancreatic Cancer in Patients Who Have Received Gemcitabine-Based Chemotherapy. J Clin Oncol. 2016 Ref ID Gill et al., 2016 Country/ies where the study was carried out: Canada Study type: Open-label Multicentre Phase 3 RCT Aim of the study: To evaluate the benefit of 5-FU/Leucovorin With or Without Oxaliplatin for Second-Line Advanced Pancreatic Cancer in Patients Who Have Received Gemcitabine-Based Chemotherapy Study dates: Data collection-patients enrolment: 2010-2012 Publication year: 2017 Source of funding: Supported by Sanofi Canada.	N= 108 patients with locally advanced/metastatic PC (mixed population) Characteristics M/F (n): 31/23 (G1); 30/24 (G2) Median age (range): 65(38-82) years (G1); 67 (48-78) years (G2) Clinical stage: LA: 4 (G1); 3 (G2) Metastatic: 50 (G1); 51 (G2) Primary tumour site within pancreas: n.r. Inclusion criteria Patients were eligible if they: had histologically or cytologically confirmed diagnosis of advanced, unresectable pancreatic cancer ECOG performance status of 0-2 Measurable disease a life expectancy of longer than 3 months, adequate hepatic function, adequate renal function and adequate hematologic function Patients must have received prior first-line treatment with gemcitabine and confirmed radiographic evidence of disease progression within 4 weeks prior to randomization. Exclusion criteria	leucovorin, and oxaliplatin) as second-line chemotherapy (n=54) - mFOLFOX6 consisted of the same therapy as G2 plus an oxaliplatin dose of 85 mg/m2 given as a 2-hour IV infusion on day 1, administered every 14 days G2: Infusional 5-FU/leucovorin alone as second-line chemotherapy (n=54) - consisted of a dose of LV 400 mg/m2 administered as a 2-hour IV infusion on day 1 and FU administered as a bolus IV dose of 400 mg/m2 on day 1 followed by a 2,400 mg/m2 continuous infusion for 46 hours, administered every 14 days Patients were treated until disease progression, unacceptable toxicity, or patient request	Randomization method: “were randomly assigned (in a 1:1 fashion) to receive … Patients were stratified according to age, sex, ECOG and presence of liver metastases.” Blinding: Open-label Duration/last follow-up: assessments were done at week 6, week 12, and until disease progression	Progression Free Survival Overall Survival Adverse Events Health Related Quality of Life	Collaboration’s ‘Risk of bias’ tool. Random sequence generation: Low risk Allocation concealment: unclear risk Blinding of participants and personnel Assessments: High risk Blinding of outcome assessment: High risk Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: serious Other information

Study details	Participants	Interventions	Methods	Outcomes*	Comments
	Exclusion criteria were: prior treatment with oxaliplatin or FU the presence of peripheral sensory or motor neuropathy greater than National Cancer Institute Common Toxicity Criteria (NCIC-CTC) grade 1 serious cardiacarrhythmia, diabetes, or serious active infection or other illness that would preclude study participation; and prior or current other malignancy within 5 years				
Full citation Gourgou-Bourgade S, Bascoul-Mollevi C, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul JL, Boige V, Bérille J, Conroy T. Impact of FOLFIRINOX compared with Gemcitabine on quality of life in patients with metastatic pancreatic cancer: results from the PRODIGE 4/ACCORD 11 randomized trial. J Clin Oncol. 2013;31(1):23-9. Ref ID Gourgou-Bourgade et al., 2013 Country/ies where the study was carried out:	Sample size N= 342 patients with metastatic PC Characteristics M/F (n): 106/65 (G1); 105/66 (G2) Median age (range): 61(25-76) years (G1); 71 (34-75) years (G2) Clinical stage: LA: 0 (G1); 0 (G2) Metastatic: 171 (G1); 171 (G2) Primary tumour site within pancreas: Head: 67 (G1); 63 (G2) Body: 53 (G1); 58 (G2) Tail: 45 (G1); 45 (G2) Multicentre: 6 (G1); 5 (G2) Inclusion criteria	Interventions G1: oxaliplatin, irinotecan, 5-FU, and leucovorin (FOLFIRINOX) (n=171) - oxaliplatin at a dose of 85 mg/m2, given as a 2-hour intravenous infusion, immediately followed by leucovorin at a dose of 400 mg/m2, given as a 2-hour intravenous infusion, with the addition, after 30 minutes, of irinotecan at a dose of 180 mg/m2, given as a 90-minute intravenous infusion through a Y-connector - followed by 5-FU at a dose of 400 mg/m2,	Details Design: Multicentre Phase 3 RCT Randomization method: "Randomization was performed centrally with stratification according to center, performance status (0 versus 1), and primary tumor localization (the head versus the body or tail of the pancreas)." Blinding: double-blinded Duration/last follow-up: 10 months	Health Related Quality of Life	Limitations - Cochrane Collaboration's 'Risk of bias' tool. Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: Low risk Incomplete outcome data: Low risk

Study details	Participants	Interventions	Methods	Outcomes*	Comments
France Study type: Multicentre Phase 3 RCT Aim of the study: To compare the quality of life (QoL) of patients receiving oxaliplatin, irinotecan, 5-FU, and leucovorin (FOLFIRINOX) with Gemcitabine in patients with metastatic pancreatic adenocarcinoma Study dates: Data collection-patients enrolment: 2005-2009 Publication year: 2013 Source of funding: Supported by Clinical Research Hospital Program grants (PHRC 2004 and 2007) from the French Ministry of Health, and grants from Amgen and the French National League against Cancer	Patients were eligible if they: Were 18 years of age or older and had histologically and cytologically confirmed, measurable metastatic pancreatic adenocarcinoma that had not previously been treated with chemotherapy Had Eastern ECOG performance status score of 0 or 1 Had adequate bone marrow, liver function, and renal function. Exclusion criteria Exclusion criteria were an age of 76 years or older, endocrine or acinar pancreatic carcinoma, previous radiotherapy for measurable lesions, cerebral metastases, a history of another major cancer, active infection, chronic Diarrhoea , a clinically significant history of cardiac disease, and pregnancy or breast-feeding.	administered by intravenous bolus. G2: GEM single-agent (n=171) - dose of 1,000 mg/m2 over 30 minutes intravenously weekly for 7 weeks, followed by 1 week of rest, then weekly for 3 weeks every 4 weeks			Selective reporting: Low risk Overall risk of bias: no serious Other information
Full citation Gresham GK, Wells GA, Gill S, Cameron C, Jonker DJ. Chemotherapy regimens for advanced pancreatic cancer: a systematic review and network meta-analysis. BMC Cancer. 2014 Jun 27;14:471.	Sample size N= 23 RCTs involving 19 treatment regimens and 9,989 patients with both pure metastatic PC or locally advanced/metastatic PC Patients with locally advanced/metastatic PC (19 studies) Abou-Alfa et al., 2006	Interventions FOLFIRINOX versus GEM single-agent Conroy et al., 2011 (n=171 versus n=171) GEM + 5-FU versus GEM single-agent Berlin et al., 2002 (n=160 versus n=162)	Details Abou-Alfa et al., 2006 Design: Multicentre Phase 3 RCT Randomization method: unclear Blinding: unclear Study setting: USA Berlin et al., 2002	NMA Overall Survival^ For the results of the NMA see Appendix 5. Primary studies Response rate Conroy et al., 2011	Limitations - ISPOR checklist for NMA (Jansen et al, 2014). Relevance: Sufficient Credibility: Sufficient Analysis: low risk of bias Reporting Quality & Transparency: low risk of bias

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Ref ID Gresham et al., 2014 Country/ies where the study was carried out: n.a. Study type: Network meta-analysis of 23 RCTs Aim of the study: To assess the comparative safety and efficacy of chemotherapy regimens for the treatment of advanced pancreatic cancer Study dates: Searches: 2002-2013 Publication year: 2014 Source of funding:None reported.	n=346 Berlin et al., 2002 n=322 Bramhall et al., 2002 n=239 Cunningham et al., 2009 n=533 Gonçalves et al., 2012 n=104 Heinemann et al., 2006 n=194 Heinemann et al., 2012 n=284 Herrmann et al., 2007~ n=319 Kindler et al., 2011 n=313 Louvet et al., 2005 n=313 Moore et al., 2007 n=569 Oettle et al., 2005 n=565 Philip et al., 2010~ n=741 Poplin et al., 2006 (2009) n=547 Reni et al., 2005 n=99 Riess et al., 2005 n=463 Rocha Lima et al., 2004	GEM + 5-FU + FA versus GEM single-agent Riess et al., 2005 (n=235 versus n=238) GEM + Axitinib versus GEM single-agent Kindler et al., 2011 (n=180 versus n=315) GEM + Capecitabine versus GEM single-agent Cunningham et al., 2009 (n=267 versus n=266) Herrmann et al., 2007 (n=160 versus n=159) GEM + Cetuximab versus GEM single-agent Philip et al., 2010 (n=372 versus n=371) GEM + Cisplatin versus GEM single-agent Colucci et al., 2010 (n=201 versus n=199) Heinemann et al., 2006 (n=98 versus n=97) PEFG versus GEM single-agent Reni et al., 2005 (n=54 versus n=50) GEM + Erlotinib versus GEM single-agent Moore et al., 2007 (n=284 versus n=285)	Design: Multicentre Phase 3 RCT Randomization method: unclear Blinding: unclear Study setting: USA Bramhall et al., 2002 Design: Phase 3 RCT Randomization method: ".. using a computer generated random code according to the method of minimisation" Blinding: double Study setting: UK Colucci et al., 2010 Design: Phase 3 RCT Randomization method: "Telephone random assignment was performed centrally, by a computer-driven minimization procedure." Blinding: Unclear Study setting: Italy Conroy et al., 2011 Design: Multicentre Phase 3 RCT	Abou-Alfa et al., 2006 Berlin et al., 2002 Bramhall et al., 2002 Colucci et al., 2010 Heinemann et al., 2006 Gonçalves et al., 2012 Herrmann et al., 2007 Cunningham et al., 2009 Kindler et al., 2011 Louvet et al., 2005 Poplin et al., 2006 Moore et al., 2007 Oettle et al., 2005 Philip et al., 2010 Reni et al., 2005 Rocha Lima et al., 2004 Stathopoulos et al., 2006	Interpretration: low risk of bias Conflict of Interest: low risk of bias Other information *: Von Holf et al., 2013 is a RCT on nab-Paclitaxel + GEM versus GEM single-agent. Since this drug is part of a NICE TA evaluation, then has been excluded from pairwise analyses. Even tough, this trial has been included in the NMA as a silent comparator – because the more data points in the NMA the more accurate it is. ^: Over survival: Data were extracted from the NMA only for this outcome, as all the necessary information was provided in theorginal paper. ~: Conroy et al., 2011; Herrmann et al., 2007; Philip et al., 2010; and Reni et al., 2005 includes data on HRQL in papers

Study details	Participants	Interventions	Methods	Outcomes*	Comments
	n=360 Stathopoulos et al., 2006 n=130 Van-Cutsem et al., 2004 n=688 Patients with metastatic PC (4 studies) Colucci et al., 2010 n=400 Conroy et al., 2011~ n=342 Van-Cutsem et al., 2009 n=607 Von-Hoff et al., 2013* n=871 Inclusion criteria Phase 3 randomized controlled trials enrolled at least 50 patients per arm Involving in patients with locally advanced/metastatic pancreatic cancer who were eligible for first-line therapy Exclusion criteria Trials including over 50% of patients with LA non-metastatic disease in their treatment arms Trials involving radiation therapy Phase II trials	GEM + Exatecan versus GEM single-agent Abou-Alfa et al., 2006 (n=175 versus n=174) GEM + Irinotecan versus GEM single-agent Rocha Lima et al., 2004 (n=180 versus n=180) Stathopoulos et al., 2006 (n=60 versus n=70) GEM + Marimastat versus GEM single-agent Bramhall et al., 2002 (n=120 versus n=119) GEM + Nab-Paclitaxel versus GEM single-agent * Von-Hoff et al., 2013 (n=431 versus n=430) GEM + Oxaliplatin versus GEM single-agent Louvet et al., 2005 (n=156 versus n=157) Poplin et al., 2006 (2009) (n=272 versus n=275) GEM + Pemetrexed versus GEM single-agent Oettle et al., 2005 (n=283 versus n=282)	Randomization method: “Randomization was performed centrally with stratification according to center, performance status, and primary tumor localization” Blinding: unclear Study setting: France Cunningham et al., 2009 Design: Multicentre Phase 3 RCT Randomization method: “Patients were randomly assigned … a computer-generated variable-size blocked randomization method. Randomization was stratified.” Blinding: open-label Study setting: Multicentre (UK, Switzyerland, Austria) Gonçalves et al., 2012 Design: Phase 3 RCT	Van-Cutsem et al., 2004 Progression Free Survival Conroy et al., 2011 Abou-Alfa et al., 2006 Berlin et al., 2002 Bramhall et al., 2002 Colucci et al., 2010 Heinemann et al., 2006 Gonçalves et al., 2012 Herrmann et al., 2007 Cunningham et al., 2009 Kindler et al., 2011 Louvet et al., 2005 Poplin et al., 2006 et al., (2009) Moore et al., 2007 Oettle et al., 2005 Philip et al., 2010	pulished ad hoc: Gourgou-Bourgade et al., 2013; Bernhard et al., 2008; Moinpour et al., 2010; and Reni et al., 2006, respectively.

Study details	Participants	Interventions	Methods	Outcomes*	Comments
		GEM + Sorafenib versus GEM single-agent Gonçalves et al., 2012 (n=52 versus n=52) GEM + Tipifarnib versus GEM single-agent Van-Cutsem et al., 2004 (n=344 versus n=344) GEM + Erlotinib + Bevacizumab versus GEM + Erlotinib Van-Cutsem et al., 2009 (n=306 versus n=301) GEM + Erlotinib versus Capecitabine + Erlotinib Heinemann et al., 2012 (n=131 versus n=143)	Randomization method: "…, using a minimization procedure based on the following parameters: disease extent and ECOG performance." Blinding: double Study setting: France Heinemann et al., 2006 Design: Multicentre Phase 3 RCT Randomization method: "Central random assignment was performed before the start of treatment…" Blinding: open-label Study setting: Germany Heinemann et al., 2012 Design: Multicentre Phase 3 RCT Randomization method: "patients were stratified according to stage and centre; randomisation was performed centrally	Reni et al., 2005 Riess et al., 2005 Rocha-Lima et al., 2004 Stathopoulos et al., 2006 Van-Cutsem et al., 2004 Overall Survival^ Adverse Events Conroy et al., 2011 Abou-Alfa et al., 2006 Berlin et al., 2002 Bramhall et al., 2002 Colucci et al., 2010 Heinemann et al., 2006 Gonçalves et al., 2012 Herrmann et al., 2007 Cunningham et al., 2009 Kindler et al., 2011 Louvet et al., 2005	

Study details	Participants	Interventions	Methods	Outcomes*	Comments
			by fax in a 1:1 ratio..." Blinding: open-label Study setting: Germany Herrmann et al., 2007 Design: Multicentre Phase 3 RCT Randomization method: unclear Blinding: unclear Study setting: Multicentre (Switzerland, Italy, Austria, Germany) Kindler et al., 2011 Design: Multicentre Phase 3 RCT Randomization method: "A centralised randomisation procedure (interactive voice randomisation system accessible via telephone or internet) …. with randomised permuted blocks within strata." Blinding: double Study setting: USA Louvet et al., 2005	Poplin et al., 2006 et al., (2009) Moore et al., 2007 Oettle et al., 2005 Philip et al., 2010 Riess et al., 2005 Rocha-Lima et al., 2004 Stathopoulos et al., 2006 Van-Cutsem et al., 2004 Health Related Quality of Life Conroy et al., 2011~ Heinemann et al., 2006 Kindler et al., 2011 Moore et al., 2007 Philip et al., 2010~ Reni et al., 2005~	

Study details	Participants	Interventions	Methods	Outcomes*	Comments
			Design: Multicentre Phase 3 RCT Randomization method: “Patients were randomized centrally…” Blinding: unclear Study setting: Multicentre (France, Italy) Moore et al., 2007 Design: Multicentre Phase 3 RCT Randomization method: unclear Blinding: double Study setting: Canada Oettle et al., 2005 Design: Multicentre Phase 3 RCT Randomization method: “…using a centralized, automated randomization procedure...” Blinding: open-label Study setting: Multicentre (Argentina, Australia, Austria, Belgium, France, Germany, Greece, Italy, The Netherlands, Peru,		

Study details	Participants	Interventions	Methods	Outcomes*	Comments
			Portugal, Spain, Sweden, Taiwan, UK, US, Venezuela) Philip et al., 2010 Design: Multicentre Phase 3 RCT Randomization method: "… using the dynamic balancing algorithm with stratification..." Blinding: open-label Study setting: USA Poplin et al., 2006 (2009) Design: Multicentre Phase 3 RCT Randomization method: "Patients were randomly assigned to treatment using a dynamic balancing algorithm that stratified …." Blinding: unclear Study setting: USA Reni et al., 2005 Design: Phase 3 RCT Randomization method: "…by use of a computer-generated random code..." Blinding: open-label		

Study details	Participants	Interventions	Methods	Outcomes*	Comments
			Study setting: Italy Riess et al., 2005 Design: Phase 3 RCT Randomization method: not reported Blinding: unclear Study setting: Germany Rocha Lima et al., 2004 Design: Multicentre Phase 3 RCT Randomization method: “Patients were centrally randomly assigned and stratified by...” Blinding: unclear Study setting: Multicentre (New Zealand, USA) Stathopoulos et al., 2006 Design: Phase 3 RCT Randomization method: “Patients were centrally randomised by computer at a one-to-one ratio” Blinding: unclear		

Study details	Participants	Interventions	Methods	Outcomes*	Comments
			Study setting: Greece Van-Cutsem et al., 2004 Design: Multicentre Phase 3 RCT Randomization method: “through a dynamic randomization procedure with stratification on...” Blinding: double Study setting: Multicentre (Belgium, Germany, Czech Republic, Poland, the Netherlands, US) Van-Cutsem et al., 2009 Design: Multicentre Phase 3 RCT Randomization method: “Randomization was performed via an interactive voice recording service...” Blinding: double Study setting: Multicentre (Australia, Austria, Belgium, Canada, China, France, Germany, Czech		

Study details	Participants	Interventions	Methods	Outcomes*	Comments
			Republic, Italy, Peru, Poland, Singapore, Sweden, Taiwan, the Netherlands, UK) Von-Hoff et al., 2013 Design: Multicentre Phase 3 RCT Randomization method: not reported Blinding: open-label Study setting: Multicentre (Australia, Austria, Belgium, Canada, France, Germany, Czech Republic, Italy, Spain, Poland, Ukraine, Russia, USA)		
Full citation Irigoyen A, Gallego J, et al. Gemcitabine-erlotinib versus gemcitabine-erlotinib-capecitabine in the first-line treatment of patients with metastatic pancreatic cancer: Efficacy and safety results of a phase IIb randomised study from the Spanish TTD Collaborative Group. Eur J Cancer. 2017;75:73-82. Ref ID	Sample size N= 120 patients with metastatic PC Characteristics M/F (n): 34/26 (G1); 34/26 (G2) Median age (range): 62(31-77) years (G1); 64 (29-78) years (G2) Clinical stage: LA: 0 (G1); 0 (G2) Metastatic: 60 (G1); 60 (G2) Primary tumour site within pancreas:	Interventions G1: GEM + capecitabine + erlotinib (n=60) – as G2 with the addition of capecitabine 830 mg/m2 orally twice daily on days 1-21 G2: GEM + erlonitib (n=60) - GEM at 1,000 mg/m2 was given intravenously over 30 minutes on days 1, 8, and 15 of a 28-day cycle with erlotinib 100	Details Design: Phase 2b RCT Randomization method: “patients were randomised 1:1 to either GE arm or GEC arm. Patients were stratified according to ECOG performance status (0/1 versus 2)” Blinding: open-label	Overall response rate (CR + PR) Progression Free Survival Overall Survival Adverse Events	Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool. Random sequence generation: Low risk Allocation concealment: unclear risk Blinding of participants and personnel Assessments: High risk

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Irigoyen et al., 2017 Country/ies where the study was carried out: Spain Study type: Open-label phase 2 RCT Aim of the study: To assess whether combining capecitabine with gem + erlotinib (GE) was safe and effective versus GE in patients with metastatic PC. Study dates: Data collection-patients enrolment: 2011-2013 Publication year: 2017 Source of funding: Supported by Roche Pharma, Spain.	n.r. Inclusion criteria Patients were eligible if they: had histologically or cytologically confirmed, measurable, metastatic pancreatic adenocarcinoma were aged >18 years and with an ECOG performance status 0-2 Patients were required to have adequate bone marrow, liver and renal function and to be able to take oral medication. Exclusion criteria Exclusion criteria were: the history of another primary neoplasm in the 5 years before study entry clinically significant cardiovascular disease or current infection grade >2. ampullary or pancreatic endocrine tumours	mg/day continuous oral administration	Duration/last follow-up: 24 months (protocol) The median followup time was 28.1 months in the GE arm and 23.5 months in the GEC arm.		Blinding of outcome assessment: High risk Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: serious Other information
Full citation Ji Z, Wang Y, Chen X, Wu T. Peripancreatic artery ligation and artery infusion chemotherapy for advanced pancreatic carcinoma. Chin Med J (Engl). 2003 Jan;116(1):89-92. Ref ID Ji et al., 2003	Sample size N= 29 patients metastatic PC Characteristics (Not reported by intervention group) M/F (n): 16/12 Mean age (range): 62.4 Clinical stage: Not reported^ Primary tumour site within pancreas: Head: 17 (TOTAL)	Interventions G1: Regional Intra-Arterial Chemotherapy (n=18) - patients underwent bilio-enterostomy and/or gastro-enterostomy combined with peripancreatic arterial ligation and arterial infusion regional chemotherapy.	Details Design: Multicentre Phase 3 RCT Randomization method: not reported Blinding: unclear Duration/last follow-up: 3 to 18 months	Overall response rate (CR + PR) Overall Survival* Adverse Events (Grade 3/4 toxicities: Nausea/vomiting)	Limitations - Cochrane Collaboration's 'Risk of bias' tool. Random sequence generation: Unclear risk (No details given in the text) Allocation concealment: Unclear risk (No details given in the text)

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Country/ies where the study was carried out: China Study type: Multicentre Phase 3 RCT Aim of the study: To compare intra-arterial chemotherapy with systemic chemotherapy in patients with LA and/or metastatic adenocarcinoma of the pancreas. Study dates: Data collection-patients enrolment: 1995-2000 Publication year: 2003 Source of funding: Not reported	Head/Body: 4 (TOTAL) Body: 2 (TOTAL) Tail: 5 (TOTAL) Multicentre: 1 (TOTAL) Site of metastases: Liver: 12 (TOTAL) Lymph node: 7 (TOTAL) Inclusion criteria Diagnosis of PC with liver metastases confirmed by surgical exploration and pathological biopsy Exclusion criteria Not reported	G2: Systemic Chemotherapy (n=11) - patients underwent bilio-enterostomy and/or gastro-enterostomy combined with systemic chemotherapy after surgery			Blinding of participants and personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: High risk Incomplete outcome data: Low risk Selective reporting: Unclear risk (no study protocol to permit judgement on this criterion) Overall risk of bias: very serious Other information * Not analytical data on results are reported (narrative reporting) ^see inclusion criteria
Full citation Kindler HL, Niedzwiecki D, Hollis D, Sutherland S, Schrag D, Hurwitz H, Innocenti F, Mulcahy MF, O'Reilly E, Wozniak TF, Picus J, Bhargava P, Mayer RJ, Schilsky RL, Goldberg RM. Gemcitabine + bevacizumab compared with Gemcitabine +	Sample size N= 602 patients with locally advanced/metastatic PC (mixed population) Characteristics M (%): 58 (G1); 51 (G2) Median age (range): 64(26-88) years (G1); 65 (35-86) years (G2) Clinical stage (%):	Interventions G1: GEM + bevacizumab (n=302) - Bevacizumab at 10 mg/kg or placebo was administered intravenously after GEM on days 1 and 15 of each cycle. G2: GEM + placebo (n=300) - GEM at 1,000	Details Design: Multicentre Phase 3 RCT Randomization method: “Patients were randomly assigned 1:1.., stratified by disease extent (LA v metastatic), ECOG performance status	Response rate Progression Free Survival Overall Survival Adverse Events	Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool. Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and

Study details	Participants	Interventions	Methods	Outcomes*	Comments
placebo in patients with advanced pancreatic cancer: phase III trial of the Cancer and Leukemia Group B (CALGB 80303). J Clin Oncol. 2010;28(22):3617-22. Ref ID Kindler et al., 2010 Country/ies where the study was carried out: USA Study type: Multicentre double-blinded Phase 3 RCT Aim of the study: To compare the effectiveness and tolerability of Gemcitabine + bevacizumab with Gemcitabine + placebo for advanced/metastatic pancreatic cancer Study dates: Data collection-patients enrolment: 2004-2006 Publication year: 2010 Source of funding: Grants No. CA31946 from the National Cancer Institute to Cancer and Leukemia Group B 80303 (CALGB 80303) trial (R.L.S.), No. CA33601 to the CALGB Statistical Center (S.G.), and No.	LA: 16 (G1); 15 (G2) Metastatic: 84 (G1); 85 (G2) Primary tumour site within pancreas: Not reported Inclusion criteria histologically or cytologically confirmed unresectable pancreatic adenocarcinoma not prior chemotherapy for metastatic disease Adjuvant chemotherapy was allowed if it did not contain GEM or bevacizumab, if it was given > 4 weeks before enrollment, and if the patient had subsequent disease progression ECOG PS 0 to 2 adequate bone marrow, renal,and hepatic function An international normalized ratio (INR) ≤ 1.5 was required unless the patient was on warfarin; warfarin-treated patients needed to be on a stable dose with an INR between 2 and 3. Eligible patients were at least 18 years of age and had a life expectancy of at least 12 weeks. Exclusion criteria significant bleeding within 6 months before registration	mg/m2 was given intravenously over 30 minutes on days 1, 8, and 15 of a 28-day cycle	(0/1 v 2), and prior radiation (no v yes)” Blinding: double-blinded Duration/last follow-up: until patients’ death		personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: Low risk Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: no serious Other information

