National Institute for Health and Care Excellence

Version 1.1

Pancreatic Cancer in adults:

diagnosis and management

NICE Guideline

Methods, evidence and recommendations

31 July 2017

Draft for Consultation

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 All NICE guidance is subject to regular review and may be updated or withdrawn.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 Introduction

Pancreatic cancer is the fifth leading cause of cancer death in the UK. On average, 23 people die each day from the disease. The UK has one of the worst survival rates in Europe, with average life expectancy on diagnosis just 4–6 months and a relative survival to 1 year of approximately 20%.

Only 3% of people survive for 5 years or longer. This figure has not improved much in over 40 years, and the more recent effects of increased surgery and use of adjuvant chemotherapy on survival outcomes is not yet established.

Because of late diagnosis only 4–10% of people with pancreatic cancer are eligible for potentially curative surgery. People who are able to have surgery to remove the tumour and be given adjuvant chemotherapy have up to a 30% chance of surviving 5 years.

The symptoms of pancreatic cancer are non-specific. One survey found that 40% of people diagnosed with pancreatic cancer in England had visited their GP 3 or more times before the diagnosis was made. Fifty per cent of people are diagnosed as an emergency in the A&E system. Even after diagnosis of pancreatic cancer there is evidence from the National Cancer Intelligence Network of wide variation in practice throughout England.

The evidence reviewed for this guideline has highlighted the lack of useful national data on pancreatic cancer in the UK. In many cancers, national datasets have contributed significantly to improving outcomes of patient management. For pancreatic cancer, there has been no comprehensive national database and therefore comparing outcomes between pancreatic centres and pancreatic specialists has not been possible. This lack of continuous audit may result in inappropriate variation in the standard of treatments between centres. The Committee is of the unanimous opinion that a national database of pancreatic cancer patients needs to be established to provide a continuous comparative audit of patient management.

2 Guideline summary

2.1 Guideline Committee membership, NGA staff and acknowledgements

Table 1: Guideline Committee Members

Name	Role
Mark Callaway	Consultant Radiologist, Department of Molecular and Clinical Cancer Medicine, Bristol Royal Infirmary, University Hospitals Bristol NHS Foundation Trust
Fiona Campbell	Consultant Gastrointestinal Pathologist, Royal Liverpool University Hospital
Margred Capel	Consultant in Palliative Medicine, George Thomas Hospice
Richard Charnley	Consultant Hepatobiliary and Pancreatic Surgeon, Freeman Hospital, Newcastle upon Tyne
Pippa Corrie	Consultant and Associate Lecturer in Medical Oncology, Cambridge University Hospitals NHS Foundation Trust and University of Cambridge
Dawn Elliot	UGI Clinical Nurse Specialist, Northumbria Healthcare Foundation Trust
Lesley Goodburn	Lay member
Anna Jewell	Lay member
Suzanne Joharchi	Lay member
Laura McGeeney	Specialist Pancreatic Dietitian, Department of Nutrition and Dietetics, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust
Somnath Mukherjee	Senior Clinical Researcher & Consultant Clinical Oncologist, CRUK/MRC Oxford Institute for Radiation Oncology, University of Oxford & Churchill Hospital
John Neoptolemos (Clinical Lead)	The Owen and Ellen Evans Chair of Surgery, University of Liverpool and The Royal Liverpool & Broadgreen University Hospital NHS Trust
Kofi Oppong	Consultant Gastroenterologist, Newcastle upon Tyne University Hospitals NHS Trust
Derek O'Reilly	Consultant Hepatobiliary and Pancreatic Surgeon, Manchester Royal Infirmary, Central Manchester NHS Foundation Trust
John Primrose (Chair)	Professor of Surgery, University of Southampton, C Level South Academic Block, Southampton General Hospital

Table 2: NGA Staff

Name	Role
Angela Bennett	Guideline Lead
Linyun Fou	Systematic Reviewer (from October 2016)
John Graham	Clinical Advisor
Elise Hasler	Information Scientist
James Hawkins	Health Economist
Fionnuala O'Brien	Project Manager (from September 2016)
Ferruccio Pelone	Systematic Reviewer
Kelly Williams	Assistant Systematic Reviewer (October 2016 – February 2017)

Acknowledgements

Additional support was received from Alex Bates (Senior Health Economist), Nathan Bromham (Senior Systematic Reviewer), Matthew Prettyjohns (Senior Health Economist) and Katie Webster (External Systematic Reviewer).