Study details	Participants	Interventions	Methods	Outcomes*	Comments
CA41287, CA 32291, CA47577, CA21115, CA17145, CA77651, CA45418, CA77440, and CA47559.	esophageal varices computed tomography scan documentation of invasion of adjacent organs clinically significant heart disease, or CNS disease				
Full citation Lee HS, Chung MJ, et al. A randomized, multicenter, phase III study of gemcitabine combined with capecitabine versus gemcitabine alone as first-line chemotherapy for advanced pancreatic cancer in South Korea. Medicine (Baltimore). 2017;96(1):e5702. Ref ID Lee et al., 2017 Country/ies where the study was carried out: South Korea Study type: Open-label Multicentre Phase 3 RCT Aim of the study: To compare the efficacy and safety of GEM + capecitabine versus single-agent GEM in advanced pancreatic cancer as first-line chemotherapy. Study dates:	Sample size N= 214 patients with locally advanced/metastatic PC (mixed population) Characteristics M/F (n): 63/45 (G1); 57/49 (G2) Median age (range): 64(37-80) years (G1); 64 (43-85) years (G2) Clinical stage: II: 6 (G1); 10 (G2) III: 23 (G1); 20 (G2) IV: 79 (G1); 76 (G2) Primary tumour site within pancreas: Head: 46 (G1); 42 (G2) Body: 21 (G1); 26 (G2) Tail: 31 (G1); 25 (G2) Multicentre: 9 (G1); 13 (G2) Inclusion criteria Patients were eligible if they: Were deemed inoperable locally advanced or metastatic pancreatic cancer according to the national comprehensive cancer network guidelines no prior history of chemotherapy or radiotherapy	Interventions G1: GEM + capecitabine + (n=108) - oral capecitabine 1660 mg/m2 daily for 3 weeks followed by a 1-week break plus Gem 1000 mg/m2 by 30-minute intravenous infusion weekly for 3 weeks every 4 weeks. G2: GEM single-agent (n=106) - 30-minute intravenous infusion weekly for 3 weeks every 4 weeks.	Details Design: Multicentre Phase 3 RCT Randomization method: "…1:1 basis according to a computer-generated variable-size blocked randomization method. Randomization was stratified by extent of disease (locally advanced stage vs metastatic stage)." Blinding: unclear Duration/last follow-up: unclear	Overall response rate (CR + PR) Progression Free Survival Overall Survival Adverse Events	Limitations - Cochrane Collaboration's 'Risk of bias' tool. Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: serious Other information

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Data collection-patients enrolment: 2007-2011 Publication year: 2017 Source of funding:None reported.	between the ages of 18 and 85 years ECOG performance status of 0 to 2 and adequate bone marrow, hepatic, and renal function Exclusion criteria Exclusion criteria were: pancreatic cancer other than adenocarcinoma concurrent malignancy brain metastasis serious uncontrollable medical conditions, and significant cardiac history				
Full citation Maisey N, Chau I, Cunningham D, Norman A, Seymour M, et al. Multicenter randomized phase III trial comparing protracted venous infusion (PVI) 5-FU (5-FU) with PVI 5-FU + mitomycin in inoperable pancreatic cancer. J Clin Oncol. 2002;20(14):3130-6. Ref ID Maisey et al., 2002 Country/ies where the study was carried out: UK Study type: Phase 3 RCT Aim of the study:	Sample size N= 209 patients with locally advanced/metastatic PC (mixed population) Characteristics M/F (n): 61/39 (G1); 64/36 (G2) Median age (range): 61(28-86) years (G1); 62(29-80) years (G2) Clinical stage (%): LA: 44 (G1); 36 (G2) Metastatic: 56 (G1); 64 (G2) Primary tumour site within pancreas: Not reported Inclusion criteria histologically confirmed LA or metastatic carcinoma of the pancreas that was not	Interventions G1: 5-FU combination chemotherapy (n=102) - 5-FU + mitomycin : 7 mg/m2 every 6 weeks for four courses G2: 5-FU single-agent chemotherapy (n=107) - 300 mg/m2/d for a maximum of 24 weeks	Details Design: Phase 3 RCT Randomization method: “Patients were randomly assigned according to a computer-generated randomization code. The patients were randomized centrally in blocks of six and stratified by centre.” Blinding: unclear Duration/last follow-up: 24 months	Response rate Overall Survival Adverse Events	Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool. Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: Unclear risk (No details given in the text)

Study details	Participants	Interventions	Methods	Outcomes*	Comments
To compare the effectiveness and tolerability of 5-FU (5-FU) with PVI 5-FU + mitomycin (MMC) for advanced/metastatic pancreatic cancer Study dates: Data collection-patients enrolment: 1994-2000 Publication year: 2002 Source of funding: Not reported	amenable to surgical resection or radical radiotherapy adequate bone marrow reserve, renal function, and hepatic function ECOG PS 0 to 2 life expectancy of more than 3 months, and no intercurrent uncontrolled medical illnesses. Exclusion criteria intracerebral metastases current alcohol or other drug abuse history of other malignancy uncontrolled angina pectoris or clinically significant cardiac dysrhythmias any psychological condition precluding informed consent.				Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: no serious Other information
Full citation Maraveyas A, Waters J, Roy R, Fyfe D, Propper D, et al. Gemcitabine versus Gemcitabine + dalteparin thromboprophylaxis in pancreatic cancer. Eur J Cancer. 2012 Jun;48(9):1283-92. Ref ID Maraveyas et al., 2012 Country/ies where the study was carried out: UK Study type: Phase 2b RCT	Sample size N= 171 patients with locally advanced/metastatic PC (mixed population) Characteristics M/F (%): 60/40 (G1); 57/43 (G2) Median age (range): 62 (40–79) years (G1); 66 (43–82) years (G2) Clinical stage: LA: 31 (G1); 26 (G2) Metastatic: 29 (G1); 37 (G2) Primary tumour site within pancreas: Not reported	Interventions G1: GEM + weight-adjusted dalteparin [WAD] (n=60) - Dalteparin was given in a weight-adjusted schedule at a dose of 200 IU/kg once daily subcutaneously for 4 weeks followed by a stepdown to 150 IU/kg for a further 8 weeks. G2: 1,000 mg/m2 administered intravenously	Details Design: Phase 2b RCT Randomization method: “Patients were randomised with software developed by York University. The block randomisation method was followed and patients were stratified for stage (LA versus metastatic) and performance status	Overall Survival* Adverse Events Grade 3/4 toxicities (Haematological and Hepatic function impairment) Vascular thromboembolism events(VTE)	Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool. Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel Assessments: Unclear risk (No details given in the text)

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Aim of the study: To compare the effectiveness and tolerability of Gemcitabine + weight-adjusted dalteparin (WAD) with Gemcitabine single-agent for advanced/metastatic pancreatic cancer Study dates: Data collection-patients enrolment: 2003-2009 Publication year: 2012 Source of funding:: The study was sponsored by the Hull and East Yorkshire Hospitals National Health Service Trust. Pfizer provided a grant covering the cost of dalteparin.	Inclusion criteria histopathological or cytological diagnosis of non-resectable, recurrent or metastatic pancreatic cancer patients who didn't have thromboembolism, anticoagulation or a thromboembolic event in the 6 months before randomisation. Central venous access devices and inferior vena cava filters were not allowed KPS of 60–100 age ⩾18 years estimated life expectancy >12 weeks measurable or evaluable disease in baseline CT of thorax/abdomen/pelvis adequate haematological and renal function international normalised ratio (INR) <1.5 no obvious contraindication to anticoagulation and adequate liver function Exclusion criteria previous GEM -containing treatment comorbidities which in the opinion of the investigator would compromise informed consent or compliance history of other advanced malignancy		(KPS 90–100 versus 60–80)." Blinding: unclear Duration/last follow-up: 12 weeks		Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: Low risk Selective reporting: Unclear risk (no protocol) Overall risk of bias: serious Other information * reported in narrative way. Not enough analytical data reported.

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Full citation Middleton G, Silcocks P, Cox T, Valle J, Wadsley J, et al. Gemcitabine and capecitabine with or without telomerase peptide vaccine GV1001 in patients with LA or metastatic pancreatic cancer (TeloVac): an open-label, randomised, phase 3 trial. Lancet Oncol. 2014;15(8):829-40. Ref ID Middleton et al., 2014 Country/ies where the study was carried out: UK Study type: Multicentre unblinded Phase 3 RCT Aim of the study: To assess the efficacy and safety of sequential or simultaneous telomerase vaccination (GV1001) in combination with chemotherapy in patients with advanced/metastatic pancreatic cancer Study dates: Data collection-patients enrolment: 2007-2011 Publication year: 2014 Source of funding:	Sample size N= 1062 patients with locally advanced/metastatic PC (mixed population) Characteristics M/F (n): 209/149 (G1); 203/147 (G2); 196/158 (G3) Median age (range): 62 (55–69)years (G1); 64 (58–69) years (G2); 63 (57–69) years (G3) Clinical stage: LA: 111 (G1) ; 104 (G2); 110 (G3) Metastatic: 247 (G1) ; 246 (G2); 244 (G3) Primary tumour site within pancreas: Head: 208 (G1) ; 203 (G2); 190 (G3) Body: 55 (G1) ; 64 (G2); 64 (G3) Tail: 35 (G1) ; 31 (G2); 40 (G3) Multicentre: 60 (G1) ; 52 (G2); 60 (G3) Inclusion criteria treatment naive patients age > than 18 years with histologically or cytologically confirmed LA or metastatic pancreatic ductal adenocarcinoma ECOG PS of 0–2 adequate end organ function.	Interventions G1: chemotherapy alone (n=358) - six cycles of GEM (1000 mg/m(2), 30 min intravenous infusion, at days 1, 8, and 15) and capecitabine (830 mg/m(2) orally twice daily for 21 days, repeated every 28 days G2: chemotherapy with sequential GV1001: sequential ICT (n=350); G3: chemotherapy with concurrent GV1001: concurrent ICT (n=354). Sequential ICT included two cycles of combination chemotherapy, then an intradermal lower abdominal injection of granulocyte-macrophage colony-stimulating factor. Concurrent ICT included giving GV1001 from the start of chemotherapy with GM-CSF as an adjuvant	Details Design: Multicentre Phase 3 RCT Randomization method: “Patients were randomised with computer-generated random permuted blocks of sizes 3 and 6 in equal proportion. Randomisation was stratifi ed on stage of disease (LA versus metastatic) and ECOG performance status (0, 1, and 2).” Blinding: open-label Duration/last follow-up: 6 months (median follow-up time)	Overall response rate (CR + PR) at 8 weeks Time to progression Overall Survival Adverse Events (Grade 3/4/5 toxicities: Nausea, vomiting, Diarrhoea, Neutropenia, Fatigue, Pain) Health Related Quality of Life at 20 weeks (EORTC QLQ-C30)	Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool. Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel Assessments: High risk Blinding of outcome assessment: unclear risk Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: serious Other information

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Cancer Research UK and KAEL-GemVax.	LA or metastatic disease precluding curative surgical resection or patients who had relapsed following previously resected pancreatic cancer contrast enhanced CT scan of the thorax, abdomen pelvis within 28 days before commencing treatment measurable disease on CT and a life expectancy longer than 3 months. Exclusion criteria Patients if they had had radiotherapy within the last 4 weeks before start of study treatment no other pre-treatment information on radiotherapy was obtained as radiotherapy was not used in the UK for LA pancreatic cancer medical or psychiatric conditions compromising informed consent intracerebral metastases or meningeal carcinomatosis clinically significant serious disease or organ system disease not currently controlled on present therapy uncontrolled angina pectoris; pregnancy or breastfeeding previous chemotherapy for LA and metastatic disease				

Study details	Participants	Interventions	Methods	Outcomes*	Comments
	concurrent malignancies or invasive cancers diagnosed within the past 5 years apart from adequately treated basal-cell carcinoma of the skin other				
Full citation Middleton G, Palmer DH, et al. Vandetanib plus gemcitabine versus placebo plus gemcitabine in locally advanced or metastatic pancreatic carcinoma (ViP): a prospective, randomised, double-blind, multicentre phase 2 trial. Lancet Oncol. 2017;18(4):486-499. Ref ID Middleton et al., 2017 Country/ies where the study was carried out: UK Study type: Double blind Multicentre Phase 2 RCT Aim of the study: To evaluate the efficacy of vandetanib when used in combination with gemcitabine in patients with locally advanced and metastatic pancreatic cancer. Study dates:	Sample size N= 142 patients with locally advanced/metastatic PC (mixed population) Characteristics M/F (n): 29/43 (G1); 30/40 (G2) Median age (range): 66.5(61-73) years (G1); 67.5 (61-73) years (G2) Clinical stage: LA: 21 (G1); 20 (G2) Metastatic: 51 (G1); 50 (G2) Primary tumour site within pancreas: Head: 31 (G1); 47 (G2) Uncinate: 4 (G1); 5 (G2) Body: 24 (G1); 13 (G2) Tail: 13 (G1); 5 (G2) Inclusion criteria Patients were eligible if they were: aged 18 years or older with histologically or cytologically proven pancreatic ductal adenocarcinoma or undifferentiated carcinoma of the pancreas LA or metastatic disease precluding curative surgical	Interventions G1: Vandetanib + GEM (n=72) - Vandetanib was prescribed orally once daily at 300 mg per day for the duration of the study. G2: GEM + placebo (n=70) – Placebo was prescribed throughout the study to replicate the vandetanib prescription In both groups, gemcitabine was administered at 1000 mg/m2 weekly as a 30-min intravenous infusion for 7 continuous weeks followed by a 1-week break. After this period, gemcitabine was prescribed on a cycle of 3 continuous weeks followed by a 1-week break.	Details Design: Multicentre Phase 2 RCT Randomization method: “Patients were randomly assigned 1:1 to receive … according to pre-generated sequences produced on the principle of randomly permuted blocks with variable block sizes of two and four. Patients were stratified at randomisation by their disease stage (locally advanced vs metastatic) and ECOG performance status (0 or 1 vs 2).” Blinding: double blind Duration/last follow-up: 12 weeks or until patients’ death	Overall response rate (CR + PR) Progression Free Survival Overall Survival Adverse Events	Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool. Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel Assessments: Low risk Blinding of outcome assessment: Low risk Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: no serious Other information

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Data collection-patients enrolment: 2011-2013 Publication year: 2017 Source of funding: Supported by Cancer Research UK and AstraZeneca.	resection or definitive locally directed therapies measurable disease, in accordance with the RECIST guidelines (version 1.1); ECOG performance status of 0–1, or in some cases 2 if the investigator felt that treatment with combination chemotherapy (eg, FOLFIRINOX) was not appropriate Patients who had relapsed following previously resected pancreatic cancer could also be included in the trial. Exclusion criteria Exclusion criteria were: Patients who had previous chemotherapy for locally advanced and metastatic disease Patients who had radiotherapy or major surgery within the last 4 weeks preceding the start of the study treatment Concurrent malignancies or invasive cancers diagnosed within the past 5 years except for adequately treated basal-cell carcinoma of the skin, in-situ carcinoma of the uterine cervix, or resected pancreatic cancer;				

Study details	Participants	Interventions	Methods	Outcomes*	Comments
	and chemotherapy directed at the tumour apart from that described in this protocol.				
Full citation Moinpour CM, Vaught NL, Goldman B, Redman MW, Philip PA, et al. Pain and emotional well-being outcomes in Southwest Oncology Group-directed intergroup trial S0205: a phase III study comparing Gemcitabine + cetuximab versus Gemcitabine as first-line therapy in patients with advanced pancreas cancer. J Clin Oncol. 2010;28(22):3611-6. Ref ID Moinpour et al., 2010 Country/ies where the study was carried out: Multicentre (Canada, USA) Study type: Multicentre unblinded Phase 3 RCT Aim of the study: To compare the effectiveness and tolerability of Gemcitabine + cetuximab with Gemcitabine single-agent for advanced/metastatic pancreatic cancer Study dates:	Sample size N= 720 patients with locally advanced/metastatic PC (mixed population) Characteristics M/F (%): 55/45 (G1); 52/48 (G2) Median age (range): 65(33-91) years (G1); 64 (30-87) years (G2) Clinical stage (%): LA: 22 (G1); 21 (G2) Metastatic: 78 (G1); 79 (G2) Primary tumour site within pancreas: Not reported Inclusion criteria histologically or cytologically confirmed adenocarcinoma of the pancreas with distant metastases or LA unresectable disease presence of either measurable or evaluable disease Zubrod performance status of 0 to 2 adequate organ function Prior radical surgery was allowed, and patients must have completed adjuvant (no GEM) therapy at least 6	Interventions G1: GEM + cetuximab (n=361) - Cetuximab was delivered intravenously at a loading dose of 400 mg/m2 (over 120 minutes) on week 1, followed by weekly maintenance doses of 250 mg/m2 (over 60 minutes). Treatment with both GEM and cetuximab was continued until disease progression, unacceptable toxicity, delay of treatment by more than 4 weeks, or patient request. G2: GEM single-agent (n=359) - GEM was administered intravenously at a dose of 1,000 mg/m2 over 30 minutes. During the first 8 weeks, GEM was administered weekly for 7 weeks followed by 1 week off. In all remaining cycles, GEM was administered for 3 weeks followed by a week of rest.	Details Design: Multicentre Phase 3 RCT Randomization method: “Patients were randomly assigned to one of the two treatment arms using the dynamic balancing algorithm with stratification based on performance status (0 to 1 v 2), extent of disease (LA v metastatic), and prior pancreatectomy (yes v no).” Blinding: open-label Duration/last follow-up: 17 weeks (median follow-up time)	Health Related Quality of Life Patient experience and PROMs	Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool. Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel Assessments: High risk Blinding of outcome assessment: High risk Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: serious Other information

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Data collection-patients enrolment: 2004-2006 Publication year: 2010 Source of funding: PublicHealth Service Cooperative Agreement Grants awarded by the National Cancer Institute, Department of Health and Human Services: CA32102, .. CA91105, CA46282 (Southwest Oncology Group); CA-25224, CA35195 (North Central Cancer Treatment Group); CA21115 (Eastern Cooperative Oncology Group); CA31946 (Cancer and Leukemia Group B [CALGB] Chairman's Grant), CA33601 (CALGB Statistical Center Grant); CA77651 (Memorial Sloan-Kettering Cancer Center Institutional Grant [CALGB]); and CA77202 (National Cancer Institute of Canada); also supported in part by ImClone Systems and Bristol-Myers Squibb.	months before entry onto the study Exclusion criteria Patients were excluded if they had: HIV-1 infection brain metastases prior systemic therapy for advanced disease therapy with EGFR-targeting agents pregnancy				
Full citation Moore MJ, Hamm J, Dancey J, Eisenberg PD, Dagenais M, et al. Comparison of Gemcitabine versus the matrix metalloproteinase	Sample size N= 277 patients with locally advanced/metastatic PC (mixed population) Characteristics M/F (n): 56/82 (G1); 63/76 (G2)	Interventions G1: BAY 12-9566 (n=138) - 800 mg orally bid continuously G2: GEM single-agent (n=139) - 1,000 mg/m2	Details Design: Multicentre Phase 3 RCT Randomization method: “Patients were stratified by prior radiation,	Overall response rate (CR + PR) at 8 weeks of therapy Progression Free Survival	Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool. Random sequence generation: Unclear

Study details	Participants	Interventions	Methods	Outcomes*	Comments
inhibitor BAY 12-9566 in patients with advanced or metastatic adenocarcinoma of the pancreas: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol. 2003;21(17):3296-302. Ref ID Moore et al., 2003 Country/ies where the study was carried out: Canada Study type: Multicentre Phase 3 RCT Aim of the study: To compare the effectiveness and tolerability of BAY 12-9566 with Gemcitabine single-agent for advanced/metastatic pancreatic cancer in patients who had not previously received chemotherapy Study dates: Data collection-patients enrolment: 1997-2006 Publication year: xxx Source of funding: Bayer Corporation, West Haven, CT.	Median age: 65 years (G1); 66 years (G2) Clinical stage: LA: 53 (G1); 74 (G2) Metastatic: 85 (G1); 65 (G2) Primary tumour site within pancreas: Not reported Site of metastases: Ascites: 24 (G1); 17 (G2) Liver: 75 (G1); 57 (G2) Lung: 17 (G1); 12 (G2) Lymph nodes: 49 (G1); 29 (G2) Pancreas: 127 (G1); 92 (G2) Pleural effusion: 10 (G1); 4 (G2) Inclusion criteria Patients with histologically confirmed, unresectable, LA or metastatic pancreatic adenocarcinoma. Patients taking analgesia were required to have stable analgesic usage No prior chemotherapy ECOG of 2 or less Exclusion criteria Patients with CNS metastases, prior MMP inhibitor therapy, and prior investigational therapy within 30 days of study entry.	administered intravenously	measurable versus nonmeasurable disease, and ECOG performance status (0 to 1 v 2).” Blinding: unclear Duration/last follow-up: unclear	Overall Survival Adverse Events (Grade 3/4 toxicities: Nausea, vomiting, Diarrhoea) Health Related Quality of Life at 8 weeks (EORTC QLQ-C30)	risk (No details given in the text) Allocation concealment: Low risk Blinding of participants and personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: serious Other information

Study details	Participants	Interventions	Methods	Outcomes*	Comments
	Pregnant and breast-feeding women were also not eligible for study Patients with any active infections Patients with other malignancies, those who were unable to swallow oral medications, those who had malabsorption, or who had had a major vascular event within 3 months of study entry				
Full citation Oettle H, Riess H, Stieler JM, Heil G, Schwaner I, et al. Second-line oxaliplatin, folinic acid, and 5-FU versus folinic acid and 5-FU alone for Gemcitabine - refractory pancreatic cancer: outcomes from the CONKO-003 trial. J Clin Oncol. 2014;32(23):2423-9. Ref ID Oettle et al., 2014 Country/ies where the study was carried out: Germany Study type: Multicentre unblinded Phase 3 RCT Aim of the study: To assess the efficacy of a second-line regimen of oxaliplatin and folinic acid-	Sample size N= 160 patients with locally advanced/metastatic PC (mixed population) Characteristics M/F (n): 48/36 (G1); 40/36 (G2) Median age (range): 61(43-78) years (G1); 62 (37-83) years (G2) Clinical stage: LA: 10 (G1); 9 (G2) Metastatic: 74 (G1); 67 (G2) Primary tumour site within pancreas: Not reported Inclusion criteria histologically confirmed advanced pancreatic cancer patients who had experienced progression during first-line GEM monotherapy age 18 years or older	Interventions G1: FA + 5-FU as second line chemotherapy (n=84) - Second-line treatment was planned to start within 4 weeks of disease progression on first-line GEM monotherapy. FF comprised intravenous (IV) FA 200 mg/m2 followed by a continuous IV infusion of 5-FU 2,000 mg/m2 over 24 hours on days 1, 8, 15, and 22 G2: oxaliplatin + 5-FU as second line chemotherapy (n=76) - OFF comprised FF and oxaliplatin 85 mg/m2 IV administered before FF on days 8 and 22.	Details Design: Multicentre Phase 3 RCT Randomization method: “Patients were randomly assigned by using computer-generated random numbers at the study coordination center” Blinding: open-label Duration/last follow-up: 54.1 months (median follow-up time)	Progression Free Survival Overall Survival (Grade 3/4 toxicities: Anaemia, Nausea/emesis, Paresthesia, Pain, Leucopoenia, Thrombocytopenia, Diarrhoea)	Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool. Random sequence generation: Low Allocation concealment: Low risk Blinding of participants and personnel Assessments: High risk Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: Low risk Selective reporting: Low risk

Study details	Participants	Interventions	Methods	Outcomes*	Comments
modulated 5-FU in patients with advanced pancreatic cancer who have experienced progression while receiving Gemcitabine monotherapy Study dates: Data collection-patients enrolment: 2004-2007 Publication year: 2014 Source of funding: Helmut Oettle, Celgene, Eli Lilly	measurable reference cancer site(s) confirmed with computed tomography or magnetic resonance imaging Karnofsky performance status of at least 70% adequate renal function, adequate hepatic function, adequate bone marrow function, Exclusion criteria presence of any severe concomitant disease intractable pain hypersensitivity to study drugs serious cardiovascular disease (eg, unstable coronary artery disease or myocardial infarction within 4 weeks of study start) National Cancer Institute Common Toxicity Criteria (NCI-CTC) grade 3 or 4 sensory or motor neuropathy prior or concurrent malignancy (other than pancreatic cancer if female, pregnancy or breastfeeding.				Overall risk of bias: no serious Other information
Full citation Oster MW, Gray R, Panasci L, Perry MC. Chemotherapy for advanced pancreatic cancer A comparison of 5-FU, adriamycin, and mitomycin (FAM) with 5-	Sample size N= 196 patients with locally advanced/metastatic PC (mixed population) Characteristics M/F (%): 52/48 (G1); 61/39 (G2)	Interventions G1: FAM: 5-FU, Adriamycin [doxorubicin], mitomycin (n=90) - FAM was administered in 8-week cycles with 5-FU, 600 mg/M2 given	Details Design: Phase 3 RCT Randomization method: unclear “patients were stratified before randomization on	Overall response rate (CR + PR) Overall Survival* Adverse Events (Grade 3/4 toxicities:	Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool. Random sequence generation: Unclear risk (No details given in the text)

Study details	Participants	Interventions	Methods	Outcomes*	Comments
FU, streptozotocin, and mitomycin (FSM). Cancer. 1986;57(1):29-33. Ref ID Oster et al., 1986 Country/ies where the study was carried out: USA Study type: Phase 3 RCT Aim of the study: To compare the effectiveness and tolerability of FAM (5-FU, Adriamycin [doxorubicin], mitomycin) with FSM (5-FU, streptozotocin, mitomycin) for advanced pancreatic cancer Study dates: Data collection-patients enrolment: 1979-1981 Publication year: 1986 Source of funding: Grant Support CA 12011/CA/NCI NIH HHS/United States CA 31809/CA/NCI NIH HHS/United States CA 33601/CA/NCI NIH HHS/United States	Age 55-65 years (%): 42 (G1);31 (G2) Clinical stage: Not reported Primary tumour site within pancreas: Not reported Inclusion criteria Patients with histologically confirmed adenocarcinoma of the pancreas with disease that was not considered suitable for surgery and/or radiotherapy. No prior chemotherapy. Exclusion criteria See inclusion criteria	intravenously on days 1, 8, 29, and 36; Adnamycin, 30 mg/M2 given intravenously on days 1 and 29; and mitomycin, 10 mg/M2 given intravenously on day 1 G2: FSM: 5-FU, streptozotocin, mitomycin (n=94) - FSM was administered in 8-week cycles with 5-FU and mitomycin as in FAM and streptozotocin 1 g/M2 intravenously on days 1,8,29, and 36	the basis of the presence or absence of objectively measurable disease by physical examination and/or radiologic evaluation." Blinding: unclear Duration/last follow-up: unclear	Nausea/vomiting, Leucopoenia Thrombocytopenia)	Allocation concealment: Unclear risk (No details given in the text) Blinding of participants and personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: Low risk Selective reporting: Unclear risk (no study protocol to permit judgement on this criterion) Overall risk of bias: very serious Other information * Not analytical data on results are reported (narrative reporting)
Full citation Pelzer U, Opitz B, Deutschinoff G, Stauch M, Reitzig PC, Hahnfeld S,	Sample size N= 312 patients with locally advanced/metastatic PC (mixed population)	Interventions G1: Chemotherapy and prophylactic use of enoxaparin (n=160) -	Details Design: Multicentre Phase 3 RCT	Progression Free Survival Overall Survival	Limitations - Cochrane Collaboration's 'Risk of bias' tool.

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Müller L, Grunewald M, Stieler JM, Sinn M, Denecke T, Bischoff S, Oettle H, Dörken B, Riess H. Efficacy of Prophylactic Low-Molecular Weight Heparin for Ambulatory Patients With Advanced Pancreatic Cancer: Outcomes From the CONKO-004 Trial. J Clin Oncol. 2015;33(18):2028-34. Ref ID Pelzer et al., 2015 Country/ies where the study was carried out: Germany Study type: Multicentre unblinded Phase 3 RCT Aim of the study: To compare the effectiveness and tolerability of first-line chemotherapy and prophylactic use of enoxaparin with chemotherapy alone for advanced/metastatic pancreatic cancer Study dates: Data collection-patients enrolment: 2004-2009 Publication year: 2015 Source of funding:	Characteristics M/F (n): 69/91 (G1); 58/94 (G2) Median age (range): 62(38-81) years (G1); 63 (27-83) years (G2) Clinical stage: LA: 41(G1); 34 (G2) Metastatic: 119 (G1); 118 (G2) Primary tumour site within pancreas: Not reported Site of metastases: Liver: 67 (G1); 69 (G2) Liver/Lung: 12 (G1); 10 (G2) Lymph nodes: 18 (G1); 10 (G2) Peritoneum: 17 (G1); 18 (G2) Other: 35 (G1); 42 (G2) Inclusion criteria outpatients with histologically confirmed APC no previous radiotherapy or chemotherapy KPS ≥ 60%, measurable tumor lesion confirmed by computed tomography or magnetic resonance imaging within the last 14 days no VTEs within the last 2 years sufficient bone marrow function age ≥ 18 years adequate compliance	After 3 months of initial enoxaparin use at half the therapeutic dosage (time point of primary end point), treatment was continued with a fixed dose of 40 mg daily until disease progression. Beyond the initial 3 months of chemotherapy, all patients with no disease progression received further treatment with GEM single-agent (GEM 1 g/m2 [30 minutes] on days 1, 8, and 15, once every 4 weeks G2: Chemotherapy alone (n=152) - Patients with a KPS 80% and normal kidney function received intensified GFFC therapy (GEM 1 g/m2 [30 minutes], 5-FU 750 mg/m2 [24 hours], FA 200 mg/m2 [30 minutes], and cisplatin 30 mg/m2 [90 minutes] on days 1 and 8, once every 3 weeks. Patients with initial KPS 80% and/or increased creatinine plasma level (but creatinine clearance 30 mL per minute) started GEM therapy (GEM 1 g/m2 [30	Randomization method: “Patients were randomly assigned between ….at a one-to-one ratio using computer-generated random numbers generated at the study coordination centre.” Blinding: open-label Duration/last follow-up: until patients' death	Adverse Events (Vascular thromboembolism events-VTE) Symptomatic VTE Major hemorrhages	Random sequence generation: Low Allocation concealment: Low risk Blinding of participants and personnel Assessments: High risk Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: serious Other information

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Helmut Oettle, Celgene, Eli Lilly	residence within geographic proximity to the particular department Exclusion criteria preexisting anticoagulation indication major hemorrhage within the last 2 weeks or severely impaired coagulation, active GI ulcers major surgery within the last 2 weeks body weight < 45 kg or > 100 kg, pregnant, lactating or insufficient contraception during study severe concomitant disease incompatible with study participation	minutes] on days 1, 8, and 15, once every 4 weeks).			
Full citation Rougier P, Riess H, Manges R, Karasek P, Humblet Y, et al. Randomised, placebo-controlled, double-blind, parallel-group phase III study evaluating aflibercept in patients receiving first-line treatment with Gemcitabine for metastatic pancreatic cancer. Eur J Cancer. 2013;49(12):2633-42. Ref ID Rougier et al., 2013	Sample size N= 546 patients with metastatic PC Characteristics M/F (n): 157/118 (G1); 160/111 (G2) Median age (range): 61.0 (34–86) years (G1); 62.0 (34–88) years (G2) Clinical stage: I-II: 16 (G1); 13 (G2) III: 11 (G1); 16 (G2) IV: 248 (G1); 241 (G2) unknown: 0 (G1); 1 (G2) Primary tumour site within pancreas:	Interventions G2: GEM + aflibercept (n=271) G1: GEM + placebo (n=275) Patients received aflibercept 4 mg/kg or placebo intravenous (i.v.) over 1 h once every 2 weeks on days 1 and 15 of every 4-week cycle, and then GEM 1000 mg/m2 i.v. over 30 min on days 1, 8, 15 and 22 of cycle 1 and then days 1	Details Design: Multicentre Phase 3 RCT Randomization method: “Patients were randomly assigned between ….at a one-to-one ratio using computer-generated random numbers generated at the study coordination center.” Blinding: double-blinded	Progression Free Survival Overall Survival Adverse Events	Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool. Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel Assessments: Low risk Blinding of outcome assessment: Low risk

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Country/ies where the study was carried out: Multicentre (Belgium, France, Germany, Czech Republic, US) Study type: Multicentre double-blinded Phase 3 RCT Aim of the study: To compare aflibercept + Gemcitabine with Gemcitabine + placebo in patients with metastatic pancreatic adenocarcinoma Study dates: Data collection-patients enrolment: 2007-2009 Publication year: 2013 Source of funding: This study was supported by sanofi-aventis.	Entire pancreas: 72 (G1); 50 (G2) Head: 117 (G1); 132 (G2) Body: 41 (G1); 41 (G2) Tail: 45 (G1); 46 (G2) Other: 0 (G1); 2 (G2) Site of metastases: Pancreas: 248 (G1); 252 (G2) Liver: 215 (G1); 208 (G2) Lung: 68 (G1); 69 (G2) Lymph nodes: 125 (G1); 134 (G2) Peritoneum: 64 (G1); 59 (G2) Inclusion criteria patients >18-year-olds with cytologically or histologically confirmed metastatic adenocarcinoma of the pancreas ECOG PS< 2 with adequate organ function no prior systemic treatment or chemotherapy for PC except for 5-FU, capecitabine or GEM as radiosensitising agents and the time between last dose. Exclusion criteria < 42 days from prior major surgery (28 days from other surgery) to the time of randomisation < 28 days from prior radiation therapy; prior treatment with anti-VEGF or VEGFR inhibitors		Duration/last follow-up: 7.9 months (median follow-up time)		Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: no serious Other information

Study details	Participants	Interventions	Methods	Outcomes*	Comments
	a history of brain metastases, uncontrolled spinal cord compression, or carcinomatous meningitis, or new evidence of brain or leptomeningeal disease previous history of neoplasm; uncontrolled severe organ or metabolic dysfunction or other severe acute or chronic medical conditions pregnancy or breast-feeding.				
Full citation Sakamoto H, Kitano M, Suetomi Y, Takeyama Y, Ohyanagi H, et al. Comparison of standard-dose and low-dose Gemcitabine regimens in pancreatic adenocarcinoma patients: a prospective randomized trial. J Gastroenterol. 2006;41(1):70-6. Ref ID Sakamoto et al., 2006 Country/ies where the study was carried out: Japan Study type: Phase 3 RCT Aim of the study: To compare Gemcitabine infusion at a low dose with the standard-dose infusion in patients with	Sample size N= 21 patients with locally advanced/metastatic PC (mixed population) Characteristics M/F (n): 5/6 (G1); 5/5 (G2) Median age (range): 66.2(50–80) years (G1); 68 (57–84) years (G2) Clinical stage: LA: 4 (G1); 3 (G2) Metastatic: 7 (G1); 7 (G2) Primary tumour site within pancreas: Head: 8 (G1); 5 (G2) Body: 2 (G1); 3 (G2) Tail: 1 (G1); 2 (G2) Multicentre: 0 (G1); 0 (G2) Inclusion criteria histologically or cytologically proven LA or distant metastasized adenocarcinoma of the pancreas	Interventions G1: GEM infusion at a low dose (n=11) - intravenous infusion of GEM at a dose of either 250mg/m2 over 30 minon days 1, 8, and 15 of every 4-week cycle G2: GEM infusion at a standard dose (n=10) - intravenous infusion of GEM at a dose of either 1000mg/m2 over 30 minon days 1, 8, and 15 of every 4-week cycle	Details Design: Phase 3 RCT Randomization method: “Patients were randomly assigned between ….using a two-envelope factorial design” Blinding: unclear Duration/last follow-up: unclear	Overall response rate (CR + PR) until DP Overall Survival* Adverse Events (Grade 3/4 toxicities: Nausea/vomiting, Diarrhoea, Fatigue, Neutropenia, Thrombocytopenia, Anaemia)	Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool. Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: U Low risk Selective reporting: Low risk

Study details	Participants	Interventions	Methods	Outcomes*	Comments
advanced/metastatic pancreatic cancer Study dates: Data collection-patients enrolment: 2001-2004 Publication year: 2006 Source of funding Japan Society for the Promotion of Science.	age > 20 years ECOG-PS of 0 to 2 life expectancy > 12 weeks and continuation of therapy for more than 1 month. adequate organ function Exclusion criteria See inclusion criteria				Overall risk of bias: no serious Other information * no analytical data reported. Reported in a narrative way
Full citation Smith D, Gallagher N. A phase II/III study comparing intravenous ZD9331 with Gemcitabine in patients with pancreatic cancer. Eur J Cancer. 2003;39(10):1377-83. Ref ID Smith et al., 2003 Country/ies where the study was carried out Multicentre (France, Germany, Sweden, the Netherlands, Norway, UK) Study type: Multicentre unblinded Phase 2/3 RCT Aim of the study: To compare Gemcitabine with ZD9331 in patients with advanced/metastatic pancreatic cancer Study dates: Data collection-patients enrolment: not reported	Sample size N= 55 patients with locally advanced/metastatic PC (mixed population) Characteristics M/F (n): 19/11 (G1); 15/10 (G2) Mean age (range): 59.8 (23–75) years (G1); 60.8 (40–76) years (G2) Clinical stage: I-II: 4 (G1); 3 (G2) III: 1 (G1); 1 (G2) IV: 10 (G1); 10 (G2) unknown: 15 (G1); 13 (G2) Primary tumour site within pancreas: Not reported Inclusion criteria histologically- or cytologically-confirmed cancer of the exocrine pancreas with chemonaïve, measurable, LA or metastatic disease. age > 18 years	Interventions G1: ZD9331 (n=30) - ZD9331 was given as a 30-min intravenous (i.v.) infusion at a dose of 130 mg/m2, on days 1 and 8 of a 3-week cycle G2: GEM single-agent (n=25) - The first cycle of GEM comprised once-weekly 30-min i.v. infusions at a dose of 1.0 g/m2 for 7 weeks, followed by a week of rest. Subsequent cycles lasted 4 weeks, with treatment given on days 1, 8 and 15. The first cycle of GEM comprised once-weekly 30-min i.v. infusions at a dose of 1.0 g/m2 for 7 weeks, followed by a week of rest.	Details Design: Multicentre Phase 2/3 RCT Randomization method: unclear "Patients were then randomised to receive….and were stratified by centre and eligibility for assessment of CBR." Blinding: open-label Duration/last follow-up: 8 weeks after disease progression (discontinuation of treatment)	Overall response rate (CR + PR) until DP Adverse Events (Grade 3/4 toxicities: Nausea, vomiting, Diarrhoea, Fatigue, Neutropenia)	Limitations - Cochrane Collaboration's 'Risk of bias' tool. Random sequence generation: Unclear risk (No details given in the text) Allocation concealment: Unclear risk (No details given in the text) Blinding of participants and personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: very serious

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Publication year: 2003 Source of funding: Not reported	Karnofsky performance status (KPS) >50 life expectancy >8 weeks Exclusion criteria prior treatment with radiosensitisers not fully recovered from previous surgery or radiotherapy current intestinal obstruction diagnosis of islet-cell tumour or lymphoma of the pancreas evidence of severe or uncontrolled systemic disease metastasis to the central nervous system or concomitant use of folic acid.				Other information
Full citation Sudo K, Ishihara T, Hirata N, Ozawa F, Ohshima T, et al. Randomized controlled study of Gemcitabine + S-1 combination Chemotherapy versus Gemcitabine for unresectable pancreatic cancer. Cancer Chemother Pharmacol. 2014;73(2):389-96. Ref ID Sudo et al., 2014 Country/ies where the study was carried out: Japan Study type: Multicentre Phase 3 RCT	Sample size N= 101 patients with locally advanced/metastatic PC (mixed population) Characteristics M/F (n): 27/24 (G1); 34/16 (G2) Median age (range): 66 (50–77) years (G1); 67 (45–73) years (G2) Clinical stage: LA: 18 (G1); 19 (G2) Metastatic: 33 (G1); 31 (G2) Primary tumour site within pancreas: Head: 22 (G1); 18 (G2) Body-Tail: 29 (G1); 32 (G2) Inclusion criteria	Interventions G1: GEM + S-1 (n=51) - oral administration of S-1 at 60 mg/m2 divided in two daily doses on days 1–15 and 30-min infusion of GEM at 1,000 mg/m2 on days 8 and 15 every 3 week G2: GEM single-agent (n=50) - GEM was administered at 1,000 mg/m2 in a 30-min infusion on days 1, 8 and 15 every 4 weeks.	Details Design: Multicentre Phase 3 RCT Randomization method: “Randomization was done centrally via a Web-based system, and patients were stratified according to centre, PS (0 versus 1), and extent of disease (LA versus metastatic) by a minimization method.” Blinding: unclear	Response rate Progression Free Survival Overall Survival Adverse Events	Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool. Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: Unclear

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Aim of the study: To compare the effectiveness and tolerability of Gemcitabine + S-1 with Gemcitabine single-agent for advanced/metastatic pancreatic cancer Study dates: Data collection-patients enrolment: 2007-2011 Publication year: 2014 Source of funding: No financial support for this study was provided	Histological or cytological confirmation of metastatic or LA adenocarcinoma 20–79 years of age ECOG PS of 0 or 1 no prior chemotherapy or radiotherapy adequate organ function Exclusion criteria Patients with: severe concurrent disease, interstitial pneumonia, massive abdominal or pleural effusion, mental disorder, active concomitant malignancy, severe Diarrhoea , brain metastasis, severe drug hypersensitivity, pregnant or lactating females, and regular use of phenytoin, warfarin or frucitocin		Duration/last follow-up: 12 months		risk (No details given in the text) Incomplete outcome data: U Low risk Selective reporting: Low risk Overall risk of bias: no serious Other information
Full citation Ueno H, Ioka T, Ikeda M, Ohkawa S, Yanagimoto H, et al. Randomized phase III study of Gemcitabine + S-1, S-1 alone, or Gemcitabine single-agent in patients with LA and metastatic pancreatic cancer in Japan and Taiwan: GEST study. J Clin Oncol. 2013;31(13):1640-8. Ref ID Ueno et al., 2013	Sample size N= 834 patients with locally advanced/metastatic PC (mixed population) Characteristics M/F (n): 170/107 (G1); 170/110 (G2); 158/117 (G3) Age <65,>=65 (n): 134/143 (G1); 145/135 (G2); 137/138 (G3) Clinical stage: LA: 66 (G1); 68 (G2); 68(G3) Metastatic: 211(G1); 212(G2) ; 207(G3)	Interventions G1: GEM single-agent (n=277) - intravenous administration of GEM at a dose of 1000 mg/m2 over 30 min on days 1, 8 and 15 of a 28-d cycle; G2: S-1 alone (n=280) - oral administration of S-1 twice daily at a dose calculated according to the body surface area (BSA) (<1.25 m2, 80 mg/d; ≥1.25 to <1.5 m2, 100 mg/d; ≥1.5 m2, 120	Details Design: Multicentre Phase 3 RCT Randomization method: “Random assignment was performed centrally with stratification by extent of disease (LA disease v metastatic disease) and institution using the minimization method” Blinding: unclear	Response rate Progression Free Survival Overall Survival Adverse Events Health Related Quality of Life	Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool. Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel Assessments: Unclear risk (No

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Country/ies where the study was carried out: Multicentre (Japan, Taiwan) Study type: Multicentre Phase 3 RCT Aim of the study: To compare the efficacy and toxicity of Gemcitabine + S-1 with Gemcitabine or S-1 alone in patients with advanced/metastatic pancreatic cancer Study dates: Data collection-patients enrolment: 2007-2009 Publication year: 2013 Source of funding: Taiho Pharmaceutical and TTY Biopharm.	Primary tumour site within pancreas: Head: 122 (G1); 110 (G2) ; 116(G3) Body: 88 (G1); 124 (G2) ; 102(G3) Tail: 68 (G1); 55 (G2) ; 66(G3) Inclusion criteria advanced or metastatic PC histologically or cytologically proven diagnosis of adenocarcinoma or adenosquamous carcinoma no prior chemotherapy or radiotherapy for PC, age of more than 20 years (the protocol was amended to restrict the eligible age to < 80 years after four of the first eight patients who were ≥ 80 years experienced serious adverse events) an Eastern Cooperative Oncology Group performance status score of 0 to 1 adequate organ functions Exclusion criteria Patients with: See inclusion criteria	mg/d) on days 1 through 28 of a 42-d cycle G1: GEM + S-1 (n=275) - Patients randomised to the GS regimen received GEM at a dose of 1000 mg/m2 on days 1 and 8 + S-1 orally twice daily at a dose based on the BSA (<1.25, 60 mg/d; ≥1.25 to <1.5 m2, 80 mg/d; ≥1.5 m2, 100 mg/d) on days 1 through 14 of a 21-d cycle.	Duration/last follow-up: until patients' death		details given in the text) Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: U Low risk Selective reporting: Low risk Overall risk of bias: no serious Other information
Full citation Ulrich-Pur H, Raderer M, Verena Kornek G, Schüll B, Schmid K, et al. Irinotecan + raltitrexed vs raltitrexed alone in patients with	Sample size N= 38 patients with metastatic PC Characteristics M/F (n): 8/11 (G1); 12/7 (G2)	Interventions G1: raltitrexed alone (n=19) G2: irinotecan + raltitrexed (n=19) - In both patients groups, an	Details Design: RCT Randomization method: not reported Blinding: unclear	Objective/complete response Adverse Events (Grade 3/4 toxicities: Nausea/	Limitations - Cochrane Collaboration's 'Risk of bias' tool. Random sequence generation: Low risk

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Gemcitabine -pretreated advanced pancreatic adenocarcinoma. Br J Cancer. 2003;88(8):1180-4. Ref ID Ulrich-Pur et al., 2003 Country/ies where the study was carried out: Austria Study type: Multicentre Phase 3 RCT Aim of the study: To compare the efficacy and toxicity of irinotecan + raltitrexed with raltitrexed alone in patients with advanced/metastatic pancreatic cancer Study dates: Data collection-patients enrolment: 2000-2001 Publication year: 2003 Source of funding: Not reported	Median age (range): 60 (40–74) years (G1); 63 (49–75) years (G2) Clinical stage: Not reported Primary tumour site within pancreas: Not reported Site of metastases: Abdominal mass: 15 (G1); 16 (G2) Liver: 14 (G1); 12 (G2) Lung: 5 (G1); 4 (G2) Spleen: 1 (G1); 2 (G2) Adrenals: 1 (G1); 1 (G2) Soft tissue: 2 (G1); 3 (G2) Inclusion criteria Patients with histologically confirmed metastatic PC measurable disease patients with progressive disease while receiving or within 6 months after discontinuing palliative GEM -based chemotherapy Karnofsky performance of at least 50% age between 19 and 75 years adequate bone marrow reserve adequate renal function and adequate hepatic function. Exclusion criteria presence of CNS metastases	identical conventional dose regimen of raltitrexed (3 mg m−2 given as a 15-min intravenous (i.v.) infusion on day 1) was used. In the intervention group, according to the described schedule-dependent synergy (Aschele et al, 1998), the thymidylate synthase inhibitor was given on day 2, 24 h after irinotecan	Duration/last follow-up: until patients' death	vomiting, Diarrhoea, Neutropenia, Leukocytopenia, Thrombocytopenia, Fatigue, and stomatitis)	Allocation concealment: Low risk Blinding of participants and personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: Unclear risk (No details given in the text) Selective reporting: Low risk Overall risk of bias: serious Other information

Study details	Participants	Interventions	Methods	Outcomes*	Comments
	serious or uncontrolled concurrent medical illness history of other malignancies, with the exception of excised cervical or basal skin/squamous cell carcinoma				
Full citation Wang M, Shi SB, Qi JL, Tang XY, Tian J. S-1 + CIK as second-line treatment for advanced pancreatic cancer. Med Oncol. 2013;30(4):747. Ref ID Wang et al., 2013 Country/ies where the study was carried out: China Study type: RCT Aim of the study: To compare the efficacy and tolerability of S-1 + CIK (Cytokine-induced killer cells) with S-1 alone in patients with advanced/metastatic pancreatic cancer who had previously received Gemcitabine -based therapy Study dates: Data collection-patients enrolment: 2009-2012 Publication year: 2013	Sample size N= 58 patients with locally advanced/metastatic PC (mixed population) Characteristics M/F (n): 15/13 (G1); 16/14 (G2) Median age (range): 62(40-76) years (G1); 48 (40-65) years (G2) Clinical stage (%): LA: 7.1 (G1); 3.4 (G2) Metastatic: 92.9 (G1); 96.7 (G2) Primary tumour site within pancreas: Head: 22 (G1); 23 (G2) Body/tail: 6 (G1); 7 (G2) Inclusion criteria histologically or cytologically proven LA or metastatic PC 18–74 years of age ECOG PS ≤2 adequate hematological manifestation, hepatic and renal functions life expectancy of at least 12 weeks	Interventions G1: S-1 + CIK (Cytokine-induced killer cells) as second-line chemotherapy (n=28) - Lymphocytes were separated from blood samples, cultured in vitro, and then applied to the patients by CIK cell intravenous reinjection. Treatment cycles were repeated every 28 days. This treatment course was repeated till disease progression, unacceptable toxicity occurred, and when the patient no longer wished to continue the treatment. G2: S-1 alone as second-line chemotherapy (n=30) - S-1 was administered orally twice daily at a dose of 80 mg/m2 for 21 consecutive days, followed by 7 days of rest. The initial doses were determined	Details Design: Multicentre Phase 3 RCT Randomization method: “Patients were stratified according to Karnofsky performance score and prior response to GEM first-line chemotherapy. Patients were then assigned ….by the central office located at the University in Vienna.” Blinding: unclear Duration/last follow-up: unclear	Response rate Overall Survival* Adverse Events (Grade 3/4 toxicities: Nausea/ vomiting, Diarrhoea, Neutropenia, Fatigue, and stomatitis)	Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool. Random sequence generation: Unclear risk (No details given in the text) Allocation concealment: Unclear risk (No details given in the text) Blinding of participants and personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: low risk Selective reporting: low risk Overall risk of bias: very serious Other information