2.2 Other versions of the guideline

NICE produces a number of versions of this guideline:

- The 'short guideline' lists the recommendations, context and recommendations for research.
- NICE Pathways brings together all connected NICE guidance.

2.3 Schedule for updating the guideline

For the most up-to-date information about guideline reviews, please see the latest version of the NICE guidelines manual available from the NICE website.

3 Development of this guideline

3.1 What is a NICE Guideline?

NICE guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care through primary and secondary care to more specialised services. We base our NICE guidelines on the best available research evidence, with the aim of improving the quality of healthcare. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific review questions.

NICE guidelines can:

- Provide recommendations for the treatment and care of people by healthcare professionals.
- Be used to develop standards to assess the clinical practice of individual healthcare professionals.
- Be used in the education and training of healthcare professionals.
- Help patients to make informed decisions.
- Improve communication between patients and healthcare professionals.

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

We produce our guidelines using the following steps:

- The guideline topic is referred to NICE from the Department of Health.
- Stakeholders register an interest in the guideline and are consulted throughout the development process.
- The scope is prepared by the NGA.
- The NGA establishes a committee.
- A draft guideline is produced after the committee members assess the available evidence and makes recommendations.
- There is a consultation on the draft guideline.
- The final guideline is produced.

The NGA and NICE produce a number of versions of this guideline.

- The ‘full guideline’ contains all the recommendations, together with details of the methods used and the underpinning evidence.
- The ‘short guideline’ lists the recommendations, context and recommendations for research.
- NICE Pathways brings together all connected NICE guidance.

3.2 Remit

NICE received the remit for this guideline from the Department of Health. It commissioned the NGA to produce the guideline and has supported the development of this guideline.

The remit for this guideline is to develop a NICE guideline on the diagnosis and management of pancreatic cancer in adults.

3.3 Who developed this guideline?

A multidisciplinary committee comprising healthcare professionals and researchers as well as lay members developed this guideline (see the list of group members and acknowledgements).

The committee was convened by the NGA and chaired by Professor John Primrose.

The group met approximately every 6 weeks during the development of the guideline. At the start of the guideline development process all group members declared interests including consultancies, fee-paid work, shareholdings, fellowships and support from the healthcare industry. At all subsequent group meetings, members declared arising conflicts of interest.

Members were either required to withdraw completely or for part of the discussion if their declared interest presented a conflict and it was considered appropriate to do so. The details of declared interests and the actions taken are shown in the Committee Member List in accordance with the NICE conflict of interest policy.

Staff from the NGA provided methodological support and guidance for the development process. The team working on the guideline included a guideline lead, a project manager, systematic reviewers, health economists, and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate and drafted the guideline in collaboration with the group.

3.4 What this guideline covers

3.4.1 Groups that will be covered

The guideline covers the following groups.

- Adults (18 and over) referred to secondary care with suspected pancreatic cancer
- Adults (18 and over) with newly diagnosed or recurrent pancreatic ductal adenocarcinoma.

3.4.2 Key clinical areas that will be covered

The following clinical areas will be covered in this guideline:

- Information and support needs for people with pancreatic cancer and their families and carers
- Referring people to specialist teams
- Diagnosing suspected pancreatic cancer
- Staging pancreatic cancer
- Managing pancreatic cancer
- Follow-up of people with pancreatic cancer.

Note that guideline recommendations will normally fall within licensed indications. Exceptionally, and only if clearly supported by evidence, the use outside a licensed indication may be recommended. This guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

For further details please refer to the scope in Appendix A and review questions in Appendix C.

3.5 What this guideline does not cover

3.5.1 Clinical areas that will not be covered

This guideline does not cover:

- Identifying people in primary care with suspected pancreatic cancer and referring them to secondary care.

3.6 Relationship between the guideline and other NICE guidance

3.6.1 Related NICE guidance

- Care of dying adults in the last days of life NICE Guideline NG31.
- Improving supportive and palliative care in adults (update) NICE guideline. Publication expected January 2018.
- Pancreatic cancer (metastatic, untreated) – liposomal cisplatin (with gemcitabine) NICE technology appraisal. Publication date to be confirmed
- Pancreatic cancer (metastatic) - nimotuzumab (1st line) NICE technology appraisal. Publication date to be confirmed

4 Guideline development methodology

This chapter describes the methods used to review the evidence and generate the recommendations presented in subsequent chapters. This guidance was developed in accordance with the methods outlined in the NICE guidelines manual 2014 (PMG 20).

Declarations of interest were recorded according to the 2014 NICE conflicts of interest policy.