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Source of funding: Not reported	and with at least 1 measurable lesion according to modified response evaluation criteria in solid tumors (RECIST) Exclusion criteria patients who had not received S-1 as part of their previous regimen patients who had massive pleural effusion, ascites, active concomitant malignancy or brain metastasis women who were pregnant or lactating were excluded from the study.	according to the body surface area (BSA).			*analytical data data not show
Full citation Yamaue H, Tsunoda T, Tani M, Miyazawa M, Yamao K, Mizuno N, Okusaka T, Ueno H, Boku N, Fukutomi A, Ishii H, Ohkawa S, Furukawa M, Maguchi H, Ikeda M, Togashi Y, Nishio K, Ohashi Y. Randomized phase II/III clinical trial of elpamotide for patients with advanced pancreatic cancer: PEGASUS-PC Study. Cancer Sci. 2015;106(7):883-90. doi: 10.1111/cas.12674. Ref ID Yamaue et al., 2015 Country/ies where the study was carried out: Japan	Sample size N= 159 allocated; 153 randomized patients with locally advanced/metastatic PC (mixed population) Characteristics M/F (n): 62/38 (G1); 31/22 (G2) Median age (range): 64(38–80) years (G1); 65(36–80) years (G2) Clinical stage: LA: 27 (G1); 14 (G2) Metastatic: 73 (G1); 39 (G2) Primary tumour site within pancreas: Not reported Inclusion criteria 20–80 years LA or metastatic PC that was histologically or cytologically	Interventions G1: GEM + elpamotide (n=105: allocated; n=100: assessed) - All patients received i.v. GEM (1000 mg/m2) on days 1, 8, and 15 as one cycle, which was repeated every 4 weeks. In the intervention group patients received a s.c. injection of emulsified elpamotide (2.0 mg/mL/body) every week G2: GEM + placebo (n=54: allocated; n=53: assessed) - patients received a placebo (1.0 mL/body) emulsion without elpamotide	Details Design: Multicentre Phase 3 RCT Randomization method: “Patients were randomly assigned by the dynamic allocation method considering disease extent (LA versus metastatic disease) and institution as allocation adjustment factors.” Blinding: double-blinded Duration/last follow-up: follow-up at every 8 weeks from the first dosage until disease progression	Progression Free Survival Overall Survival Adverse Events	Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool. Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: U Low risk

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Study type: Multicentre double-blinded Phase 3 RCT Aim of the study: To compare Gemcitabine + elpamotide vs Gemcitabine single-agent in patients with advanced/metastatic pancreatic cancer. Study dates: Data collection-patients enrolment: 2009-2010 Publication year: 2015 Source of funding: OncoTherapy Science, Inc., Fuso Pharmaceutical Industries Ltd. and Otsuka Pharmaceutical Co., Ltd.	diagnosed as adenocarcinoma or adenosquamous carcinoma no prior chemotherapy or radiotherapy for pancreatic cancer ECOG PS of 0 or 1 life expectancy longer than 3 months, adequate or acceptable function of bone marrow, liver and kidney Exclusion criteria Patients with: symptomatic brain metastases active bleeding, malignant ascites requiring drainage, or serious medical conditions such as uncontrolled hypertension, arrhythmia, or heart failure. serious illness or concomitant non-malignant disease that was more than grade 3 according to RECIST criteria				Selective reporting: Low risk Overall risk of bias: no serious Other information
*(please see Forest plots and Evidence grade profiles for full detail about study's findings)					

1

2

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Full citation Aigner KR, Gailhofer S, Kopp S. Regional *versus* systemic	**Sample size**	**Interventions** G1: Regional Intra-Arterial Chemotherapy (n=9) -	**Details** Design: Multicentre Phase 3 RCT	Overall response rate (CR + PR)	**Limitations - Cochrane**

Study details	Participants	Interventions	Methods	Outcomes*	Comments
chemotherapy for advanced pancreatic cancer: a randomized study. Hepatogastroenterology. 1998;45(22):1125-9. **Ref Id** Aigner et al., 1998 **Country/ies where the study was carried out** Germany **Study type** Multicentre Phase 3 RCT **Aim of the study** To compare regional chemotherapy with systemic chemotherapy in advanced/metastatic pancreatic cancer **Study dates** Data collection-patients enrolment: not reported Publication year: 1998 **Source of funding** Not reported	N= 14 patients with locally advanced/metastatic PC (mixed population) **Characteristics** M/F (n): 1/8 (G1); 2/3 (G2) Median age (range): 56(n.r.) years (G1); 59 (n.r.) years (G2) Clinical stage: Stage III: 2 (G1); 1 (G2) Stage IV: 7 (G1); 4 (G2) Primary tumour site within pancreas: Head: 7 (G1); 3 (G2) Body: 1 (G1); 1 (G2) Tail: 1 (G1); 1 (G2) Multicentre: 0 (G1); 0 (G2) **Inclusion criteria** Not reported **Exclusion criteria** Not reported	Celiac axis infusion regional chemotherapy with SpherexR microembolization. G2: Systemic Chemotherapy (n=5) - including mitomycin, mitoxanthrone and cisplatin (5pts.)	Randomization method: not reported Blinding: unclear Duration/last follow-up: unclear		**Collaboration's 'Risk of bias' tool.** Random sequence generation: Unclear risk (No details given in the text) Allocation concealment: Unclear risk (No details given in the text) Blinding of participants and personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: Unclear risk (No details given in the text) Selective reporting: Low risk Overall risk of bias: very serious **Other information**

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Full citation Azmy A, Abdelwahab S, Yassen M. Oxaliplatin and Bolus-Modulated 5-FU as a Second-Line Treatment for Advanced Pancreatic Cancer: Can Bolus Regimens Replace FOLFOX When Considered for Second Line?. ISRN Oncol. 2013;2013:358538. **Ref Id** Azmy et al., 2013 **Country/ies where the study was carried out** Egypt **Study type** Unblinded Phase 3 RCT **Aim of the study** To compare the activity of 2 regimens combining oxaliplatin to bolus modulated 5-FU as second line treatment in advanced/metastatic pancreatic cancer pretreated	**Sample size** N= 48 patients with locally advanced/metastatic PC (mixed population) **Characteristics** M/F (n): 16/8 (G1); 17/7 (G2) Median age (range): 56(44–69) years (G1); 54 (41–68) years (G2) Clinical stage: LA: 15 (G1); 14 (G2) Metastatic: 9 (G1); 10 (G2) Site of metastases: Liver: 5 (G1); 6 (G2) Lung: 1 (G1); 1 (G2) LN: 2 (G1); 2 (G2) Peritoneal: 1 (G1); 1 (G2) **Inclusion criteria** Patients with histologically or cytologically proven LA or metastatic pancreatic adenocarcinoma,	**Interventions** G1: Oxaliplatin + 5-FU as second line chemotherapy (n=24) - FU 500 mg/m(2) IV bolus weekly x6 weeks + leucovorin 500mg/m(2) IV weekly for 6 weeks during each 8-week cycle + oxaliplatin 85mg/m(2) IV on weeks 1, 3, and 5 of each 8-week (FLOX) G2: Bolus leucovorin + bolus 5-FU as second line chemotherapy (n=24) - intravenous infusions of oxaliplatin 40mg/m(2), 5-FU 500 mg/m(2), and leucovorin 250mg/m(2) (3 weeks on, 1 week off)	**Details** Design: Phase 3 RCT Randomization method: “Patients were randomly assigned to one of the treatment regimens (block randomization at 4)” Blinding: open-label Duration/last follow-up: until patients' death	Overall response rate (CR + PR) Progression Free Survival* Overall Survival* Adverse Events (Grade 3/4 toxicities: Nausea/vomiting, Diarrhoea, Stomatitis, and haematological [including Neutropenia, Anaemia , Thrombocytopenia)	**Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool.** Random sequence generation: Low risk Allocation concealment: Unclear risk (No details given in the text) Blinding of participants and personnel Assessments: High risk Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: serious **Other information** * Not analytical data on results are reported (narrative reporting)

Study details	Participants	Interventions	Methods	Outcomes*	Comments
with Gemcitabine -containing schedule. **Study dates** Data collection-patients enrolment: 2008-2011 Publication year: 2013 **Source of funding** Not reported	with at least 1 bidimensionally measurable lesion (World Health Organization (WHO) criteria); Eastern Cooperative Oncology Group (ECOG) PS of 1-2; (IV) tumor progression after first line GEM (whether GEM pretreated or GEM resistance); absence of severe uncontrolled cardiovascular, metabolic, infectious, or neurological diseases; adequate bone marrow reserve (neutrophil count > 1.5 × 109/L, platelet count > 100.000/mm3 and Hb > 10 g/dL); (VII) adequate liver function (serum bilirubin < 1.5 mg/dL, serum transaminases < 2x the upper limit of normal); adequate renal function (serum creatinine < 1.5 mg/dL); age between 18 and 75 years. **Exclusion criteria** Patients with: Histologic types other than adenocarcinoma.				

Study details	Participants	Interventions	Methods	Outcomes*	Comments
	Neuropathy ≥ CTCAE grade 1. Ototoxicity > CTCAE grade 2. Serious, active comorbidity,				
Full citation Bernhard J, Dietrich D, Scheithauer W, Gerber D, Bodoky G, et al. Clinical benefit and quality of life in patients with advanced pancreatic cancer receiving Gemcitabine + capecitabine *versus* Gemcitabine single-agent : a randomized multicenter phase III clinical trial--SAKK 44/00-CECOG/PAN13001. J Clin Oncol. 2008;26(22):3695-701. **Ref Id** Bernhard et al., 2008 Country/ies where the study was carried out Multicentre (Switzerland, Italy, Austria, Germany) **Study type**	Sample size N= 319 patients with locally advanced/metastatic PC (mixed population) **Characteristics** M/F (n): 86/74 (G1); 85/74 (G2) Median age (range): 62(27-83) years (G1); 62 (36-84) years (G2) Clinical stage: LA: 32 (G1); 34 (G2) Metastatic: 128 (G1); 125 (G2) Inclusion criteria histologic/cytologic proof of primary inoperable/metastatic pancreatic adenocarcinoma; age more than 18 years; Karnofsky performance score (KPS) ≥ 60;	Interventions G1: GEM + capecitabine (n=160) - oral Cap 650 mg/m2 twice daily on days 1 through 14 + Gem 1,000 mg/m2 in a 30-minute infusion on days 1 and 8 every 3 weeks G2: GEM single-agent (n=159) - 1,000 mg/m2 in a 30-minute infusion weekly for 7 weeks, followed by a 1-week break, and then weekly for 3 weeks every 4 weeks	Details Design: Multicentre Phase 3 RCT Randomization method: not reported Blinding: open-label Duration/last follow-up: 24 weeks	Response rate Overall Survival Adverse Events Health Related Quality of Life	**Limitations - Cochrane Collaboration's 'Risk of bias' tool.** Random sequence generation: Unclear risk (No details given in the text) Allocation concealment: Unclear risk (No details given in the text) Blinding of participants and personnel Assessments: High risk Blinding of outcome assessment: Low risk Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: serious

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Multicentre unblinded Phase 3 RCT Aim of the study To compare clinical benefit response and quality of life in patients receiving Gemcitabine (Gem) + capecitabine *versus* single-agent Gem in advanced/metastatic pancreatic cancer Study dates Data collection-patients enrolment: 2001-2004 Publication year: 2008 **Source of funding** The trial was sponsored by the Swiss Group for Clinical Cancer Research, and the Central European Cooperative Oncology Group played a supportive role in Austria.	no prior chemotherapy; and adequate bone marrow reserve **Exclusion criteria** known CNS metastases history of other primary malignancy within 5 years except for adequately treated cervical carcinoma in situ or basal cell skin carcinoma insufficient liver function creatinine clearance less than 30 mL/min active infection; breast feeding/pregnancy; reproductive potential without using effective contraception; serious concomitant systemic disorder incompatible with the trial in the investigator's judgment; known hypersensitivity or anticipated severe reaction to fluoropyrimidines; concomitant treatment with sorivudine or related analogs; grade 2 nausea or grade 1 vomiting				Other information

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Full citation Bukowski RM, Balcerzak SP, O'Bryan RM, Bonnet JD, Chen TT. Randomized trial of 5-FU and mitomycin C with or without streptozotocin for advanced pancreatic cancer A Southwest Oncology Group study. Cancer. 1983;52(9):1577-82. **Ref Id** Bukowski et al., 1983 Country/ies where the study was carried out USA **Study type** Phase 3 RCT Aim of the study To compare streptozotocin, mitomycin C, and 5-FU (SMF) with mitomycin C and 5-FU (MF) in advanced/metastatic pancreatic cancer Study dates	Sample size N= 181 patients with locally advanced/metastatic PC (mixed population) Characteristics Clinical stage: LA: 26 (G1); 22 (G2) Metastatic: 46 (G1); 51 (G2) All other population characteristics are reported unclearly. **Inclusion criteria** histologic or cytologic confirmation of pancreatic adenocarcinoma; no previous chemotherapy or radiation therapy adequate renal function (BUN)l 25 mg% and creatinine 5 2.0 mg%). **Exclusion criteria** Patients with: not reported	Interventions G1: First line chemotherapy combination (n=70) streptozotocin, mitomycin C, and 5-FU (SMF) G2: First line chemotherapy combination (n=70) - mitomycin C and 5-FU (MF)	Details Design: Phase 3 RCT Randomization method: unclear “Patients were stratified according to risk status, and the presence of measurable or nonmeasurable disease, and randomized to receive either the MF or SMF regimens” Blinding: unclear Duration/last follow-up: unclear	Overall response rate (CR + PR) Overall Survival* Adverse Events (Grade 3/4 toxicities: Nausea/vomiting, Diarrhoea, Leucopoenia Thrombocytopenia) Drug-related deaths	**Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool.** Random sequence generation: Unclear risk (No details given in the text) Allocation concealment: Unclear risk (No details given in the text) Blinding of participants and personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: very serious Other information

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Data collection-patients enrolment: not reported Publication year: 1983 Source of funding Grant Support CA-04915/CA/NCI NIH HHS/United States; CA-04919/CA/NCI NIH HHS/United States; CA-04920/CA/NCI NIH HHS/United States;					* Not analytical data on results are reported (narrative reporting)
Full citation Burris HA 3rd, Moore MJ, Andersen J, Green MR, Rothenberg ML, et al. Improvements in survival and clinical benefit with Gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol. 1997;15(6):2403-13. Ref Id Burris et al., 1997	**Sample size** N= 160 patients with locally advanced/metastatic PC (mixed population) **Characteristics** M/F (n): 34/29 (G1); 34/29 (G2) Median age (range): 62(37-79) years (G1); 61 (36-77) years (G2) Clinical stage: Stage II/III: 18 (G1); 15 (G2) Stage IV: 45 (G1); 48 (G2)	**Interventions** G1: 5-FU single-agent (n=63) - 600 mg/m2 once weekly G2: GEM single-agent (n=63) -1,000 mg/m2 weekly x 7 followed by 1 week of rest, then weekly x 3 every 4 weeks thereafter	**Details** Design: Phase 3 RCT Randomization method: unclear “Randomization of patients …... was performed at a central location.” Blinding: Single(patients)-blinded Duration/last follow-up: 24 weeks	Response rate Progression Free Survival Overall Survival Adverse Events	**Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool.** Random sequence generation: Unclear risk (No details given in the text) Allocation concealment: Low risk Blinding of participants and personnel Assessments: Low risk

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Country/ies where the study was carried out USA **Study type** Single(patients)-blinded Phase 3 RCT **Aim of the study** To compare single-agent 5-FU with Gemcitabine in advanced/metastatic pancreatic cancer **Study dates** Data collection-patients enrolment: 1992-1994 Publication year: 1997 **Source of funding** Supported by a grant from Eli Lilly and Company, Indianapolis, IN.	Primary tumour site within pancreas: Not reported **Inclusion criteria** baseline Karnofsky performance status of less than 80; baseline analgesic consumption of - 10 morphine equivalent mg/d baseline pain intensity score of > 20 mm **Exclusion criteria** see inclusion criteria				Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: no serious **Other information**
Full citation Cantore M, Fiorentini G, Luppi G, Rosati G, Caudana R, Piazza E, Comella G, Ceravolo C, Miserocchi L,	Sample size N= 138 patients with locally advanced/metastatic PC (mixed population)	Interventions G1: FLEC (n=71) - 5-fluoruracil 1,000 mg/m2, leucovorin 100 mg/m2, epirubicin 60 mg/m2,	Details Design: Phase 3 RCT Randomization method: not reported	Overall response rate (CR + PR) Overall Survival	Limitations - Cochrane Collaboration's 'Risk of bias' tool. Random sequence generation: Low risk

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Mambrini A, Del Freo A, Zamagni D, Rabbi C, Marangolo. Gemcitabine *versus* FLEC regimen given intra-arterially to patients with nresectable pancreatic cancer: a prospective, randomized phase III trial of the Italian Society for Integrated Locoregional Therapy in Oncology. J Chemother. 2004;16(6):589-94. **Ref Id** Cantore et al., 2004 **Country/ies where the study was carried out** Italy **Study type** Phase 3 RCT Aim of the study To compare FLEC (5-fluoruracil 1,000 mg/m2, leucovorin 100 mg/m2, epirubicin 60 mg/m2, carboplatin 300 mg/m2 infused bolus intra-arterially into celiac axis) with	Characteristics M/F (n): 45/26 (G1); 47/20 (G2) Median age (range): 61 (38-76) years (G1); 64 (37-79) years (G2) Clinical stage: LA: 35 (G1); 32 (G2) Metastatic: 36 (G1); 35 (G2) Primary tumour site within pancreas: Head: 42 (G1); 40 (G2) Body: 19 (G1); 19 (G2) Tail: 10 (G1); 8 (G2) **Inclusion criteria** histologically-proven adenocarcinoma of the pancreas not suitable for curative resection, baseline Karnofsky performance status of at least 50. adequate baseline bone marrow reserve,	carboplatin 300 mg/m2 infused bolus intra-arterially into celiac axis G2: GEM single-agent (n=67) - dose of 1,000 mg/m2 over 30 minutes intravenously weekly for 7 weeks, followed by 1 week of rest, then weekly for 3 weeks every 4 weeks	Blinding: unclear Duration/last follow-up: 12 months	Adverse Events (Grade 3/4 toxicities: Nausea/vomiting, Diarrhoea, Leucopoenia Thrombocytopenia)	Allocation concealment: Low risk Blinding of participants and personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: no serious Other information

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Gemcitabine in advanced/metastatic pancreatic cancer Study dates Data collection-patients enrolment: 1998-2002 Publication year: 2004 Source of funding Not reported	adequate baseline hepatic function adequate renal function .Exclusion criteria peritoneal metastases previous chemotherapy or radiotherapy or combination of both previous myocardial infarction, severe coagulopathy second malignancy (except cell skin cancer and in situ carcinoma of the cervix), pregnancy				
Full citation Chao Y, Wu CY, Wang JP, Lee RC, Lee WP, Li CP. A randomized controlled trial of Gemcitabine + cisplatin *versus* Gemcitabine single-agent in the treatment of metastatic pancreatic cancer. Cancer Chemother Pharmacol. 2013 Sep;72(3):637-42.	Sample size N= 46 patients with metastatic PC Characteristics M/F (n): 17/4 (G1); 18/7 (G2) Median age (range): 69 (47–81) years (G1); 69 (46–83) years (G2) Clinical stage:	Interventions G1: GEM + cisplatin (n=21) - 1,000 mg/m2 GEM and 25 mg/m2 cisplatin G2: GEM single-agent (n=25) - 1,000 mg/m2	Details Design: RCT Randomization method: not reported Blinding: open-label Duration/last follow-up: until patients' death	Response rate Progression Free Survival Overall Survival Adverse Events Health Related Quality of Life	Limitations - Cochrane Collaboration's 'Risk of bias' tool. Random sequence generation: Unclear risk (No details given in the text) Allocation concealment: Unclear risk (No details given in the text)

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Ref Id Chao et al., 2013 Country/ies where the study was carried out Taiwan Study type Unblinded RCT Aim of the study To compare the efficacy and toxicity of single-agent Gemcitabine with Gemcitabine + cisplatin (G + C) in patients with metastatic pancreatic cancer Study dates Data collection-patients enrolment: 2000-2002 Publication year: 2013 Source of funding This work was supported by grants from Taipei Veterans General Hospital (V101C-178), National Science Council (NSC 98-2314-B-	LA: 0 (G1); 0 (G2) Metastatic: 21 (G1); 25 (G2) Primary tumour site within pancreas: Head: 7 (G1); 7 (G2) Body: 7 (G1); 6 (G2) Tail: 7 (G1); 12 (G2) site of metastases: Liver: 13 (G1); 21 (G2) Lung: 7 (G1); 3 (G2) Bone: 1 (G1); 0 (G2) **Inclusion criteria** stage IV (metastatic) disease according to the Cancer Staging Manual of the American Joint Committee on Cancer Karnofsky performance score ≥50 absolute neutrophil count (ANC) ≥1,500 mm−3 platelet count ≥100,000 mm−3				Blinding of participants and personnel Assessments: High risk Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: very serious Other information

Study details	Participants	Interventions	Methods	Outcomes*	Comments
075-029), and National Research Program for Biopharmaceutics of Taiwan (100CT202).	serum creatinine level ≤1.5 mg dl−1 aspartate aminotransferase (AST) alanine aminotransferase (ALT) level <5 times the upper limit of normal measurable disease no prior chemotherapy or radiotherapy no other malignancy and no serious medical or psychological illness that would preclude informed consent Exclusion criteria see Inclusion criteria				
Full citation Ciuleanu TE, Pavlovsky AV, Bodoky G, Garin AM, Langmuir VK, et al. A randomised Phase III trial of glufosfamide compared with best supportive care in metastatic pancreatic adenocarcinoma previously	Sample size N= 303 patients with metastatic PC Characteristics M/F (n): 90/58 (G1); 90/65 (G2)	Interventions G1: Second line chemotherapy + best supportive care (n=148) - glufosfamide in patients previously treated with GEM . G2: Best supportive care (n=155) - BSC was	Details Design: Multicentre Phase 3 RCT Randomization method: unclear “Randomisation was stratified by KPS (70 *versus* P80)”	Progression Free Survival Overall Survival Adverse effects	Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool. Random sequence generation: Unclear risk (No details given in the text)

Study details	Participants	Interventions	Methods	Outcomes*	Comments
treated with Gemcitabine . Eur J Cancer. 2009;45(9):1589-96. Ref Id Ciuleanu et al., 2009 Country/ies where the study was carried out Multicentre (Argentina, Brazil, Czech Republic, Hungary, India, Russia) Study type Multicentre unblinded Phase 3 RCT Aim of the study To compare the efficacy and safety of glufosfamide as compared with best supportive care (BSC) in patients with metastatic pancreatic cancer Study dates Data collection-patients enrolment: 2004-2006 Publication year: 2009 Source of funding	Median age (range): 58(27–78) years (G1); 57 (29–80) years (G2) Clinical stage: LA: 0 (G1); 0 (G2) Metastatic: 148 (G1); 155 (G2) Sites of metastatic disease: Liver: 114 (G1); 120 (G2) Non-liver: 34 (G1); 35 (G2) Region: EU: 62 (G1); 63 (G2) Russia: 41 (G1); 39 (G2) South America: 26 (G1); 35 (G2) USA: 10 (G1); 11 (G2) India: 9 (G1); 7 (G2) Inclusion criteria at least 18 years of age at least one target or non-target lesion by RECIST recovered from reversible toxicities of prior therapy	defined as analgesics, antibiotics, transfusions, therapeutic haematopoietic colony-stimulating factors, erythropoietin and other appropriate supportive measures including concomitant medications that do not have anti-tumour effects.	Blinding: open-label Duration/last follow-up: until patients' death		Allocation concealment: Unclear risk (No details given in the text) Blinding of participants and personnel Assessments: High risk Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: high risk Selective reporting: Low risk Overall risk of bias: serious Other information

Study details	Participants	Interventions	Methods	Outcomes*	Comments
This study was funded by Threshold Pharmaceuticals.	adequate organ reserve including haematopoietic, hepatic and renal function (CrCL ⩾ 1.0 mL/s calculated by the Cockcroft-Gault formula) Karnofsky performance status (KPS) of at least 70. Exclusion criteria Patients were excluded if they had received more than one prior systemic therapy regimen for advanced disease				
Full citation Cullinan S, Moertel CG, Wieand HS, Schutt AJ, Krook JE, Foley JF, Norris BD, Kardinal CG, Tschetter LK, Barlow JF. A phase III trial on the therapy of advanced pancreatic carcinoma. Evaluations of the Mallinson regimen and combined 5-FU, doxorubicin, and cisplatin. Cancer. 1990;65(10):2207-12. Ref Id Cullinan et al., 1990	Sample size N= 187 patients with metastatic PC Characteristics M (%): 66 (G1); 56 (G2); 64 (G3) Median age (range): 60(35-80) years (G1); 62 (34-19) years (G2); 62 (27-76) years (G3) Clinical stage: LA: 0 (G1); 0 (G2); 0 (G3) Metastatic: 64 (G1); 61 (G2) ; 59 (G3)	Interventions G1: Single-agent 5-FU alone chemotherapy (n=64) G2: Mallisom regimen (n=61) - combined and sequential 5-FU, cyclophosphamide, methotrexate, vincristine, and mitomycin C; G3: 5-FU combination chemotherapy (n=59) - 5-FU, doxorubicin, and cisplatin.	Details Design: Phase 3 RCT Randomization method: unclear "Patients were stratified according to the presence of measurable disease, the extent of metastasis (abdominal and/or retroperitoneal only, hepatic, or extra-abdominal), and ECOG performance	Response rate Progression Free Survival Overall Survival Adverse Events	Limitations - Cochrane Collaboration's 'Risk of bias' tool. Random sequence generation: Unclear risk (No details given in the text) Allocation concealment: Unclear risk (No details given in the text) Blinding of participants and personnel Assessments: High risk Blinding of outcome assessment: Unclear

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Country/ies where the study was carried out USA Study type Phase 3 RCT Aim of the study To compare the efficacy and toxicity of a combination chemotherapy regimen consisting of 5-FU (5-FU) alone, or the Mallinson regimen (combined and sequential 5-FU, cyclophosphamide, methotrexate, vincristine, and mitomycin C), or to combined 5-FU, doxorubicin, and cisplatinin patients with metastatic pancreatic cancer Study dates Data collection-patients enrolment: not reported Publication year: 1990 Source of funding Grant Support	Extent of metastatic disease (%): Abdominal: 28 (G1); 30 (G2) ; 31 (G3) Hepatic: 59 (G1); 64 (G2) ; 59 (G3) Extra-abdominal: 13 (G1); 7 (G2) ; 10 (G3) Inclusion criteria histologic proof of ductal or undifferentiated adenocarcinoma consistent with a pancreatic primary and to have a pancreatic primary that could be reasonably established by surgical inspection, computed tomography (CT) scan, or sonography. ambulatory, maintaining an unassisted oral food intake of at least 1200 calories daily, and have a minimum of 3 weeks recovery from any major surgical procedure involving resection or bypass or 2 weeks recovery from exploration and biopsy only **Exclusion criteria**		status (0 or 1 *versus* 2 or 3)” Blinding: unclear Duration/last follow-up: until patients' death		risk (No details given in the text) Incomplete outcome data: Low risk Selective reporting: Unclear risk (No protocol published a-priori) Overall risk of bias: very serious Other information

Study details	Participants	Interventions	Methods	Outcomes*	Comments
CA-31224/CA/NCI NIH HHS/United States CA-37404/CA/NCI NIH HHS/United States	see inclusion criteria				
Full citation Cullinan SA, Moertel CG, Fleming TR, Rubin JR, Krook JE, Everson LK, Windschitl HE, Twito DI, Marschke RF, Foley JF, et al. A comparison of three chemotherapeutic regimens in the treatment of advanced pancreatic and gastric carcinoma. 5-FU vs 5-FU and doxorubicin vs 5-FU, doxorubicin, and mitomycin. JAMA. 1985;253(14):2061-7 Ref Id Cullinan et al., 1985 Country/ies where the study was carried out USA Study type Multicentre Phase 3 RCT Aim of the study	Sample size N= 187 patients with metastatic PC Characteristics M (%): 68 (G1); 59 (G2); 64 (G3) Age 50-69 years (%): 70 (G1); 86 (G2); 76 (G3) Clinical stage (%): LA: 28 (G1); 36 (G2); 26 (G3) Metastatic: not reported Extent of metastatic disease (%): Not reported Inclusion criteria histologic proof of ductal or undifferentiated adenocarcinoma ambulatory, maintaining an unassisted oral food intake of at least 1200 calories daily,	Interventions G1: Single-agent 5-FU alone chemotherapy (n=50) G2/3: 2) 5-FU combination chemotherapy (n=44) 5-FU, 5-FU + doxorubicin; 3) 5-FU combination chemotherapy (n=50) 5-FU + doxorubicin + mitomycin	Details Design: Multicentre Phase 3 RCT Randomization method: unclear "Patients were stratified according to the presence of measurable disease, the extent of metastasis (abdominal and/or retroperitoneal only, hepatic, or extra-abdominal), and ECOG performance status (0 or 1 *versus* 2 or 3)" Blinding: unclear Duration/last follow-up: unclear	Response rate Progression Free Survival Overall Survival Adverse Events	**Limitations - Cochrane Collaboration's 'Risk of bias' tool.** Random sequence generation: Unclear risk (No details given in the text) Allocation concealment: Unclear risk (No details given in the text) Blinding of participants and personnel Assessments: High risk Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: Low risk Selective reporting: Unclear risk (No

Study details	Participants	Interventions	Methods	Outcomes*	Comments
To compare single-agent 5-FU alone with 5-FU combination chemotherapy (a. 5-FU + doxorubicin, or b. 5-FU + doxorubicin + mitomycin) in advanced/metastatic pancreatic cancer Study dates Data collection-patients enrolment: not reported Publication year: 1985 Source of funding Grant Support CA 25224/CA/NCI NIH HHS/United States CA 31224/CA/NCI NIH HHS/United States CA 37404/CA/NCI NIH HHS/United States	have a minimum of 3 weeks recovery from any major surgical procedure involving resection or Exclusion criteria see inclusion criteria				protocol published a-priori) Overall risk of bias: very serious **Other information**
Full citation Dahan L, Bonnetain F, Ychou M, Mitry E, Gasmi M, et al. Combination 5-FU, folinic acid and cisplatin (LV5FU2-	**Sample size** N= 202 patients with metastatic PC **Characteristics**	**Interventions** G1: Chemotherapy combination of 5-FU, FA and cisplatin (LV5FU2-CDDP) followed by GEM	**Details** Design: Multicentre Phase 3 RCT Randomization method: "Patients	Overall response rate (CR + PR) Progression free survival Overall Survival	**Limitations - Cochrane Collaboration's 'Risk of bias' tool.**

Study details	Participants	Interventions	Methods	Outcomes*	Comments
CDDP) followed by Gemcitabine or the reverse sequence in metastatic pancreatic cancer: final results of a randomised strategic phase III trial (FFCD 0301). Gut. 2010;59(11):1527-34. **Ref Id** Dahan et al., 2010 **Country/ies where the study was carried out** France **Study type** Multicentre Phase 3 RCT **Aim of the study** To compare the combination of 5-FU (5FU), folinic acid and cisplatin (LV5FU2-CDDP) followed by Gemcitabine with Gemcitabine followed by LV5FU2-CDDP for patients with metastatic pancreatic adenocarcinoma **Study dates**	M/F (n): 65/37 (G1); 65/35 (G2) Median age (range): xx(xx-xx) years (G1); xx (xx-xx) years (G2) Clinical stage: LA: 0 (G1); 0 (G2) Metastatic: 102 (G1); 100 (G2) Primary tumour site within pancreas: Head: 57 (G1); 49 (G2) Other: 44 (G1); 50 (G2) Unknown: 1 (G1); 1 (G2) Site of metastases: Liver: 87 (G1); 90 (G2) Lung: 15 (G1); 12 (G2) Lymph nodes: 18 (G1); 24 (G2) Peritoneum: 11 (G1); 17 (G2) Other: 7 (G1); 8 (G2) **Inclusion criteria** proven metastatic pancreatic adenocarcinoma by histological or cytological biopsy	after progression (n=102) - LV5FU2-CDDP included a 2 h infusion of leucovorin (LV) 200 mg/m2 followed by 5FU as a bolus 400 mg/m2 then a 46 h infusion of 2400 mg/m2 with cisplatin 50 mg/m2 as a 2 h infusion on day 1, every 2 weeks. GEM included 1000 mg/m2 as a 30 min weekly infusion for 7/8 weeks and then a weekly infusion for 3/4 weeks according to a classic Burris regimen G2: GEM followed by LV5FU2-CDDP after progression (n=100)	were randomised 1:1 through a minimisation program. Patients were stratified according to WHO PS (0, 1 *versus* 2), tumour localisation (head *versus* other) and participating institutions (centre).” Blinding: unclear Duration/last follow-up: until disease progression or death.	Adverse Events (Grade 3/4 toxicities: Nausea/ vomiting)	Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: no serious **Other information**

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Data collection-patients enrolment: 2003-2006 Publication year: 2010 **Source of funding** Not reported	at least one measurable metastasis ≥10 mm on CT or MRI or ≥20 mm with a conventional scan. the targeted metastasis should not have been treated by radiotherapy. patients over 18, who had a WHO performance status (PS) ≤2 and a life expectancy of >2 months. adequate bone marrow, liver function , and renal function **Exclusion criteria** previous palliative or adjuvant chemotherapy prior radiotherapy <4 weeks brain metastases a medical history of malignant tumours, pregnant women or woman who were breast feeding, and LA cancer with no evidence of metastases.				
Full citation	**Sample size**	**Interventions**	**Details**	Progression Free Survival	**Limitations - Cochrane**

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Deplanque G, Demarchi M, Hebbar M, Flynn P, Melichar B, et al. A randomized, placebo-controlled phase III trial of masitinib + Gemcitabine in the treatment of advanced pancreatic cancer. Ann Oncol. 2015;26(6):1194-200. **Ref Id** Deplanque et al., 2015 **Country/ies where the study was carried out** Multicentre (France, Czech Republic, US) **Study type** Multicentre double-blinded Phase 3 RCT **Aim of the study** To compare masitinib combined with Gemcitabine with Gemcitabine single-agent in advanced/metastatic pancreatic cancer **Study dates**	N= 348 patients with locally advanced/metastatic PC (mixed population) **Characteristics** M/F (n): 86/87 (G1); 102/73 (G2) Median age (range): 62.6 (36.0–84.0) years (G1); 61.7 (31.0–79.0) years (G2) Clinical stage: LA: 22 (G1); 24 (G2) Metastatic: 151 (G1); 151 (G2) Primary tumour site within pancreas: Head: 93 (G1); 94 (G2) Body: 50 (G1); 59 (G2) Tail: 54 (G1); 49 (G2) **Inclusion criteria** Histologically or cytologically confirmed adenocarcinoma of the pancreas Chemo naïve patients with advanced/metastatic disease	G1: GEM + masitinib (n=173) - Masitinib (9 mg/kg/day) was administered orally in two daily doses, while GEM (1000 mg/m2) was administered according to standard clinical practice. G2: GEM + placebo (n=175)	Design: Multicentre Phase 3 RCT Randomization method: "Patients were centrally randomized to treatments groups (1:1) using an Interactive Voice Response System (IVRS), with treatment allocated according to a modified minimization method. Stratification was done according to geographic region and disease status (LA *versus* metastatic)." Blinding: double-blinded Duration/last follow-up: 26 months (median follow-up time)	Overall Survival Adverse Events	**Collaboration's 'Risk of bias' tool.** Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel Assessments: Low risk Blinding of outcome assessment: Low risk Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: no serious **Other information**

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Data collection-patients enrolment: 2008-2013 Publication year: 2015 **Source of funding** This study was financially supported by AB Science, Paris, France (no grant number) and by Acobiom, Montpellier, France (no grant number)	Documented decision justifying non eligibility for surgical resection. The documentation of the non eligibility for surgical resection will be reviewed by an independent committee. Men and women, age >18 years Men and women of childbearing potential (entering the study after a confirmed menstrual period and who have a negative pregnancy test), must agree to use two methods (one for the patient and one for the partner) of medically acceptable forms of contraception during the study and for 3 months after the last treatment intake. Patient should be able and willing to comply with study visits and procedures as per protocol. Patient should understand, sign, and date the written voluntary informed consent form at the screening visit prior to any protocol-specific procedures performed. **Exclusion criteria**				

Study details	Participants	Interventions	Methods	Outcomes*	Comments
	Patient treated for a cancer other than PC within 5 years before enrollment, with the exception of basal cell carcinoma or in situ cervical cancer Any condition that the physician judges could be detrimental to subjects participating in this study; including any clinically important deviations from normal clinical laboratory values or concurrent medical events Previous treatment Any anti-tumor therapy (any chemotherapy, radiotherapy, immunotherapy, biologic or hormonal therapy) within 6 months prior to baseline Treatment with any investigational agent within 4 weeks prior to baseline				
Full citation Ducreux M, Rougier P, Pignon JP, Douillard JY, Seitz JF, Bugat R, Bosset JF, Merouche Y, Raoul JL, Ychou M, Adenis A, Berthault-Cvitkovic F, Luboinski M; Groupe Digestif	**Sample size** N= 207 patients with metastatic PC **Characteristics** M/F (n): 67/36 (G1); 67/37 (G2)	**Interventions** G1: 5-FU single-agent (n=103) 500 mg/m2/day for 5 days G2: 5-FU combination chemotherapy (n=104) - continuous 5-FU 1000	**Details** Design: Phase 3 RCT Randomization method: "Patients were stratified according to risk status, and the	Overall response rate (CR + PR) Progression free survival Overall Survival	**Limitations - Cochrane Collaboration's 'Risk of bias' tool.** Random sequence generation: Low risk

Study details	Participants	Interventions	Methods	Outcomes*	Comments
of the Fédération Nationale des Centres de Lutte Contre le Cancer Digestif. A randomised trial comparing 5-FU with 5-FU + cisplatin in advanced pancreatic carcinoma. Ann Oncol. 2002;13(8):1185-91. **Ref Id** Ducreux et al., 2002 **Country/ies where the study was carried out** France **Study type** Phase 3 RCT **Aim of the study** To compare 5-FU (5-FU) + cisplatin with 5-FU alone in patients with metastatic pancreatic adenocarcinoma **Study dates** Data collection-patients enrolment: 1992-1998 Publication year: 2002 **Source of funding**	Mean age (SD): 59.9 (9) years (G1); 60.0 (9.1) years (G2) Clinical stage: LA: 0 (G1); 0 (G2) Metastatic: 103 (G1); 104 (G2) Site of metastases: Pancreas only: 12 (G1); 6 (G2) Liver: 75 (G1); 75 (G2) Lung: 9 (G1); 12 (G2) Lymph nodes: 16 (G1); 24 (G2) Peritoneum: 2 (G1); 6 (G2) Other: 7 (G1); 8 (G2) No PC: Ampulloma: 4 (G1); 5 (G2) **Inclusion criteria** Histological or cytological proof of ductal or undifferentiated adenocarcinoma of the pancreas. Disease was also to be either LA or metastatic, and lesions were to be measurable or evaluable.	mg/m(2)/day for 5 days + cisplatin 100 mg/m(2) on day 1 or day 2	presence of measurable or nonmeasurable disease, using minimizzation." Blinding: unclear Duration/last follow-up: until patients' death	Adverse Events (Grade 3/4 toxicities: Vomiting, Diarrhoea, Stomatits)	Allocation concealment: Unclear risk (No details given in the text) Blinding of participants and personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: serious **Other information**

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Not reported	Patients with ampulloma were also deemed eligible. a life expectancy of at least 2 months, a WHO performance status (PS) of <3 age <75 years no previous chemotherapy, no hormonotherapy during the previous 3 months, and no radiotherapy treatment of indicator lesions. adequate hepatic, renal and bone marrow functions **Exclusion criteria** leucopoenia thrombocytopenia elevated serum creatinine (>110 µmol/l), hyperbilirubinemia active heart disease any known previous second primary malignant disease.				
Full citation	**Sample size**	**Interventions**	**Details**	Response rate Overall Survival	**Limitations - Cochrane**

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Eckhardt SG, De Porre P, Smith D, Maurel J, Steward WP, et al. Patient-reported outcomes as a component of the primary endpoint in a double-blind, placebo-controlled trial in advanced pancreatic cancer. J Pain Symptom Manage. 2009;37(2):135-43. **Ref Id** Eckhardt et al., 2009 **Country/ies where the study was carried out** Multicentre (Australia, Austria, France, Germany, Portugal, Spain, Sweden, UK, US) **Study type** Multicentre double-blinded Phase 3 RCT **Aim of the study** To compare Gemcitabine + tipifarnib with Gemcitabine + placebo in advanced/metastatic pancreatic cancer	N= 244 patients with locally advanced/metastatic PC (mixed population) **Characteristics** F (n): 45 (G1); 49 (G2) Median age (range): 63 (35–81) years (G1); 60 (35–86) years (G2) Clinical stage: LA: 36 (G1); 33 (G2) Metastatic: 88 (G1); 87 (G2) Primary tumour site within pancreas: Not reported **Inclusion criteria** patients with pathologically confirmed, LA or metastatic, chemotherapy-naïve adenocarcinoma of the pancreas. ECOG-PS score of 0 to 2 adequate bone marrow, and adequate hepatic and renal function	G1: GEM + tipifarnib (n=124) - The starting dose of Tipifarnib (placebo) was 200 mg twice daily in a continuous daily dosing schedule G2: GEM + placebo (n=120) - Starting GEM dose of 1000 mg/m2 intravenously weekly for seven weeks, followed by one week of rest, and then weekly for three weeks of each subsequent four-week period.	Design: Multicentre Phase 3 RCT Randomization method: "Patients were randomized centrally to the...through a dynamic randomization procedure, with stratification for the presence or absence of metastatic disease, ECOG-PS (0 *versus* 1 *versus* 2), and investigator site." Blinding: double-blinded Duration/last follow-up: until patients' death	Adverse Events	**Collaboration's 'Risk of bias' tool.** Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel Assessments: Low risk Blinding of outcome assessment: Low risk Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: no serious **Other information**

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Study dates Data collection-patients enrolment: 2000-2001 Publication year: 2009 **Source of funding** This study was supported by Johnson & Johnson Pharmaceutical Research & Development, LLC.	**Exclusion criteria** Patients with: See inclusion criteria				
Full citation Fuchs CS, Azevedo S, Okusaka T, Van Laethem JL, Lipton LR, et al. A phase 3 randomized, double-blind, placebo-controlled trial of ganitumab or placebo in combination with Gemcitabine as first-line therapy for metastatic adenocarcinoma of the pancreas: the GAMMA trial. Ann Oncol. 2015;26(5):921-7. **Ref Id** Fuchs et al., 2015 **Country/ies where the study was carried out**	**Sample size** N= 800 patients with metastatic PC **Characteristics** M/F (n): 188/134 (G1); 159/159 (G2) ; 85/75 (G3) Median age (range): 63 (36–83) years (G1); 62 (36–85) years (G2) ; 62 (31–81) years (G3) Clinical stage: LA: 0 (G1); 0 (G2); 0 (G3) Metastatic: 322 (G1); 318 (G2) ; 160 (G3)	**Interventions** G1: GEM + placebo (n=322) - patients received GEM on days 1, 8, and 15, and placebo/ganitumab on days 1 and 15 of each 28-day cycle. G2: GEM + ganitumab 12 mg/kg (n=318) - GEM could be withheld or reduced depending on timing and toxicity severity; ganitumab was withheld until GEM was resumed. Ganitumab dose reductions up to 50% were allowed for toxicity;	**Details** Design: Multicentre Phase 3 RCT Randomization method: "Patients were randomly assigned 2 : 2 : 1 to .... Randomization was stratified by ECOG PS (0 versus 1), liver metastases (yes versus no), and region (Australia, Western Europe, USA, and Canada versus rest of world).." Blinding: double-blinded	Response rate Progression Free Survival Overall Survival Adverse Events	**Limitations - Cochrane Collaboration's 'Risk of bias' tool.** Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel Assessments: Low risk Blinding of outcome assessment: Low risk Incomplete outcome data: Low risk

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Multicentre (Australia, Canada, Japan, Brazil, Czech Republic, Poland, Spain, UK, US) **Study type** Multicentre double-blinded Phase 3 RCT **Aim of the study** To compare ganitumab combined with Gemcitabine with Gemcitabine single-agent in patients with metastatic pancreatic adenocarcinoma **Study dates** Data collection-patients enrolment: 2011-2012 Publication year: 2015 **Source of funding** This study was supported by Amgen Inc. in collaboration with Takeda Global Research & Development Center, Inc.	Primary tumour site within pancreas: Head: 115 (G1); 124 (G2) ; 159 (G3) Head & Body: 20 (G1); 21 (G2) ; 8 (G3) Head & Tail: 4 (G1); 1 (G2) ; 0 (G3) Head & Body & Tail : 2 (G1); 5 (G2) ; 2 (G3) Body: 71 (G1); 60 (G2) ; 30 (G3) Body & Tail: xx (G1); xx (G2) ; xx (G3) Tail: 44 (G1); 50 (G2) ; 33 (G3) No pancreas: 11 (G1); 12 (G2) ; 8 (G3) Site of metastases: Liver: 249 (G1); 255 (G2) ; 125 (G3) Lung: 76 (G1); 70 (G2) ; 37(G3) Lymph nodes: 97 (G1); 37 (G2) ; 8 (G3)	reductions were permanent. Ganitumab could be withheld or permanently discontinued for certain adverse events G3: GEM + ganitumab 20 mg/kg (n=160)	Duration/last follow-up: until patients' death		Selective reporting: Low risk Overall risk of bias: no serious **Other information**

Study details	Participants	Interventions	Methods	Outcomes*	Comments
	Other: 104 (G1); 116 (G2) ; 51 (G3) **Inclusion criteria** Eligible patients (≥18 years) had previously untreated histologically or cytologically confirmed metastatic pancreatic adenocarcinoma; Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤1; and adequate hematologic, renal, hepatic, and cardiac function. **Exclusion criteria** histology other than pancreatic adenocarcinoma central nervous system metastases external biliary drain paracentesis or thoracentesis for malignant effusion within previous 14 days prior or synchronous malignancy major or minor surgery within previous 30 or 7 days				

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Full citation Gill S, Ko YJ, et al. PANCREOX: A Randomized Phase III Study of 5-Fluorouracil/Leucovorin With or Without Oxaliplatin for Second-Line Advanced Pancreatic Cancer in Patients Who Have Received Gemcitabine-Based Chemotherapy. J Clin Oncol. 2016 **Ref Id** Gill et al., 2016 **Country/ies where the study was carried out** Canada **Study type** Open-label Multicentre Phase 3 RCT **Aim of the study** To evaluate the benefit of 5-FU/Leucovorin With or Without Oxaliplatin for Second-Line Advanced Pancreatic Cancer in Patients	**Sample size** N= 108 patients with locally advanced/metastatic PC (mixed population) **Characteristics** M/F (n): 31/23 (G1); 30/24 (G2) Median age (range): 65(38-82) years (G1); 67 (48-78) years (G2) Clinical stage: LA: 4 (G1); 3 (G2) Metastatic: 50 (G1); 51 (G2) Primary tumour site within pancreas: n.r. **Inclusion criteria** Patients were eligible if they: had histologically or cytologically confirmed diagnosis of advanced, unresectable pancreatic cancer ECOG performance status of 0-2 Measurable disease	**Interventions** G1: Modified FOLFOX6 (infusion 5-FU, leucovorin, and oxaliplatin) as second-line chemotherapy (n=54) - mFOLFOX6 consisted of the same therapy as G2 plus an oxaliplatin dose of 85 mg/m2 given as a 2-hour IV infusion on day 1, administered every 14 days G2: Infusional 5-FU/leucovorin alone as second-line chemotherapy (n=54) - consisted of a dose of LV 400 mg/m2 administered as a 2-hour IV infusion on day 1 and FU administered as a bolus IV dose of 400 mg/m2 on day 1 followed by a 2,400 mg/m2 continuous infusion for 46 hours, administered every 14 days Patients were treated until disease progression, unacceptable toxicity, or patient request	**Details** Design: Multicentre Phase 3 RCT Randomization method: “were randomly assigned (in a 1:1 fashion) to receive … Patients were stratified according to age .. sex, ECOG …, and presence of liver metastases.” Blinding: Open-label Duration/last follow-up: assessments were done at week 6, week 12, and until disease progression	Overall response rate (CR + PR) Progression Free Survival Overall Survival Adverse Events Health Related Quality of Life	**Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool.** Random sequence generation: Low risk Allocation concealment: unclear risk Blinding of participants and personnel Assessments: High risk Blinding of outcome assessment: High risk Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: serious **Other information**

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Who Have Received Gemcitabine-Based Chemotherapy **Study dates** Data collection-patients enrolment: 2010-2012 Publication year: 2017 **Source of funding** Supported by Sanofi Canada.	a life expectancy of longer than 3 months, adequate hepatic function, adequate renal function and adequate hematologic function Patients must have received prior first-line treatment with gemcitabine and confirmed radiographic evidence of disease progression within 4 weeks prior to randomization. **Exclusion criteria** Exclusion criteria were: prior treatment with oxaliplatin or FU the presence of peripheral sensory or motor neuropathy greater than National Cancer Institute Common Toxicity Criteria (NCIC-CTC) grade 1 serious cardiacarrhythmia, diabetes, or serious active infection or other illness that would preclude study participation; and prior or current other malignancy within 5 years				

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Full citation Gourgou-Bourgade S, Bascoul-Mollevi C, Desseigne F, Ychou M, Bouché O,Guimbaud R, Bécouarn Y, Adenis A, Raoul JL, Boige V, Bérille J, Conroy T. Impact of FOLFIRINOX compared with Gemcitabine on quality of life in patients withmetastatic pancreatic cancer: results from the PRODIGE 4/ACCORD 11 randomized trial. J Clin Oncol. 2013;31(1):23-9. **Ref Id** Gourgou-Bourgade et al., 2013 **Country/ies where the study was carried out** France **Study type** Multicentre Phase 3 RCT **Aim of the study** To compare the quality of life (QoL) of patients receiving	**Sample size** N= 342 patients with metastatic PC **Characteristics** M/F (n): 106/65 (G1); 105/66 (G2) Median age (range): 61(25-76) years (G1); 71 (34-75) years (G2) Clinical stage: LA: 0 (G1); 0 (G2) Metastatic: 171 (G1); 171 (G2) Primary tumour site within pancreas: Head: 67 (G1); 63 (G2) Body: 53 (G1); 58 (G2) Tail: 45 (G1); 45 (G2) Multicentre: 6 (G1); 5 (G2) **Inclusion criteria** Patients were eligible if they: Were 18 years of age or older and had histologically and cytologically confirmed,	**Interventions** G1: oxaliplatin, irinotecan, 5-FU, and leucovorin (FOLFIRINOX) (n=171) - oxaliplatin at a dose of 85 mg/m2, given as a 2-hour intravenous infusion, immediately followed by leucovorin at a dose of 400 mg/m2, given as a 2-hour intravenous infusion, with the addition, after 30 minutes, of irinotecan at a dose of 180 mg/m2, given as a 90-minute intravenous infusion through a Y-connector - followed by 5-FU at a dose of 400 mg/m2, administered by intravenous bolus. G2: GEM single-agent (n=171) - dose of 1,000 mg/m2 over 30 minutes intravenously weekly for 7 weeks, followed by 1 week of rest, then weekly for 3 weeks every 4 weeks	**Details** Design: Multicentre Phase 3 RCT Randomization method: “Randomization was performed centrally with stratification according to center, performance status (0 *versus* 1), and primary tumor localization (the head *versus* the body or tail of the pancreas).” Blinding: double-blinded Duration/last follow-up: 10 months	Health Related Quality of Life	**Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool.** Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: Low risk Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: no serious **Other information**