4.1 Developing the review questions and outcomes

The review questions were drafted by the NGA, and refined and validated by the committee. The questions were based on the key areas identified in the guideline scope (See Appendix A).

A total of 17 questions were identified (See Table 3).

The review questions were based on the following frameworks:

- intervention reviews – using population, intervention, comparator and outcome (PICO framework)
- reviews of diagnostic test accuracy – using population, diagnostic test (index tests), reference standard and target condition
- qualitative reviews – using population, area of interest and themes of interest

These frameworks guided the literature searching process, critical appraisal and synthesis of evidence and facilitated the development of recommendations by the committee.

Full literature searches, critical appraisals and evidence reviews were completed for all review questions.

Table 3: Description of review questions

Chapter or section number	Type of review	Review questions	Outcomes
8.1	• Qualitative Evidence • Mixed Methods (including quantitative and qualitative analysis) • Audits (patient experience survey)	What are the specific psychological support needs (including information) of adults with newly diagnosed or recurrent pancreatic cancer and their families or carers (as appropriate) throughout the care pathway?	• Health Related Quality of Life • Patient satisfaction • Patient/family/carer understanding of disease impact • Patient reported outcomes • Patient experience
6	Interventional	Does referral of all people with suspected pancreatic cancer to a specialist MDT for review improve patient management and outcomes?	• Survival Outcomes • Proportion receiving chemotherapy • Entry into clinical trials • Resection rates • Post-operative mortality • Patient Satisfaction • Quality of Life

Chapter or section number	Type of review	Review questions	Outcomes
5.1	Diagnostic	What is the most effective diagnostic pathway (imaging +/-CA 19–9, biopsy (cytology or histology)) for adults with suspected pancreatic cancer in secondary care who have jaundice?	Diagnostic Accuracy including: ○ Sensitivity ○ Specificity ○ Positive Predictive Value ○ Negative Predictive Value ○ Adverse events
5.2	Diagnostic	What is the most effective diagnostic pathway (imaging +/- CA 19–9, biopsy (cytology or histology)) for adults with suspected pancreatic cancer in secondary care who do not have jaundice but have a pancreatic abnormality on imaging?	Diagnostic Accuracy including: ○ Sensitivity ○ Specificity ○ Positive Predictive Value ○ Negative Predictive Value ○ Adverse events
5.3	Diagnostic	In adults with a pancreatic cyst, what is the diagnostic pathway to identify the cyst(s) at high risk of pancreatic malignancy?	Diagnostic Accuracy including: ○ Sensitivity ○ Specificity ○ Positive Predictive Value ○ Negative Predictive Value ○ Adverse events
5.4	Diagnostic	What is the most effective monitoring protocol for adults with an inherited high risk of pancreatic cancer in secondary care to ensure early diagnosis?	• Early diagnosis • Survival • Diagnostic Accuracy including: ○ Sensitivity ○ Specificity ○ Positive Predictive Value ○ Negative Predictive Value • Adverse events of interventions • HRQoL
7	Diagnostic	What is the most effective investigative pathway for staging adults with newly diagnosed pancreatic cancer or a non-definitive diagnostic result as resectable, borderline resectable, locally advanced and metastatic disease?	• Diagnostic test accuracy data (diagnostic accuracy, sensitivity, specificity, positive predictive value, negative predictive value) for the following outcomes: • Precise Staging • N Staging • M Staging • Resectability • Vascular invasion • Adverse events
10.2	Interventional	What is the most effective surgery (type and extent) for adults with resectable and borderline resectable pancreatic cancer?	• Local Recurrence • Distant Recurrence • Overall Survival • Post-operative death (30 day/90 day) • Treatment related morbidity • Treatment related mortality • Lymph node harvest