Study details	Participants	Interventions	Methods	Outcomes*	Comments
oxaliplatin, irinotecan, 5-FU, and leucovorin (FOLFIRINOX) with Gemcitabine in patients with metastatic pancreatic adenocarcinoma **Study dates** Data collection-patients enrolment: 2005-2009 Publication year: 2013 **Source of funding** Supported by Clinical Research Hospital Program grants (PHRC 2004 and 2007) from the French Ministry of Health, and grants from Amgen and the French National League against Cancer	measurable metastatic pancreatic adenocarcinoma that had not previously been treated with chemotherapy Had Eastern ECOG performance status score of 0 or 1 Had adequate bone marrow, liver function, and renal function. **Exclusion criteria** Exclusion criteria were an age of 76 years or older, endocrine or acinar pancreatic carcinoma, previous radiotherapy for measurable lesions, cerebral metastases, a history of another major cancer, active infection, chronic Diarrhoea , a clinically significant history of cardiac disease, and pregnancy or breast-feeding.				
Full citation Gresham GK, Wells GA, Gill S, Cameron C, Jonker DJ. Chemotherapy regimens for advanced pancreatic cancer: a systematic review and network meta-analysis. BMC Cancer. 2014 Jun 27;14:471.	**Sample size** N= 23 RCTs involving 19 treatment regimens and 9,989 patients with both pure metastatic PC or locally advanced/metastatic PC	**Interventions** FOLFIRINOX *versus* GEM single-agent Conroy et al., 2011 (n=171 *versus* n=171) GEM + 5-FU *versus* GEM single-agent	**Details** Abou-Alfa et al., 2006 Design: Multicentre Phase 3 RCT Randomization method: unclear Blinding: unclear	***NMA*** Overall Survival^ For the results of the NMA see Appendix 5. ***Primary studies*** Response rate	**Limitations - ISPOR checklist for NMA (Jansen et al, 2014).** Relevance: Sufficient Credibility: Sufficient Analysis: low risk of bias

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Ref Id Gresham et al., 2014 **Country/ies where the study was carried out** n.a. **Study type** Network meta-analysis of 23 RCTs **Aim of the study** To assess the comparative safety and efficacy of chemotherapy regimens for the treatment of advanced pancreatic cancer **Study dates** Searches: 2002-2013 Publication year: 2014 **Source of funding** xxxxx	Patients with locally advanced/metastatic PC (19 studies) Abou-Alfa et al., 2006 n=346 Berlin et al., 2002 n=322 Bramhall et al., 2002 n=239 Cunningham et al., 2009 n=533 Gonçalves et al., 2012 n=104 Heinemann et al., 2006 n=194 Heinemann et al., 2012 n=284 Herrmann et al., 2007~ n=319 Kindler et al., 2011	Berlin et al., 2002 (n=160 *versus* n=162) GEM + 5-FU + FA *versus* GEM single-agent Riess et al., 2005 (n=235 *versus* n=238) GEM + Axitinib *versus* GEM single-agent Kindler et al., 2011 (n=180 *versus* n=315) GEM + Capecitabine *versus* GEM single-agent Cunningham et al., 2009 (n=267 *versus* n=266) Herrmann et al., 2007 (n=160 *versus* n=159) GEM + Cetuximab *versus* GEM single-agent Philip et al., 2010 (n=372 *versus* n=371) GEM + Cisplatin *versus* GEM single-agent Colucci et al., 2010 (n=201 *versus* n=199)	Study setting: USA Berlin et al., 2002 Design: Multicentre Phase 3 RCT Randomization method: unclear Blinding: unclear Study setting: USA Bramhall et al., 2002 Design: Phase 3 RCT Randomization method: ".. using a computer generated random code according to the method of minimisation" Blinding: double Study setting: UK Colucci et al., 2010 Design: Phase 3 RCT Randomization method: "Telephone	Conroy et al., 2011 Abou-Alfa et al., 2006 Berlin et al., 2002 Bramhall et al., 2002 Colucci et al., 2010 Heinemann et al., 2006 Gonçalves et al., 2012 Herrmann et al., 2007 Cunningham et al., 2009 Kindler et al., 2011 Louvet et al., 2005 Poplin et al., 2006 Moore et al., 2007	Reporting Quality & Transparency: low risk of bias Interpretration: low risk of bias Conflict of Interest: low risk of bias **Other information** *: Von Holf et al., 2013 is a RCT on nab-Paclitaxel + GEM *versus* GEM single-agent . Since this drug is part of a NICE TA evaluation, then has been excluded from pairwise analyses. Even tough, this trial has been included in the NMA as a silent comparator – because the more data points in the NMA the more accurate it is. ^: Over survival: Data were extracted from the NMA only for this outcome., as all the necessary information

Study details	Participants	Interventions	Methods	Outcomes*	Comments
	n=313 Louvet et al., 2005 n=313 Moore et al., 2007 n=569 Oettle et al., 2005 n=565 Philip et al., 2010~ n=741 Poplin et al., 2006 (2009) n=547 Reni et al., 2005 n=99 Riess et al., 2005 n=463 Rocha Lima et al., 2004 n=360 Stathopoulos et al., 2006 n=130	Heinemann et al., 2006 (n=98 *versus* n=97) PEFG *versus* GEM single-agent Reni et al., 2005 (n=54 *versus* n=50) GEM + Erlotinib *versus* GEM single-agent Moore et al., 2007 (n=284 *versus* n=285) GEM + Exatecan *versus* GEM single-agent Abou-Alfa et al., 2006 (n=175 *versus* n=174) GEM + Irinotecan *versus* GEM single-agent Rocha Lima et al., 2004 (n=180 *versus* n=180) Stathopoulos et al., 2006 (n=60 *versus* n=70) GEM + Marimastat *versus* GEM single-agent Bramhall et al., 2002 (n=120 *versus* n=119)	random assignment was performed centrally, by a computer-driven minimization procedure." Blinding: Unclear Study setting: Italy Conroy et al., 2011 Design: Multicentre Phase 3 RCT Randomization method: "Randomization was performed centrally with stratification according to center, performance status, and primary tumor localization" Blinding: unclear Study setting: France Cunningham et al., 2009 Design: Multicentre Phase 3 RCT	Oettle et al., 2005 Philip et al., 2010 Reni et al., 2005 Rocha Lima et al., 2004 Stathopoulos et al., 2006 Van-Cutsem et al., 2004 Progression Free Survival Conroy et al., 2011 Abou-Alfa et al., 2006 Berlin et al., 2002 Bramhall et al., 2002 Colucci et al., 2010 Heinemann et al., 2006	was provided in theorginal paper. ~: Conroy et al., 2011; Herrmann et al., 2007; Philip et al., 2010; and Reni et al., 2005 includes data on HRQL in papers pulished ad hoc: Gourgou-Bourgade et al., 2013; Bernhard et al., 2008; Moinpour et al., 2010; and Reni et al., 2006, respectively.

Study details	Participants	Interventions	Methods	Outcomes*	Comments
	Van-Cutsem et al., 2004 n=688 Patients with metastatic PC (4 studies) Colucci et al., 2010 n=400 Conroy et al., 2011˜ n=342 Van-Cutsem et al., 2009 n=607 Von-Hoff et al., 2013* n=871 **Inclusion criteria** Phase 3 randomized controlled trials enrolled at least 50 patients per arm Involving in patients with locally advanced/metastatic pancreatic cancer who were eligible for first-line therapy **Exclusion criteria**	GEM + Nab-Paclitaxel *versus* GEM single-agent * Von-Hoff et al., 2013 (n=431 *versus* n=430) GEM + Oxaliplatin *versus* GEM single-agent Louvet et al., 2005 (n=156 *versus* n=157) Poplin et al., 2006 (2009) (n=272 *versus* n=275) GEM + Pemetrexed *versus* GEM single-agent Oettle et al., 2005 (n=283 *versus* n=282) GEM + Sorafenib *versus* GEM single-agent Gonçalves et al., 2012 (n=52 *versus* n=52) GEM + Tipifarnib *versus* GEM single-agent Van-Cutsem et al., 2004 (n=344 *versus* n=344) GEM + Erlotinib + Bevacizumab *versus* GEM + Erlotinib	Randomization method: “Patients were randomly assigned … a computer-generated variable-size blocked randomization method. Randomization was stratified ..” Blinding: open-label Study setting: Multicentre (UK, Swityzerland, Austria) Gonçalves et al., 2012 Design: Phase 3 RCT Randomization method: “…, using a minimization procedure based on the following parameters: disease extent and ECOG performance.” Blinding: double Study setting: France	Gonçalves et al., 2012 Herrmann et al., 2007 Cunningham et al., 2009 Kindler et al., 2011 Louvet et al., 2005 Poplin et al., 2006 et al., (2009) Moore et al., 2007 Oettle et al., 2005 Philip et al., 2010 Reni et al., 2005 Riess et al., 2005 Rocha-Lima et al., 2004 Stathopoulos et al., 2006	

Study details	Participants	Interventions	Methods	Outcomes*	Comments
	Trials including over 50% of patients with LA non-metastatic disease in their treatment arms Trials involving radiation therapy Phase II trials	Van-Cutsem et al., 2009 (n=306 *versus* n=301) GEM + Erlotinib *versus* Capecitabine + Erlotinib Heinemann et al., 2012 (n=131 *versus* n=143)	Heinemann et al., 2006 Design: Multicentre Phase 3 RCT Randomization method: “Central random assignment was performed before the start of treatment…” Blinding: open-label Study setting: Germany Heinemann et al., 2012 Design: Multicentre Phase 3 RCT Randomization method: “patients were stratified according to stage and centre; randomisation was performed centrally by fax in a 1:1 ratio...” Blinding: open-label	Van-Cutsem et al., 2004 Overall Survival^ Adverse Events Conroy et al., 2011 Abou-Alfa et al., 2006 Berlin et al., 2002 Bramhall et al., 2002 Colucci et al., 2010 Heinemann et al., 2006 Gonçalves et al., 2012 Herrmann et al., 2007 Cunningham et al., 2009 Kindler et al., 2011	

Study details	Participants	Interventions	Methods	Outcomes*	Comments
			Study setting: Germany Herrmann et al., 2007 Design: Multicentre Phase 3 RCT Randomization method: unclear Blinding: unclear Study setting: Multicentre (Switzerland, Italy, Austria, Germany) Kindler et al., 2011 Design: Multicentre Phase 3 RCT Randomization method: “A centralised randomisation procedure (interactive voice randomisation system accessible via telephone or internet) …. with randomised permuted blocks within strata.”	Louvet et al., 2005 Poplin et al., 2006 et al., (2009) Moore et al., 2007 Oettle et al., 2005 Philip et al., 2010 Riess et al., 2005 Rocha-Lima et al., 2004 Stathopoulos et al., 2006 Van-Cutsem et al., 2004 Health Related Quality of Life Conroy et al., 2011~ Heinemann et al., 2006 Kindler et al., 2011	

Study details	Participants	Interventions	Methods	Outcomes*	Comments
			Blinding: double Study setting: USA Louvet et al., 2005 Design: Multicentre Phase 3 RCT Randomization method: “Patients were randomized centrally…” Blinding: unclear Study setting: Multicentre (France, Italy) Moore et al., 2007 Design: Multicentre Phase 3 RCT Randomization method: unclear Blinding: double Study setting: Canada Oettle et al., 2005 Design: Multicentre Phase 3 RCT	Moore et al., 2007 Philip et al., 2010~ Reni et al., 2005~	

Study details	Participants	Interventions	Methods	Outcomes*	Comments
			Randomization method: "…using a centralized, automated randomization procedure..." Blinding: open-label Study setting: Multicentre (Argentina, Australia, Austria, Belgium, France, Germany, Greece, Italy, The Netherlands, Peru, Portugal, Spain, Sweden, Taiwan, UK, US, Venezuela) Philip et al., 2010 Design: Multicentre Phase 3 RCT Randomization method: "…using the dynamic balancing algorithm with stratification..." Blinding: open-label Study setting: USA		

Study details	Participants	Interventions	Methods	Outcomes*	Comments
			Poplin et al., 2006 (2009) Design: Multicentre Phase 3 RCT Randomization method: “Patients were randomly assigned to treatment using a dynamic balancing algorithm that stratified ….” Blinding: unclear Study setting: USA Reni et al., 2005 Design: Phase 3 RCT Randomization method: “…by use of a computer-generated random code...” Blinding: open-label Study setting: Italy Riess et al., 2005 Design: Phase 3 RCT		

Study details	Participants	Interventions	Methods	Outcomes*	Comments
			Randomization method: not reported Blinding: unclear Study setting: Germany Rocha Lima et al., 2004 Design: Multicentre Phase 3 RCT Randomization method: “Patients were centrally randomly assigned and stratified by...” Blinding: unclear Study setting: Multicentre (New Zealand, USA) Stathopoulos et al., 2006 Design: Phase 3 RCT Randomization method: “Patients were centrally randomised by		

Study details	Participants	Interventions	Methods	Outcomes*	Comments
			computer at a one-to-one ratio” Blinding: unclear Study setting: Greece Van-Cutsem et al., 2004 Design: Multicentre Phase 3 RCT Randomization method: “through a dynamic randomization procedure with stratification on...” Blinding: double Study setting: Multicentre (Belgium, Germany, Czech Republic, Poland, the Netherlands, US) Van-Cutsem et al., 2009 Design: Multicentre Phase 3 RCT Randomization method:		

Study details	Participants	Interventions	Methods	Outcomes*	Comments
			"Randomization was performed via an interactive voice recording service..." Blinding: double Study setting: Multicentre (Australia, Austria, Belgium, Canada, China, France, Germany, Czech Republic, Italy, Peru, Poland, Singapore, Sweden, Taiwan, the Netherlands, UK) Von-Hoff et al., 2013 Design: Multicentre Phase 3 RCT Randomization method: not reported Blinding: open-label Study setting: Multicentre (Australia, Austria, Belgium, Canada, France, Germany, Czech Republic, Italy, Spain,		

Study details	Participants	Interventions	Methods	Outcomes*	Comments
			Poland, Ukraine, Russia, USA)		
Full citation Irigoyen A, Gallego J, et al. Gemcitabine-erlotinib versus gemcitabine-erlotinib-capecitabine in the first-line treatment of patients with metastatic pancreatic cancer: Efficacy and safety results of a phase IIb randomised study from the Spanish TTD Collaborative Group. Eur J Cancer. 2017;75:73-82. **Ref Id** Irigoyen et al., 2017 **Country/ies where the study was carried out** Spain **Study type** Open-label phase 2 RCT **Aim of the study** To assess whether combining capecitabine with gem + erlotinib (GE) was safe	**Sample size** N= 120 patients with metastatic PC **Characteristics** M/F (n): 34/26 (G1); 34/26 (G2) Median age (range): 62(31-77) years (G1); 64 (29-78) years (G2) Clinical stage: LA: 0 (G1); 0 (G2) Metastatic: 60 (G1); 60 (G2) Primary tumour site within pancreas: n.r. **Inclusion criteria** Patients were eligible if they: had histologically or cytologically confirmed, measurable, metastatic pancreatic adenocarcinoma were aged >18 years and with an	**Interventions** G1: GEM + capecitabine + erlotinib (n=60) – as G2 with the addition of capecitabine 830 mg/m2 orally twice daily on days 1-21 G2: GEM + erlonitib (n=60) - GEM at 1,000 mg/m2 was given intravenously over 30 minutes on days 1, 8, and 15 of a 28-day cycle with erlotinib 100 mg/day continuous oral administration	**Details** Design: Phase 2b RCT Randomization method: “patients were randomised 1:1 to either GE arm or GEC arm. Patients were stratified according to ECOG performance status (0/1 versus 2)” Blinding: open-label Duration/last follow-up: 24 months (protocol) The median followup time was 28.1 months in the GE arm and 23.5 months in the GEC arm.	Overall response rate (CR + PR) Progression Free Survival Overall Survival Adverse Events	**Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool.** Random sequence generation: Low risk Allocation concealment: unclear risk Blinding of participants and personnel Assessments: High risk Blinding of outcome assessment: High risk Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: serious **Other information**

Study details	Participants	Interventions	Methods	Outcomes*	Comments
and effective versus GE in patients with metastatic PC. **Study dates** Data collection-patients enrolment: 2011-2013 Publication year: 2017 **Source of funding** Supported by Roche Pharma, Spain.	ECOG performance status 0-2 Patients were required to have adequate bone marrow, liver and renal function and to be able to take oral medication. **Exclusion criteria** Exclusion criteria were: the history of another primary neoplasm in the 5 years before study entry clinically significant cardiovascular disease or current infection grade >2. ampullary or pancreatic endocrine tumours				
Full citation Ji Z, Wang Y, Chen X, Wu T. Peripancreatic artery ligation and artery infusion chemotherapy for advanced pancreatic carcinoma. Chin Med J (Engl). 2003 Jan;116(1):89-92. **Ref Id** Ji et al., 2003	**Sample size** N= 29 patients metastatic PC **Characteristics (Not reported by intervention group)** M/F (n): 16/12 Mean age (range): 62.4 Clinical stage: Not reported^	**Interventions** G1: Regional Intra-Arterial Chemotherapy (n=18) - patients underwent bilio-enterostomy and/or gastro-enterostomy combined with peripancreatic arterial ligation and arterial infusion regional chemotherapy.	**Details** Design: Multicentre Phase 3 RCT Randomization method: not reported Blinding: unclear Duration/last follow-up: 3 to 18 months	Overall response rate (CR + PR) Overall Survival* Adverse Events (Grade 3/4 toxicities: Nausea/vomiting)	**Limitations - Cochrane Collaboration's 'Risk of bias' tool.** Random sequence generation: Unclear risk (No details given in the text) Allocation concealment: Unclear risk (No details given in the text)

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Country/ies where the study was carried out China **Study type** Multicentre Phase 3 RCT **Aim of the study** To compare intra-arterial chemotherapy with systemic chemotherapy in patients with LA and/or metastatic adenocarcinoma of the pancreas. **Study dates** Data collection-patients enrolment: 1995-2000 Publication year: 2003 **Source of funding** Not reported	Primary tumour site within pancreas: Head: 17 (TOTAL) Head/Body: 4 (TOTAL) Body: 2 (TOTAL) Tail: 5 (TOTAL) Multicentre: 1 (TOTAL) Site of metastases: Liver: 12 (TOTAL) Lymph node: 7 (TOTAL) **Inclusion criteria** Diagnosis of PC with liver metastases confirmed by surgical exploration and pathological biopsy **Exclusion criteria** Not reported	G2: Systemic Chemotherapy (n=11) - patients underwent bilio-enterostomy and/or gastro-enterostomy combined with systemic chemotherapy after surgery			Blinding of participants and personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: High risk Incomplete outcome data: Low risk Selective reporting: Unclear risk (no study protocol to permit judgement on this criterion) Overall risk of bias: very serious **Other information** * Not analytical data on results are reported (narrative reporting) ^see inclusion criteria
Full citation Kindler HL, Niedzwiecki D, Hollis D, Sutherland S, Schrag D, Hurwitz H, Innocenti F, Mulcahy MF,	**Sample size** N= 602 patients with locally advanced/metastatic PC (mixed population)	**Interventions** G1: GEM + bevacizumab (n=302) - Bevacizumab at 10 mg/kg or placebo was administered intravenously	**Details** Design: Multicentre Phase 3 RCT	Response rate Progression Free Survival Overall Survival	**Limitations - Cochrane Collaboration's 'Risk of bias' tool.**

Study details	Participants	Interventions	Methods	Outcomes*	Comments
O'Reilly E, Wozniak TF, Picus J, Bhargava P, Mayer RJ, Schilsky RL, Goldberg RM. Gemcitabine + bevacizumab compared with Gemcitabine + placebo in patients with advanced pancreatic cancer: phase III trial of the Cancer and Leukemia Group B (CALGB 80303). J Clin Oncol. 2010;28(22):3617-22. **Ref Id** Kindler et al., 2010 **Country/ies where the study was carried out** USA **Study type** Multicentre double-blinded Phase 3 RCT **Aim of the study** To compare the effectiveness and tolerability of Gemcitabine + bevacizumab with Gemcitabine + placebo for advanced/metastatic pancreatic cancer	**Characteristics** M (%): 58 (G1); 51 (G2) Median age (range): 64(26-88) years (G1); 65 (35-86) years (G2) Clinical stage (%): LA: 16 (G1); 15 (G2) Metastatic: 84 (G1); 85 (G2) Primary tumour site within pancreas: Not reported **Inclusion criteria** histologically or cytologically confirmed unresectable pancreatic adenocarcinoma not prior chemotherapy for metastatic disease Adjuvant chemotherapy was allowed if it did not contain GEM or bevacizumab, if it was given > 4 weeks before enrollment, and if the patient had subsequent disease progression ECOG PS 0 to 2	after GEM on days 1 and 15 of each cycle. G2: GEM + placebo (n=300) - GEM at 1,000 mg/m2 was given intravenously over 30 minutes on days 1, 8, and 15 of a 28-day cycle	Randomization method: “Patients were randomly assigned 1:1.., stratified by disease extent (LA v metastatic), ECOG performance status (0/1 v 2), and prior radiation (no v yes)” Blinding: double-blinded Duration/last follow-up: until patients’ death	Adverse Events	Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: Low risk Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: no serious **Other information**

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Study dates Data collection-patients enrolment: 2004-2006 Publication year: 2010 **Source of funding** Grants No. CA31946 from the National Cancer Institute to Cancer and Leukemia Group B 80303 (CALGB 80303) trial (R.L.S.), No. CA33601 to the CALGB Statistical Center (S.G.), and No. CA41287, CA 32291, CA47577, CA21115, CA17145, CA77651, CA45418, CA77440, and CA47559.	adequate bone marrow, renal,and hepatic function An international normalized ratio (INR) ≤ 1.5 was required unless the patient was on warfarin; warfarin-treated patients needed to be on a stable dose with an INR between 2 and 3. Eligible patients were at least 18 years of age and had a life expectancy of at least 12 weeks. **Exclusion criteria** significant bleeding within 6 months before registration esophageal varices computed tomography scan documentation of invasion of adjacent organs clinically significant heart disease, or CNS disease				
Full citation Lee HS, Chung MJ, et al. A randomized, multicenter, phase III study of gemcitabine combined with capecitabine versus	**Sample size** N= 214 patients with locally advanced/metastatic PC (mixed population) **Characteristics**	**Interventions** G1: GEM + capecitabine + (n=108) - oral capecitabine 1660 mg/m^2 daily for 3 weeks followed by a 1-	**Details** Design: Multicentre Phase 3 RCT Randomization method: “..1:1 basis	Overall response rate (CR + PR) Progression Free Survival Overall Survival	**Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool.** Random sequence generation: Low risk

Study details	Participants	Interventions	Methods	Outcomes*	Comments
gemcitabine alone as first-line chemotherapy for advanced pancreatic cancer in South Korea. Medicine (Baltimore). 2017;96(1):e5702. **Ref Id** Lee et al., 2017 **Country/ies where the study was carried out** South Korea **Study type** Open-label Multicentre Phase 3 RCT **Aim of the study** To compare the efficacy and safety of GEM + capecitabine versus single-agent GEM in advanced pancreatic cancer as first-line chemotherapy. **Study dates** Data collection-patients enrolment: 2007-2011 Publication year: 2017 **Source of funding**	M/F (n): 63/45 (G1); 57/49 (G2) Median age (range): 64(37-80) years (G1); 64 (43-85) years (G2) Clinical stage: II: 6 (G1); 10 (G2) III: 23 (G1); 20 (G2) IV: 79 (G1); 76 (G2) Primary tumour site within pancreas: Head: 46 (G1); 42 (G2) Body: 21 (G1); 26 (G2) Tail: 31 (G1); 25 (G2) Multicentre: 9 (G1); 13 (G2) **Inclusion criteria** Patients were eligible if they: Were deemed inoperable locally advanced or metastatic pancreatic cancer according to the national comprehensive cancer network guidelines no prior history of chemotherapy or radiotherapy	week break plus Gem 1000 mg/m^2 by 30-minute intravenous infusion weekly for 3 weeks every 4 weeks. G2: GEM single-agent(n=106) - 30-minute intravenous infusion weekly for 3 weeks every 4 weeks.	according to a computer-generated variable-size blocked randomization method. Randomization was stratified by extent of disease (locally advanced stage vs metastatic stage).” Blinding: unclear Duration/last follow-up: unclear	Adverse Events	Allocation concealment: Low risk Blinding of participants and personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: serious **Other information**

Study details	Participants	Interventions	Methods	Outcomes*	Comments
n.r	between the ages of 18 and 85 years ECOG performance status of 0 to 2 and adequate bone marrow, hepatic, and renal function **Exclusion criteria** Exclusion criteria were: pancreatic cancer other than adenocarcinoma concurrent malignancy brain metastasis serious uncontrollable medical conditions, and significant cardiac history				
Full citation Maisey N, Chau I, Cunningham D, Norman A, Seymour M, et al. Multicenter randomized phase III trial comparing protracted venous infusion (PVI) 5-FU (5-FU) with PVI 5-FU + mitomycin in inoperable pancreatic cancer.	**Sample size** N= 209 patients with locally advanced/metastatic PC (mixed population) **Characteristics** M/F (n): 61/39 (G1); 64/36 (G2) Median age (range): 61(28-86) years (G1); 62(29-80) years (G2)	**Interventions** G1: 5-FU combination chemotherapy (n=102) - 5-FU + mitomycin : 7 mg/m2 every 6 weeks for four courses G2: 5-FU single-agent chemotherapy (n=107) - 300 mg/m2/d for a maximum of 24 weeks	**Details** Design: Phase 3 RCT Randomization method: “Patients were randomly assigned according to a computer-generated randomization code. The patients were randomized centrally	Response rate Overall Survival Adverse Events	**Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool.** Random sequence generation: Low risk Allocation concealment: Low risk

Study details	Participants	Interventions	Methods	Outcomes*	Comments
J Clin Oncol. 2002;20(14):3130-6. **Ref Id** Maisey et al., 2002 **Country/ies where the study was carried out** UK **Study type** Phase 3 RCT **Aim of the study** To compare the effectiveness and tolerability of 5-FU (5-FU) with PVI 5-FU + mitomycin (MMC) for advanced/metastatic pancreatic cancer **Study dates** Data collection-patients enrolment: 1994-2000 Publication year: 2002 **Source of funding** Not reported	Clinical stage (%): LA: 44 (G1); 36 (G2) Metastatic: 56 (G1); 64 (G2) Primary tumour site within pancreas: Not reported **Inclusion criteria** histologically confirmed LA or metastatic carcinoma of the pancreas that was not amenable to surgical resection or radical radiotherapy adequate bone marrow reserve, renal function, and hepatic function ECOG PS 0 to 2 life expectancy of more than 3 months, and no intercurrent uncontrolled medical illnesses. **Exclusion criteria** intracerebral metastases current alcohol or other drug abuse		in blocks of six and stratified by centre." Blinding: unclear Duration/last follow-up: 24 months		Blinding of participants and personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: no serious **Other information**

Study details	Participants	Interventions	Methods	Outcomes*	Comments
	history of other malignancy uncontrolled angina pectoris or clinically significant cardiac dysrhythmias any psychological condition precluding informed consent.				
Full citation Maraveyas A, Waters J, Roy R, Fyfe D, Propper D, et al. Gemcitabine *versus* Gemcitabine + dalteparin thromboprophylaxis in pancreatic cancer. Eur J Cancer. 2012 Jun;48(9):1283-92. **Ref Id** Maraveyas et al., 2012 **Country/ies where the study was carried out** UK **Study type** Phase 2b RCT **Aim of the study**	**Sample size** N= 171 patients with locally advanced/metastatic PC (mixed population) **Characteristics** M/F (%): 60/40 (G1); 57/43 (G2) Median age (range): 62 (40–79) years (G1); 66 (43–82) years (G2) Clinical stage: LA: 31 (G1); 26 (G2) Metastatic: 29 (G1); 37 (G2) Primary tumour site within pancreas: Not reported **Inclusion criteria**	**Interventions** G1: GEM + weight-adjusted dalteparin [WAD] (n=60) - Dalteparin was given in a weight-adjusted schedule at a dose of 200 IU/kg once daily subcutaneously for 4 weeks followed by a stepdown to 150 IU/kg for a further 8 weeks. G2: 1,000 mg/m2 administered intravenously	**Details** Design: Phase 2b RCT Randomization method: “Patients were randomised with software developed by York University. The block randomisation method was followed and patients were stratified for stage (LA *versus* metastatic) and performance status (KPS 90–100 *versus* 60–80).” Blinding: unclear Duration/last follow-up: 12 weeks	Overall Survival* Adverse Events Grade 3/4 toxicities (Haematological and Hepatic function impairment) Vascular thromboembolism events(VTE)	**Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool.** Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: Low risk

Study details	Participants	Interventions	Methods	Outcomes*	Comments
To compare the effectiveness and tolerability of Gemcitabine + weight-adjusted dalteparin (WAD) with Gemcitabine single-agent for advanced/metastatic pancreatic cancer **Study dates** Data collection-patients enrolment: 2003-2009 Publication year: 2012 **Source of funding** The study was sponsored by the Hull and East Yorkshire Hospitals National Health Service Trust. Pfizer provided a grant covering the cost of dalteparin.	histopathological or cytological diagnosis of non-resectable, recurrent or metastatic PC patients who didn't have thromboembolism, anticoagulation or a thromboembolic event in the 6 months before randomisation. Central venous access devices and inferior vena cava filters were not allowed KPS of 60–100 age ⩾18 years estimated life expectancy >12 weeks measurable or evaluable disease in baseline CT of thorax/abdomen/pelvis adequate haematological and renal function international normalised ratio (INR) <1.5 no obvious contraindication to anticoagulation and adequate liver function **Exclusion criteria**				Selective reporting: Unclear risk (no protocol) Overall risk of bias: serious **Other information** * reported in narrative way. Not enough analytical data reported.

Study details	Participants	Interventions	Methods	Outcomes*	Comments
	previous GEM -containing treatment comorbidities which in the opinion of the investigator would compromise informed consent or compliance history of other advanced malignancy				
Full citation Middleton G, Silcocks P, Cox T, Valle J, Wadsley J, et al. Gemcitabine and capecitabine with or without telomerase peptide vaccine GV1001 in patients with LA or metastatic pancreatic cancer (TeloVac): an open-label, randomised, phase 3 trial. Lancet Oncol. 2014;15(8):829-40. **Ref Id** Middleton et al., 2014 **Country/ies where the study was carried out** UK **Study type**	**Sample size** N= 1062 patients with locally advanced/metastatic PC (mixed population) **Characteristics** M/F (n): 209/149 (G1); 203/147 (G2); 196/158 (G3) Median age (range): 62 (55–69)years (G1); 64 (58–69) years (G2); 63 (57–69) years (G3) Clinical stage: LA: 111 (G1) ; 104 (G2); 110 (G3) Metastatic: 247 (G1) ; 246 (G2); 244 (G3) Primary tumour site within pancreas:	**Interventions** G1: chemotherapy alone (n=358) - six cycles of GEM (1000 mg/m(2), 30 min intravenous infusion, at days 1, 8, and 15) and capecitabine (830 mg/m(2) orally twice daily for 21 days, repeated every 28 days G2: chemotherapy with sequential GV1001: sequential ICT (n=350); G3: chemotherapy with concurrent GV1001: concurrent ICT (n=354). Sequential ICT included two cycles of combination chemotherapy, then an	**Details** Design: Multicentre Phase 3 RCT Randomization method: “Patients were randomised with computer-generated random permuted blocks of sizes 3 and 6 in equal proportion. Randomisation was stratifi ed on stage of disease (LA *versus* metastatic) and ECOG performance status (0, 1, and 2).” Blinding: open-label	Overall response rate (CR + PR) at 8 weeks Time to progression Overall Survival Adverse Events (Grade 3/4/5 toxicities: Nausea, vomiting, Diarrhoea, Neutropenia, Fatigue, Pain) Health Related Quality of Life at 20 weeks (EORTC QLQ-C30)	**Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool.** Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel Assessments: High risk Blinding of outcome assessment: unclear risk Incomplete outcome data: Low risk Selective reporting: Low risk

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Multicentre unblinded Phase 3 RCT **Aim of the study** To assess the efficacy and safety of sequential or simultaneous telomerase vaccination (GV1001) in combination with chemotherapy in patients with advanced/metastatic pancreatic cancer **Study dates** Data collection-patients enrolment: 2007-2011 Publication year: 2014 **Source of funding** Cancer Research UK and KAEL-GemVax.	Head: 208 (G1) ; 203 (G2); 190 (G3) Body: 55 (G1) ; 64 (G2); 64 (G3) Tail: 35 (G1) ; 31 (G2); 40 (G3) Multicentre: 60 (G1) ; 52 (G2); 60 (G3) **Inclusion criteria** treatment naive patients age > than 18 years with histologically or cytologically confirmed LA or metastatic pancreatic ductal adenocarcinoma ECOG PS of 0–2 adequate end organ function. LA or metastatic disease precluding curative surgical resection or patients who had relapsed following previously resected pancreatic cancer contrast enhanced CT scan of the thorax, abdomen pelvis within 28 days before commencing treatment	intradermal lower abdominal injection of granulocyte-macrophage colony-stimulating factor. Concurrent ICT included giving GV1001 from the start of chemotherapy with GM-CSF as an adjuvant	Duration/last follow-up: 6 months (median follow-up time)		Overall risk of bias: serious **Other information**

Study details	Participants	Interventions	Methods	Outcomes*	Comments
	measurable disease on CT and a life expectancy longer than 3 months. **Exclusion criteria** Patients if they had had radiotherapy within the last 4 weeks before start of study treatment no other pre-treatment information on radiotherapy was obtained as radiotherapy was not used in the UK for LA pancreatic cancer medical or psychiatric conditions compromising informed consent intracerebral metastases or meningeal carcinomatosis clinically significant serious disease or organ system disease not currently controlled on present therapy uncontrolled angina pectoris; pregnancy or breastfeeding previous chemotherapy for LA and metastatic disease				

Study details	Participants	Interventions	Methods	Outcomes*	Comments
	concurrent malignancies or invasive cancers diagnosed within the past 5 years apart from adequately treated basal-cell carcinoma of the skin				
Full citation Middleton G, Palmer DH, et al. Vandetanib plus gemcitabine versus placebo plus gemcitabine in locally advanced or metastatic pancreatic carcinoma (ViP): a prospective, randomised, double-blind, multicentre phase 2 trial. Lancet Oncol. 2017;18(4):486-499. **Ref Id** Middleton et al., 2017 **Country/ies where the study was carried out** **UK** **Study type** Double blind Multicentre Phase 2 RCT	**Sample size** N= 142 patients with locally advanced/metastatic PC (mixed population) **Characteristics** M/F (n): 29/43 (G1); 30/40 (G2) Median age (range): 66.5(61-73) years (G1); 67.5 (61-73) years (G2) Clinical stage: LA: 21 (G1); 20 (G2) Metastatic: 51 (G1); 50 (G2) Primary tumour site within pancreas: Head: 31 (G1); 47 (G2) Uncinate: 4 (G1); 5 (G2) Body: 24 (G1); 13 (G2)	**Interventions** G1: Vandetanib + GEM (n=72) - Vandetanib was prescribed orally once daily at 300 mg per day for the duration of the study. G2: GEM + placebo (n=70) – Placebo was prescribed throughout the study to replicate the vandetanib prescription In both groups, gemcitabine was administered at 1000 mg/m^2 weekly as a 30-min intravenous infusion for 7 continuous weeks followed by a 1-week break. After this period, gemcitabine was prescribed on a cycle of 3 continuous weeks followed by a 1-week break.	**Details** Design: Multicentre Phase 2 RCT Randomization method: “Patients were randomly assigned 1:1 to receive … according to pre-generated sequences produced on the principle of randomly permuted blocks with variable block sizes of two and four. Patients were stratified at randomisation by their disease stage (locally advanced vs metastatic) and ECOG performance status (0 or 1 vs 2).” Blinding: double blind	Overall response rate (CR + PR) Progression Free Survival Overall Survival Adverse Events	**Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool.** Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel Assessments: Low risk Blinding of outcome assessment: Low risk Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: no serious

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Aim of the study To evaluate the efficacy of vandetanib when used in combination with gemcitabine in patients with locally advanced and metastatic pancreatic cancer. **Study dates** Data collection-patients enrolment: 2011-2013 Publication year: 2017 **Source of funding** Supported by Cancer Research UK and AstraZeneca.	Tail: 13 (G1); 5 (G2) **Inclusion criteria** Patients were eligible if they were: aged 18 years or older with histologically or cytologically proven pancreatic ductal adenocarcinoma or undifferentiated carcinoma of the pancreas LA or metastatic disease precluding curative surgical resection or definitive locally directed therapies measurable disease, in accordance with the RECIST guidelines (version 1.1); ECOG performance status of 0–1, or in some cases 2 if the investigator felt that treatment with combination chemotherapy (eg, FOLFIRINOX) was not appropriate Patients who had relapsed following previously resected pancreatic cancer could also be included in the trial.		Duration/last follow-up: 12 weeks or until patients' death		**Other information**

Study details	Participants	Interventions	Methods	Outcomes*	Comments
	Exclusion criteria Exclusion criteria were: Patients who had previous chemotherapy for locally advanced and metastatic disease Patients who had radiotherapy or major surgery within the last 4 weeks preceding the start of the study treatment Concurrent malignancies or invasive cancers diagnosed within the past 5 years except for adequately treated basal-cell carcinoma of the skin, in-situ carcinoma of the uterine cervix, or resected pancreatic cancer; and chemotherapy directed at the tumour apart from that described in this protocol.				
Full citation Moinpour CM, Vaught NL, Goldman B, Redman MW, Philip PA, et al. Pain and emotional well-being outcomes in Southwest Oncology Group-directed intergroup trial S0205: a	**Sample size** N= 720 patients with locally advanced/metastatic PC (mixed population) **Characteristics** M/F (%): 55/45 (G1); 52/48 (G2)	**Interventions** G1: GEM + cetuximab (n=361) - Cetuximab was delivered intravenously at a loading dose of 400 mg/m2 (over 120 minutes) on week 1, followed by weekly maintenance	**Details** Design: Multicentre Phase 3 RCT Randomization method: “Patients were randomly assigned to one of the two treatment arms	Health Related Quality of Life Patient experience and PROMs	**Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool.** Random sequence generation: Low risk Allocation concealment: Low risk

Study details	Participants	Interventions	Methods	Outcomes*	Comments
phase III study comparing Gemcitabine + cetuximab *versus* Gemcitabine as first-line therapy in patients with advanced pancreas cancer. J Clin Oncol. 2010;28(22):3611-6. **Ref Id** Moinpour et al., 2010 **Country/ies where the study was carried out** Multicentre (Canada, USA) **Study type** Multicentre unblinded Phase 3 RCT **Aim of the study** To compare the effectiveness and tolerability of Gemcitabine + cetuximab with Gemcitabine single-agent for advanced/metastatic pancreatic cancer **Study dates** Data collection-patients enrolment: 2004-2006	Median age (range): 65(33-91) years (G1); 64 (30-87) years (G2) Clinical stage (%): LA: 22 (G1); 21 (G2) Metastatic: 78 (G1); 79 (G2) Primary tumour site within pancreas: Not reported **Inclusion criteria** histologically or cytologically confirmed adenocarcinoma of the pancreas with distant metastases or LA unresectable disease presence of either measurable or evaluable disease Zubrod performance status of 0 to 2 adequate organ function Prior radical surgery was allowed, and patients must have completed adjuvant (no GEM) therapy at least 6 months before entry onto the study **Exclusion criteria**	doses of 250 mg/m2 (over 60 minutes). Treatment with both GEM and cetuximab was continued until disease progression, unacceptable toxicity, delay of treatment by more than 4 weeks, or patient request. G2: GEM single-agent (n=359) - GEM was administered intravenously at a dose of 1,000 mg/m2 over 30 minutes. During the first 8 weeks, GEM was administered weekly for 7 weeks followed by 1 week off. In all remaining cycles, GEM was administered for 3 weeks followed by a week of rest.	using the dynamic balancing algorithm with stratification based on performance status (0 to 1 v 2), extent of disease (LA v metastatic), and prior pancreatectomy (yes v no).” Blinding: open-label Duration/last follow-up: 17 weeks (median follow-up time)		Blinding of participants and personnel Assessments: High risk Blinding of outcome assessment: High risk Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: serious **Other information**

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Publication year: 2010 **Source of funding** PublicHealth Service Cooperative Agreement Grants awarded by the National Cancer Institute, Department of Health and Human Services: CA32102, .. CA91105, CA46282 (Southwest Oncology Group); CA-25224, CA35195 (North Central Cancer Treatment Group); CA21115 (Eastern Cooperative Oncology Group); CA31946 (Cancer and Leukemia Group B [CALGB] Chairman's Grant), CA33601 (CALGB Statistical Center Grant); CA77651 (Memorial Sloan-Kettering Cancer Center Institutional Grant [CALGB]); and CA77202 (National Cancer Institute of Canada); also supported in part by ImClone Systems and Bristol-Myers Squibb.	Patients were excluded if they had: HIV-1 infection brain metastases prior systemic therapy for advanced disease therapy with EGFR-targeting agents pregnancy				
Full citation Moore MJ, Hamm J, Dancey J, Eisenberg PD, Dagenais	**Sample size**	**Interventions**	**Details** Design: Multicentre Phase 3 RCT	Overall response rate (CR + PR) at	**Limitations - Cochrane**

Study details	Participants	Interventions	Methods	Outcomes*	Comments
M, et al. Comparison of Gemcitabine *versus* the matrix metalloproteinase inhibitor BAY 12-9566 in patients with advanced or metastatic adenocarcinoma of the pancreas: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol. 2003;21(17):3296-302. **Ref Id** Moore et al., 2003 **Country/ies where the study was carried out** Canada **Study type** Multicentre Phase 3 RCT **Aim of the study** To compare the effectiveness and tolerability of BAY 12-9566 with Gemcitabine single-agent for advanced/metastatic pancreatic cancer in patients who had not previously received chemotherapy	N= 277 patients with locally advanced/metastatic PC (mixed population) **Characteristics** M/F (n): 56/82 (G1); 63/76 (G2) Median age: 65 years (G1); 66 years (G2) Clinical stage: LA: 53 (G1); 74 (G2) Metastatic: 85 (G1); 65 (G2) Primary tumour site within pancreas: Not reported Site of metastases: Ascites: 24 (G1); 17 (G2) Liver: 75 (G1); 57 (G2) Lung: 17 (G1); 12 (G2) Lymph nodes: 49 (G1); 29 (G2) Pancreas: 127 (G1); 92 (G2) Pleural effusion: 10 (G1); 4 (G2) **Inclusion criteria**	G1: BAY 12-9566 (n=138) - 800 mg orally bid continuously G2: GEM single-agent (n=139) - 1,000 mg/m2 administered intravenously	Randomization method: “Patients were stratified by prior radiation, measurable *versus* nonmeasurable disease, and ECOG performance status (0 to 1 v 2).” Blinding: unclear Duration/last follow-up: unclear	8 weeks of therapy Progression Free Survival Overall Survival Adverse Events (Grade 3/4 toxicities: Nausea, vomiting, Diarrhoea) Health Related Quality of Life at 8 weeks (EORTC QLQ-C30)	**Collaboration’s ‘Risk of bias’ tool.** Random sequence generation: Unclear risk (No details given in the text) Allocation concealment: Low risk Blinding of participants and personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: serious **Other information**

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Study dates Data collection-patients enrolment: 1997-2006 Publication year: xxx **Source of funding** Bayer Corporation, West Haven, CT.	Patients with histologically confirmed, unresectable, LA or metastatic pancreatic adenocarcinoma. Patients taking analgesia were required to have stable analgesic usage No prior chemotherapy ECOG of 2 or less **Exclusion criteria** Patients with CNS metastases, prior MMP inhibitor therapy, and prior investigational therapy within 30 days of study entry. Pregnant and breast-feeding women were also not eligible for study Patients with any active infections Patients with other malignancies, those who were unable to swallow oral medications, those who had malabsorption, or who had had a major vascular event within 3 months of study entry				

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Full citation Oettle H, Riess H, Stieler JM, Heil G, Schwaner I, et al. Second-line oxaliplatin, folinic acid, and 5-FU *versus* folinic acid and 5-FU alone for Gemcitabine -refractory pancreatic cancer: outcomes from the CONKO-003 trial. J Clin Oncol. 2014;32(23):2423-9. **Ref Id** Oettle et al., 2014 **Country/ies where the study was carried out** Germany **Study type** Multicentre unblinded Phase 3 RCT **Aim of the study** To assess the efficacy of a second-line regimen of oxaliplatin and folinic acid-modulated 5-FU in patients with advanced pancreatic cancer who have	**Sample size** N= 160 patients with locally advanced/metastatic PC (mixed population) **Characteristics** M/F (n): 48/36 (G1); 40/36 (G2) Median age (range): 61(43-78) years (G1); 62 (37-83) years (G2) Clinical stage: LA: 10 (G1); 9 (G2) Metastatic: 74 (G1); 67 (G2) Primary tumour site within pancreas: Not reported **Inclusion criteria** histologically confirmed advanced PC patients who had experienced progression during first-line GEM monotherapy age 18 years or older measurable reference cancer site(s) confirmed with computed	**Interventions** G1: FA + 5-FU as second line chemotherapy (n=84) - Second-line treatment was planned to start within 4 weeks of disease progression on first-line GEM monotherapy. FF comprised intravenous (IV) FA 200 mg/m2 followed by a continuous IV infusion of 5-FU 2,000 mg/m2 over 24 hours on days 1, 8, 15, and 22 G2: oxaliplatin + 5-FU as second line chemotherapy (n=76) - OFF comprised FF and oxaliplatin 85 mg/m2 IV administered before FF on days 8 and 22.	**Details** Design: Multicentre Phase 3 RCT Randomization method: “Patients were randomly assigned by using computer-generated random numbers at the study coordination center” Blinding: open-label Duration/last follow-up: 54.1 months (median follow-up time)	Progression Free Survival Overall Survival (Grade 3/4 toxicities: Anaemia, Nausea/emesis, Paresthesia, Pain, Leucopoenia, Thrombocytopenia, Diarrhoea)	**Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool.** Random sequence generation: Low Allocation concealment: Low risk Blinding of participants and personnel Assessments: High risk Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: no serious **Other information**

Study details	Participants	Interventions	Methods	Outcomes*	Comments
experienced progression while receiving Gemcitabine monotherapy **Study dates** Data collection-patients enrolment: 2004-2007 Publication year: 2014 **Source of funding** Helmut Oettle, Celgene, Eli Lilly	tomography or magnetic resonance imaging Karnofsky performance status of at least 70% adequate renal function, adequate hepatic function, adequate bone marrow function, **Exclusion criteria** presence of any severe concomitant disease intractable pain hypersensitivity to study drugs serious cardiovascular disease (eg, unstable coronary artery disease or myocardial infarction within 4 weeks of study start) National Cancer Institute Common Toxicity Criteria (NCI-CTC) grade 3 or 4 sensory or motor neuropathy prior or concurrent malignancy (other than pancreatic cancer if female, pregnancy or breastfeeding.				

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Full citation Oster MW, Gray R, Panasci L, Perry MC. Chemotherapy for advanced pancreatic cancer A comparison of 5-FU, adriamycin, and mitomycin (FAM) with 5-FU, streptozotocin, and mitomycin (FSM). Cancer. 1986;57(1):29-33. **Ref Id** Oster et al., 1986 **Country/ies where the study was carried out** USA **Study type** Phase 3 RCT **Aim of the study** To compare the effectiveness and tolerability of FAM (5-FU, Adriamycin [doxorubicin], mitomycin) with FSM (5-FU, streptozotocin, mitomycin) for advanced pancreatic cancer **Study dates**	**Sample size** N= 196 patients with locally advanced/metastatic PC (mixed population) **Characteristics** M/F (%): 52/48 (G1); 61/39 (G2) Age 55-65 years (%): 42 (G1);31 (G2) Clinical stage: Not reported Primary tumour site within pancreas: Not reported **Inclusion criteria** Patients with histologically confirmed adenocarcinoma of the pancreas with disease that was not considered suitable for surgery and/or radiotherapy. None no prior chemotherapy. **Exclusion criteria** See inclusion criteria	**Interventions** G1: FAM: 5-FU, Adriamycin [doxorubicin], mitomycin (n=90) - FAM was administered in 8-week cycles with 5-FU, 600 mg/M2 given intravenously on days 1, 8, 29, and 36; Adnamycin, 30 mg/M2 given intravenously on days 1 and 29; and mitomycin, 10 mg/M2 given intravenously on day 1 G2: FSM: 5-FU, streptozotocin, mitomycin (n=94) - FSM was administered in 8-week cycles with 5-FU and mitomycin as in FAM and streptozotocin 1 g/M2 intravenously on days 1,8,29, and 36	**Details** Design: Phase 3 RCT Randomization method: unclear "patients were stratified before randomization on the basis of the presence or absence of objectively measurable disease by physical examination and/or radiologic evaluation." Blinding: unclear Duration/last follow-up: unclear	Overall response rate (CR + PR) Overall Survival* Adverse Events (Grade 3/4 toxicities: Nausea/vomiting, Leucopoenia Thrombocytopenia)	**Limitations - Cochrane Collaboration's 'Risk of bias' tool.** Random sequence generation: Unclear risk (No details given in the text) Allocation concealment: Unclear risk (No details given in the text) Blinding of participants and personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: Low risk Selective reporting: Unclear risk (no study protocol to permit judgement on this criterion)

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Data collection-patients enrolment: 1979-1981 Publication year: 1986 **Source of funding** Grant Support CA 12011/CA/NCI NIH HHS/United States CA 31809/CA/NCI NIH HHS/United States CA 33601/CA/NCI NIH HHS/United States					Overall risk of bias: very serious **Other information** * Not analytical data on results are reported (narrative reporting)
Full citation Pelzer U, Opitz B, Deutschinoff G, Stauch M, Reitzig PC, Hahnfeld S, Müller L, Grunewald M, Stieler JM, Sinn M, Denecke T, Bischoff S, Oettle H, Dörken B, Riess H. Efficacy of Prophylactic Low-Molecular Weight Heparin for Ambulatory Patients With Advanced Pancreatic Cancer: Outcomes From the CONKO-004 Trial. J Clin Oncol. 2015;33(18):2028-34.	**Sample size** N= 312 patients with locally advanced/metastatic PC (mixed population) **Characteristics** M/F (n): 69/91 (G1); 58/94 (G2) Median age (range): 62(38-81) years (G1); 63 (27-83) years (G2) Clinical stage: LA: 41(G1); 34 (G2) Metastatic: 119 (G1); 118 (G2)	**Interventions** G1: Chemotherapy and prophylactic use of enoxaparin (n=160) - After 3 months of initial enoxaparin use at half the therapeutic dosage (time point of primary end point), treatment was continued with a fixed dose of 40 mg daily until disease progression. Beyond the initial 3 months of chemotherapy, all patients with no disease progression received	**Details** Design: Multicentre Phase 3 RCT Randomization method: “Patients were randomly assigned between ….at a one-to-one ratio using computer-generated random numbers generated at the study coordination centre.” Blinding: open-label	Progression Free Survival Overall Survival Adverse Events (Vascular thromboembolism events-VTE) Symptomatic VTE Major hemorrhages	**Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool.** Random sequence generation: Low Allocation concealment: Low risk Blinding of participants and personnel Assessments: High risk Blinding of outcome assessment: Unclear

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Ref Id Pelzer et al., 2015 **Country/ies where the study was carried out** Germany **Study type** Multicentre unblinded Phase 3 RCT **Aim of the study** To compare the effectiveness and tolerability of first-line chemotherapy and prophylactic use of enoxaparin with chemotherapy alone for advanced/metastatic pancreatic cancer **Study dates** Data collection-patients enrolment: 2004-2009 Publication year: 2015 **Source of funding** Helmut Oettle, Celgene, Eli Lilly	Primary tumour site within pancreas: Not reported Site of metastases: Liver: 67 (G1); 69 (G2) Liver/Lung: 12 (G1); 10 (G2) Lymph nodes: 18 (G1); 10 (G2) Peritoneum: 17 (G1); 18 (G2) Other: 35 (G1); 42 (G2) **Inclusion criteria** outpatients with histologically confirmed APC no previous radiotherapy or chemotherapy KPS ≥ 60%, measurable tumor lesion confirmed by computed tomography or magnetic resonance imaging within the last 14 days no VTEs within the last 2 years sufficient bone marrow function age ≥ 18 years	further treatment with GEM single-agent (GEM 1 g/m2 [30 minutes] on days 1, 8, and 15, once every 4 weeks G2: Chemotherapy alone (n=152) - Patients with a KPS 80% and normal kidney function received intensified GFFC therapy (GEM 1 g/m2 [30 minutes], 5-FU 750 mg/m2 [24 hours], FA 200 mg/m2 [30 minutes], and cisplatin 30 mg/m2 [90 minutes] on days 1 and 8, once every 3 weeks. Patients with initial KPS 80% and/or increased creatinine plasma level (but creatinine clearance 30 mL per minute) started GEM therapy (GEM 1 g/m2 [30 minutes] on days 1, 8, and 15, once every 4 weeks).	Duration/last follow-up: until patients' death		risk (No details given in the text) Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: serious **Other information**

Study details	Participants	Interventions	Methods	Outcomes*	Comments
	adequate compliance residence within geographic proximity to the particular department **Exclusion criteria** preexisting anticoagulation indication major hemorrhage within the last 2 weeks or severely impaired coagulation, active GI ulcers major surgery within the last 2 weeks body weight < 45 kg or > 100 kg, pregnant, lactating or insufficient contraception during study severe concomitant disease incompatible with study participation				
Full citation Rougier P, Riess H, Manges R, Karasek P, Humblet Y, et al. Randomised, placebo-controlled, double-blind, parallel-group phase III study evaluating aflibercept in patients receiving first-line	**Sample size** N= 546 patients with metastatic PC **Characteristics** M/F (n): 157/118 (G1); 160/111 (G2)	**Interventions** G2: GEM + aflibercept (n=271) G1: GEM + placebo (n=275) Patients received aflibercept 4 mg/kg or	**Details** Design: Multicentre Phase 3 RCT Randomization method: “Patients were randomly assigned between	Progression Free Survival Overall Survival Adverse Events	**Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool.** Random sequence generation: Low risk

Study details	Participants	Interventions	Methods	Outcomes*	Comments
treatment with Gemcitabine for metastatic pancreatic cancer. Eur J Cancer. 2013;49(12):2633-42. **Ref Id** Rougier et al., 2013 **Country/ies where the study was carried out** Multicentre (Belgium, France, Germany, Czech Republic, US) **Study type** Multicentre double-blinded Phase 3 RCT **Aim of the study** To compare aflibercept + Gemcitabine with Gemcitabine + placebo in patients with metastatic pancreatic adenocarcinoma **Study dates** Data collection-patients enrolment: 2007-2009 Publication year: 2013 **Source of funding**	Median age (range): 61.0 (34–86) years (G1); 62.0 (34–88) years (G2) Clinical stage: I-II: 16 (G1); 13 (G2) III: 11 (G1); 16 (G2) IV: 248 (G1); 241 (G2) unknown: 0 (G1); 1 (G2) Primary tumour site within pancreas: Entire pancreas: 72 (G1); 50 (G2) Head: 117 (G1); 132 (G2) Body: 41 (G1); 41 (G2) Tail: 45 (G1); 46 (G2) Other: 0 (G1); 2 (G2) Site of metastases: Pancreas: 248 (G1); 252 (G2) Liver: 215 (G1); 208 (G2) Lung: 68 (G1); 69 (G2) Lymph nodes: 125 (G1); 134 (G2)	placebo intravenous (i.v.) over 1 h once every 2 weeks on days 1 and 15 of every 4-week cycle, and then GEM 1000 mg/m2 i.v. over 30 min on days 1, 8, 15 and 22 of cycle 1 and then days 1	….at a one-to-one ratio using computer-generated random numbers generated at the study coordination center.” Blinding: double-blinded Duration/last follow-up: 7.9 months (median follow-up time)		Allocation concealment: Low risk Blinding of participants and personnel Assessments: Low risk Blinding of outcome assessment: Low risk Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: no serious **Other information**

Study details	Participants	Interventions	Methods	Outcomes*	Comments
This study was supported by sanofi-aventis.	Peritoneum: 64 (G1); 59 (G2) **Inclusion criteria** patients >18-year-olds with cytologically or histologically confirmed metastatic adenocarcinoma of the pancreas ECOG PS< 2 with adequate organ function no prior systemic treatment or chemotherapy for PC except for 5-FU, capecitabine or GEM as radiosensitising agents and the time between last dose. **Exclusion criteria** < 42 days from prior major surgery (28 days from other surgery) to the time of randomisation < 28 days from prior radiation therapy; prior treatment with anti-VEGF or VEGFR inhibitors a history of brain metastases, uncontrolled spinal cord compression, or carcinomatous meningitis, or new evidence of brain or leptomeningeal disease				

Study details	Participants	Interventions	Methods	Outcomes*	Comments
	previous history of neoplasm; uncontrolled severe organ or metabolic dysfunction or other severe acute or chronic medical conditions pregnancy or breast-feeding.				
Full citation Sakamoto H, Kitano M, Suetomi Y, Takeyama Y, Ohyanagi H, et al. Comparison of standard-dose and low-dose Gemcitabine regimens in pancreatic adenocarcinoma patients: a prospective randomized trial. J Gastroenterol. 2006;41(1):70-6. **Ref Id** Sakamoto et al., 2006 **Country/ies where the study was carried out** Japan **Study type** Phase 3 RCT **Aim of the study**	**Sample size** N= 21 patients with locally advanced/metastatic PC (mixed population) **Characteristics** M/F (n): 5/6 (G1); 5/5 (G2) Median age (range): 66.2(50–80) years (G1); 68 (57–84) years (G2) Clinical stage: LA: 4 (G1); 3 (G2) Metastatic: 7 (G1); 7 (G2) Primary tumour site within pancreas: Head: 8 (G1); 5 (G2) Body: 2 (G1); 3 (G2) Tail: 1 (G1); 2 (G2)	**Interventions** G1: GEM infusion at a low dose (n=11) - intravenous infusion of GEM at a dose of either 250mg/m2 over 30 minon days 1, 8, and 15 of every 4-week cycle G2: GEM infusion at a standard dose (n=10) - intravenous infusion of GEM at a dose of either 1000mg/m2 over 30 minon days 1, 8, and 15 of every 4-week cycle	**Details** Design: Phase 3 RCT Randomization method: “Patients were randomly assigned between ….using a two-envelope factorial design” Blinding: unclear Duration/last follow-up: unclear	Overall response rate (CR + PR) until DP Overall Survival* Adverse Events (Grade 3/4 toxicities: Nausea/vomiting, Diarrhoea, Fatigue, Neutropenia, Thrombocytopenia, Anaemia)	**Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool.** Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: Low risk Selective reporting: Low risk

Study details	Participants	Interventions	Methods	Outcomes*	Comments
To compare Gemcitabine infusion at a low dose with the standard-dose infusion in patients with advanced/metastatic pancreatic cancer **Study dates** Data collection-patients enrolment: 2001-2004 Publication year: 2006 **Source of funding** Japan Society for the Promotion of Science.	Multicentre: 0 (G1); 0 (G2) **Inclusion criteria** histologically or cytologically proven LA or distant metastasized adenocarcinoma of the pancreas age > 20 years ECOG-PS of 0 to 2 life expectancy > 12 weeks and continuation of therapy for more than 1 month. adequate organ function **Exclusion criteria** See inclusion criteria				Overall risk of bias: no serious **Other information** * no analytical data reported. Reported in a narrative way
Full citation Smith D, Gallagher N. A phase II/III study comparing intravenous ZD9331 with Gemcitabine in patients with pancreatic cancer. Eur J Cancer. 2003;39(10):1377-83. **Ref Id**	**Sample size** N= 55 patients with locally advanced/metastatic PC (mixed population) **Characteristics** M/F (n): 19/11 (G1); 15/10 (G2)	**Interventions** G1: ZD9331 (n=30) - ZD9331 was given as a 30-min intravenous (i.v.) infusion at a dose of 130 mg/m2, on days 1 and 8 of a 3-week cycle G2: GEM single-agent (n=25) - The first cycle of GEM comprised once-	**Details** Design: Multicentre Phase 2/3 RCT Randomization method: unclear "Patients were then randomised to receive….and were stratified by centre	Overall response rate (CR + PR) until DP Adverse Events (Grade 3/4 toxicities: Nausea, vomiting, Diarrhoea, Fatigue, Neutropenia)	**Limitations - Cochrane Collaboration's 'Risk of bias' tool.** Random sequence generation: Unclear risk (No details given in the text)

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Smith et al., 2003 **Country/ies where the study was carried out** Multicentre (France, Germany, Sweden, the Netherlands, Norway, UK) **Study type** Multicentre unblinded Phase 2/3 RCT **Aim of the study** To compare Gemcitabine with ZD9331 in patients with advanced/metastatic pancreatic cancer **Study dates** Data collection-patients enrolment: not reported Publication year: 2003 **Source of funding** Not reported	Mean age (range): 59.8 (23–75) years (G1); 60.8 (40–76) years (G2) Clinical stage: I-II: 4 (G1); 3 (G2) III: 1 (G1); 1 (G2) IV: 10 (G1); 10 (G2) unknown: 15 (G1); 13 (G2) Primary tumour site within pancreas: Not reported **Inclusion criteria** histologically- or cytologically-confirmed cancer of the exocrine pancreas with chemonaïve, measurable, LA or metastatic disease. age > 18 years Karnofsky performance status (KPS) >50 life expectancy >8 weeks **Exclusion criteria**	weekly 30-min i.v. infusions at a dose of 1.0 g/m2 for 7 weeks, followed by a week of rest. Subsequent cycles lasted 4 weeks, with treatment given on days 1, 8 and 15. The first cycle of GEM comprised once-weekly 30-min i.v. infusions at a dose of 1.0 g/m2 for 7 weeks, followed by a week of rest.	and eligibility for assessment of CBR.” Blinding: open-label Duration/last follow-up: 8 weeks after disease progression (discontinuation of treatment)		Allocation concealment: Unclear risk (No details given in the text) Blinding of participants and personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: Incomplete outcome data: Low risk Selective reporting: Low risk Overall risk of bias: very serious **Other information**

Study details	Participants	Interventions	Methods	Outcomes*	Comments
	prior treatment with radiosensitisers not fully recovered from previous surgery or radiotherapy current intestinal obstruction diagnosis of islet-cell tumour or lymphoma of the pancreas evidence of severe or uncontrolled systemic disease metastasis to the central nervous system or concomitant use of folic acid.				
Full citation Sudo K, Ishihara T, Hirata N, Ozawa F, Ohshima T, et al. Randomized controlled study of Gemcitabine + S-1 combination Chemotherapy *versus* Gemcitabine for unresectable pancreatic cancer. Cancer Chemother Pharmacol. 2014;73(2):389-96. **Ref Id** Sudo et al., 2014	**Sample size** N= 101 patients with locally advanced/metastatic PC (mixed population) **Characteristics** M/F (n): 27/24 (G1); 34/16 (G2) Median age (range): 66 (50–77) years (G1); 67 (45–73) years (G2) Clinical stage: LA: 18 (G1); 19 (G2)	**Interventions** G1: GEM + S-1 (n=51) - oral administration of S-1 at 60 mg/m2 divided in two daily doses on days 1–15 and 30-min infusion of GEM at 1,000 mg/m2 on days 8 and 15 every 3 week G2: GEM single-agent (n=50) - GEM was administered at 1,000 mg/m2 in a 30-min infusion on days 1, 8 and 15 every 4 weeks.	**Details** Design: Multicentre Phase 3 RCT Randomization method: “Randomization was done centrally via a Web-based system, and patients were stratified according to centre, PS (0 *versus* 1), and extent of disease (LA *versus* metastatic) by a minimization method.”	Response rate Progression Free Survival Overall Survival Adverse Events	**Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool.** Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel Assessments: Unclear risk (No details given in the text)

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Country/ies where the study was carried out Japan **Study type** Multicentre Phase 3 RCT **Aim of the study** To compare the effectiveness and tolerability of Gemcitabine + S-1 with Gemcitabine single-agent for advanced/metastatic pancreatic cancer **Study dates** Data collection-patients enrolment: 2007-2011 Publication year: 2014 **Source of funding** No financial support for this study was provided	Metastatic: 33 (G1); 31 (G2) Primary tumour site within pancreas: Head: 22 (G1); 18 (G2) Body-Tail: 29 (G1); 32 (G2) **Inclusion criteria** Histological or cytological confirmation of metastatic or LA adenocarcinoma 20–79 years of age ECOG PS of 0 or 1 no prior chemotherapy or radiotherapy adequate organ function **Exclusion criteria** Patients with: severe concurrent disease, interstitial pneumonia, massive abdominal or pleural effusion, mental disorder, active concomitant malignancy, severe Diarrhoea , brain metastasis, severe drug hypersensitivity, pregnant or lactating females,		Blinding: unclear Duration/last follow-up: 12 months		Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: U Low risk Selective reporting: Low risk Overall risk of bias: no serious **Other information**

Study details	Participants	Interventions	Methods	Outcomes*	Comments
	and regular use of phenytoin, warfarin or frucitocin				
Full citation Ueno H, Ioka T, Ikeda M, Ohkawa S, Yanagimoto H, et al. Randomized phase III study of Gemcitabine + S-1, S-1 alone, or Gemcitabine single-agent in patients with LA and metastatic pancreatic cancer in Japan and Taiwan: GEST study. J Clin Oncol. 2013;31(13):1640-8. **Ref Id** Ueno et al., 2013 **Country/ies where the study was carried out** Multicentre (Japan, Taiwan) **Study type** Multicentre Phase 3 RCT **Aim of the study** To compare the efficacy and toxicity of Gemcitabine + S-1 with Gemcitabine or S-1 alone in patients with	**Sample size** N= 834 patients with locally advanced/metastatic PC (mixed population) **Characteristics** M/F (n): 170/107 (G1); 170/110 (G2); 158/117 (G3) Age <65,>=65 (n): 134/143 (G1); 145/135 (G2); 137/138 (G3) Clinical stage: LA: 66 (G1); 68 (G2); 68(G3) Metastatic: 211(G1); 212(G2) ; 207(G3) Primary tumour site within pancreas: Head: 122 (G1); 110 (G2) ; 116(G3) Body: 88 (G1); 124 (G2) ; 102(G3) Tail: 68 (G1); 55 (G2) ; 66(G3) **Inclusion criteria**	**Interventions** G1: GEM single-agent (n=277) - intravenous administration of GEM at a dose of 1000 mg/m2 over 30 min on days 1, 8 and 15 of a 28-d cycle; G2: S-1 alone (n=280) - oral administration of S-1 twice daily at a dose calculated according to the body surface area (BSA) (<1.25 m2, 80 mg/d; ≥1.25 to <1.5 m2, 100 mg/d; ≥1.5 m2, 120 mg/d) on days 1 through 28 of a 42-d cycle G1: GEM + S-1 (n=275) - Patients randomised to the GS regimen received GEM at a dose of 1000 mg/m2 on days 1 and 8 + S-1 orally twice daily at a dose based on the BSA (<1.25, 60 mg/d; ≥1.25 to <1.5 m2, 80 mg/d; ≥1.5 m2, 100 mg/d) on days 1 through 14 of a 21-d cycle.	**Details** Design: Multicentre Phase 3 RCT Randomization method: “Random assignment was performed centrally with stratification by extent of disease (LA disease v metastatic disease) and institution using the minimization method” Blinding: unclear Duration/last follow-up: until patients' death	Response rate Progression Free Survival Overall Survival Adverse Events Health Related Quality of Life	**Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool.** Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: U Low risk Selective reporting: Low risk Overall risk of bias: no serious **Other information**

Study details	Participants	Interventions	Methods	Outcomes*	Comments
advanced/metastatic pancreatic cancer **Study dates** Data collection-patients enrolment: 2007-2009 Publication year: 2013 **Source of funding** Taiho Pharmaceutical and TTY Biopharm.	advanced or metastatic PC histologically or cytologically proven diagnosis of adenocarcinoma or adenosquamous carcinoma no prior chemotherapy or radiotherapy for PC, age of more than 20 years (the protocol was amended to restrict the eligible age to < 80 years after four of the first eight patients who were ≥ 80 years experienced serious adverse events) an Eastern Cooperative Oncology Group performance status score of 0 to 1 adequate organ functions **Exclusion criteria** Patients with: See inclusion criteria				
Full citation Ulrich-Pur H, Raderer M, Verena Kornek G, Schüll B, Schmid K, et al. Irinotecan + raltitrexed vs raltitrexed alone in patients with Gemcitabine -	**Sample size** N= 38 patients with metastatic PC **Characteristics** M/F (n): 8/11 (G1); 12/7 (G2)	**Interventions** G1: raltitrexed alone (n=19) G2: irinotecan + raltitrexed (n=19) - In both patients	**Details** Design: RCT Randomization method: not reported Blinding: unclear	Objective/complete response Adverse Events (Grade 3/4 toxicities: Nausea/ vomiting,	**Limitations - Cochrane Collaboration's 'Risk of bias' tool.** Random sequence generation: Low risk

Study details	Participants	Interventions	Methods	Outcomes*	Comments
pretreated advanced pancreatic adenocarcinoma. Br J Cancer. 2003;88(8):1180-4. **Ref Id** Ulrich-Pur et al., 2003 **Country/ies where the study was carried out** Austria **Study type** Multicentre Phase 3 RCT **Aim of the study** To compare the efficacy and toxicity of irinotecan + raltitrexed with raltitrexed alone in patients with advanced/metastatic pancreatic cancer **Study dates** Data collection-patients enrolment: 2000-2001 Publication year: 2003 **Source of funding** Not reported	Median age (range): 60 (40–74) years (G1); 63 (49–75) years (G2) Clinical stage: Not reported Primary tumour site within pancreas: Not reported Site of metastases: Abdominal mass: 15 (G1); 16 (G2) Liver: 14 (G1); 12 (G2) Lung: 5 (G1); 4 (G2) Spleen: 1 (G1); 2 (G2) Adrenals: 1 (G1); 1 (G2) Soft tissue: 2 (G1); 3 (G2) **Inclusion criteria** Patients with histologically confirmed metastatic PC measurable disease patients with progressive disease while receiving or within 6 months after discontinuing	groups, an identical conventional dose regimen of raltitrexed (3 mg m−2 given as a 15-min intravenous (i.v.) infusion on day 1) was used. In the intervention group, according to the described schedule-dependent synergy (Aschele et al, 1998), the thymidylate synthase inhibitor was given on day 2, 24 h after irinotecan	Duration/last follow-up: until patients' death	Diarrhoea, Neutropenia, Leukocytopenia, Thrombocytopenia, Fatigue, and stomatitis)	Allocation concealment: Low risk Blinding of participants and personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: Unclear risk (No details given in the text) Selective reporting: Low risk Overall risk of bias: serious **Other information**

Study details	Participants	Interventions	Methods	Outcomes*	Comments
	palliative GEM -based chemotherapy Karnofsky performance of at least 50% age between 19 and 75 years adequate bone marrow reserve adequate renal function and adequate hepatic function. **Exclusion criteria** presence of CNS metastases serious or uncontrolled concurrent medical illness history of other malignancies, with the exception of excised cervical or basal skin/squamous cell carcinoma				
Full citation Wang M, Shi SB, Qi JL, Tang XY, Tian J. S-1 + CIK as second-line treatment for advanced pancreatic cancer. Med Oncol. 2013;30(4):747. **Ref Id** Wang et al., 2013	**Sample size** N= 58 patients with locally advanced/metastatic PC (mixed population) **Characteristics** M/F (n): 15/13 (G1); 16/14 (G2)	**Interventions** G1: S-1 + CIK (Cytokine-induced killer cells) as second-line chemotherapy (n=28) - Lymphocytes were separated from blood samples, cultured in vitro, and then applied to the patients by CIK cell	**Details** Design: Multicentre Phase 3 RCT Randomization method: “Patients were stratified according to Karnofsky performance score	Response rate Overall Survival* Adverse Events (Grade 3/4 toxicities: Nausea/ vomiting, Diarrhoea, Neutropenia,	**Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool.** Random sequence generation: Unclear risk (No details given in the text)

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Country/ies where the study was carried out China **Study type** RCT **Aim of the study** To compare the efficacy and tolerability of S-1 + CIK (Cytokine-induced killer cells) with S-1 alone in patients with advanced/metastatic pancreatic cancer who had previously received Gemcitabine -based therapy **Study dates** Data collection-patients enrolment: 2009-2012 Publication year: 2013 **Source of funding** Not reported	Median age (range): 62(40-76) years (G1); 48 (40-65) years (G2) Clinical stage(%): LA: 7.1 (G1); 3.4 (G2) Metastatic: 92.9 (G1); 96.7 (G2) Primary tumour site within pancreas: Head: 22 (G1); 23 (G2) Body/tail: 6 (G1); 7 (G2) **Inclusion criteria** histologically or cytologically proven LA or metastatic PC 18–74 years of age ECOG PS ≤2 adequate hematological manifestation, hepatic and renal functions life expectancy of at least 12 weeks and with at least 1 measurable lesion according to modified response evaluation criteria in solid tumors (RECIST)	intravenous reinjection. Treatment cycles were repeated every 28 days. This treatment course was repeated till disease progression, unacceptable toxicity occurred, and when the patient no longer wished to continue the treatment. G2: S-1 alone as second-line chemotherapy (n=30) - S-1 was administered orally twice daily at a dose of 80 mg/m2 for 21 consecutive days, followed by 7 days of rest. The initial doses were determined according to the body surface area (BSA).	and prior response to GEM first-line chemotherapy. Patients were then assigned ….by the central office located at the University in Vienna." Blinding: unclear Duration/last follow-up: unclear	Fatigue, and stomatitis)	Allocation concealment: Unclear risk (No details given in the text) Blinding of participants and personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: Unclear risk (No details given in the text) Incomplete outcome data: low risk Selective reporting: low risk Overall risk of bias: very serious **Other information** *analytical data data not show

Study details	Participants	Interventions	Methods	Outcomes*	Comments
	Exclusion criteria patients who had not received S-1 as part of their previous regimen patients who had massive pleural effusion, ascites, active concomitant malignancy or brain metastasis women who were pregnant or lactating were excluded from the study.				
Full citation Yamaue H, Tsunoda T, Tani M, Miyazawa M, Yamao K, Mizuno N, Okusaka T, Ueno H, Boku N, Fukutomi A, Ishii H, Ohkawa S, Furukawa M, Maguchi H, Ikeda M, Togashi Y, Nishio K, Ohashi Y. Randomized phase II/III clinical trial of elpamotide for patients with advanced pancreatic cancer: PEGASUS-PC Study. Cancer Sci. 2015;106(7):883-90. doi: 10.1111/cas.12674. **Ref Id**	**Sample size** N= 159 allocated; 153 randomized patients with locally advanced/metastatic PC (mixed population) **Characteristics** M/F (n): 62/38 (G1); 31/22 (G2) Median age (range): 64(38–80) years (G1); 65(36–80) years (G2) Clinical stage: LA: 27 (G1); 14 (G2) Metastatic: 73 (G1); 39 (G2)	**Interventions** G1: GEM + elpamotide (n=105: allocated; n=100: assessed) - All patients received i.v. GEM (1000 mg/m2) on days 1, 8, and 15 as one cycle, which was repeated every 4 weeks. In the intervention group patients received a s.c. injection of emulsified elpamotide (2.0 mg/mL/body) every week G2: GEM + placebo (n=54: allocated; n=53: assessed) - patients received a placebo (1.0	**Details** Design: Multicentre Phase 3 RCT Randomization method: “Patients were randomly assigned by the dynamic allocation method considering disease extent (LA *versus* metastatic disease) and institution as allocation adjustment factors.”	Progression Free Survival Overall Survival Adverse Events	**Limitations - Cochrane Collaboration’s ‘Risk of bias’ tool.** Random sequence generation: Low risk Allocation concealment: Low risk Blinding of participants and personnel Assessments: Unclear risk (No details given in the text) Blinding of outcome assessment: Unclear

Study details	Participants	Interventions	Methods	Outcomes*	Comments
Yamaue et al., 2015 **Country/ies where the study was carried out** Japan **Study type** Multicentre double-blinded Phase 3 RCT **Aim of the study** To compare Gemcitabine + elpamotide vs Gemcitabine single-agent in patients with advanced/metastatic pancreatic cancer. **Study dates** Data collection-patients enrolment: 2009-2010 Publication year: 2015 **Source of funding** OncoTherapy Science, Inc., Fuso Pharmaceutical Industries Ltd. and Otsuka Pharmaceutical Co., Ltd.	Primary tumour site within pancreas: Not reported **Inclusion criteria** 20–80 years LA or metastatic PC that was histologically or cytologically diagnosed as adenocarcinoma or adenosquamous carcinoma no prior chemotherapy or radiotherapy for pancreatic cancer ECOG PS of 0 or 1 life expectancy longer than 3 months, adequate or acceptable function of bone marrow, liver and kidney **Exclusion criteria** Patients with: symptomatic brain metastases active bleeding, malignant ascites requiring drainage, or serious medical conditions such	mL/body) emulsion without elpamotide	Blinding: double-blinded Duration/last follow-up: follow-up at every 8 weeks from the first dosage until disease progression		risk (No details given in the text) Incomplete outcome data: U Low risk Selective reporting: Low risk Overall risk of bias: no serious **Other information**

Study details	Participants	Interventions	Methods	Outcomes*	Comments
	as uncontrolled hypertension, arrhythmia, or heart failure. serious illness or concomitant non-malignant disease that was more than grade 3 according to RECIST criteria				

(please see Forest plots and Evidence grade profiles for full detail about study's findings)

1

2

3

4

1