Chapter or section number	Type of review	Review questions	Outcomes
			• Health Related Quality of Life • Patient experience • PROMS
10.1	Interventional	Is neoadjuvant therapy for adults with resectable and borderline resectable pancreatic adenocarcinoma an effective treatment?	• Response to neoadjuvant treatment pre- surgery • Disease-free interval • Relapse-free survival • Overall Survival • Resection rate • Time from initiating treatment to Surgery • Adverse Events • Health Related Quality of Life • Patient experience • PROMS
10.3	Interventional	What is the most effective adjuvant therapy (chemotherapy, chemoradiotherapy, biological therapy, immunotherapy, combinations of therapies) for adults who have undergone surgical resection of pancreatic adenocarcinoma?	• Disease-free interval • Relapse-free survival • Overall Survival • Adverse Events • Health Related Quality of Life • Patient experience • PROMS
11.2	Interventional	What is the most effective treatment (chemotherapy, chemoradiotherapy, radiotherapy, combinations of chemotherapy and chemoradiotherapy, biological therapies, immunotherapy or other local therapies) for adults with newly diagnosed or recurrent unresectable locally advanced non-metastatic pancreatic cancer?	• Objective Response (CR/PR/PD/SD/) • Resection rate • Progression Free Survival (local, distant) • Overall Survival • Adverse Events • Health Related Quality of Life • pain control • Patient experience • PROMS
8.2	Interventional	What is the role of interventional techniques (including sympathectomy or neurolytic techniques) in the management of pain in adults with newly diagnosed or recurrent pancreatic ductal adenocarcinoma?	• Reduction in opioid medication • Pain Relief/ improved analgesia (pain scores) • Duration of effect/ duration of relief • Adverse Events (Diarrhoea, reduction in Opioid induced side effects) • Health Related Quality of Life (functional domains) • Patient experience • PROMS • Overall survival
11.1	Interventional	What are the most effective interventions (excluding	• Response rate • Progression Free Survival

Chapter or section number	Type of review	Review questions	Outcomes
		relevant NICE TAs) for adults with newly diagnosed or recurrent metastatic pancreatic cancer (chemotherapy, surgery, radiotherapy)?	• Overall Survival • Adverse Events • Health Related Quality of Life • Patient experience and PROMs • Symptom control
9.2	Interventional	What is the optimal treatment of adults with newly diagnosed or recurrent resectable pancreatic cancer, borderline resectable pancreatic cancer and unresectable/metastatic pancreatic cancer who have duodenal obstruction?	• Relief of obstruction • Change in symptoms • Nutritional status • Adverse events • Overall Survival • Health Related Quality of Life • Patient experience • PROMS
9.1	Interventional	What is the optimal treatment of biliary obstruction in adults with newly diagnosed or recurrent pancreatic cancer?	• Relief of obstruction • Relief of symptoms • Treatment-related mortality • Treatment related morbidity • Treatment-related complications • Overall Survival • Time to definitive treatment • Health Related Quality of Life • Patient experience • PROMS
8.3	Interventional	What nutritional interventions (e.g. pancreatic enzyme replacement therapy, oral nutritional supplements, dietary manipulation, omega 3 fatty acids) are effective for patients with newly diagnosed or recurrent pancreatic cancer?	• Overall Survival • Treatment related morbidity • Health Related Quality of Life • Symptom control • Nutritional status (weight, BMI, lean body mass, strength test/ muscle function, sarcopenia, percentage weight change) • Adverse events • Patient experience • recurrence • tolerance to treatment (as in chemo/ surgery) • Ability to carry out normal activities?
10.4	Interventional	What is the optimal follow-up protocol for people with resected pancreatic adenocarcinoma?	• Survival • Time to detection of recurrence • Proportion of asymptomatic recurrence (imaging) • Fitness for further intervention • HRQL • Adverse events • Risk of increased radiation (following repeated imaging)

Chapter or section number	Type of review	Review questions	Outcomes
			• PROMS • Patient acceptability / patient choice?

4.2 Searching for evidence

Systematic literature searches were undertaken to identify all published clinical evidence relevant to the review questions.

Databases were searched using relevant medical subject headings, free-text terms and study type filters where appropriate. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to retrieve only articles published in English. All searches were conducted in MEDLINE, Embase and The Cochrane Library, with some additional database searching in AMED, PsycINFO and Web of Science Core Collection for certain topic areas. The following searches were updated in April 2017.

- Diagnosing suspected pancreatic cancer
- Staging pancreatic cancer
- Managing pancreatic cancer
- Follow-up of people with pancreatic cancer.

The following searches were run in June 2016 and October 2016 respectively

- Information and support needs of pancreatic cancer patients
- Referral of pancreatic cancer patients to a specialist MDT

The decision not to re-run these two topics was based on the limited evidence identified for these two topics and the likelihood that there wouldn't be evidence identified in a re-run. The committee were asked to keep abreast of the literature in these areas.

We prioritised the list below for re-runs based on the following criteria:

- Topics with significant evidence movement where it is likely that new evidence will have been published
- Topics where HE modelling work had been conducted

Any studies added to the databases after the search dates (even those published prior to the search dates) were not included unless specifically stated in the text.

Search strategies were quality assured by cross-checking reference lists of highly relevant papers, analysing search strategies in other systematic reviews and asking the group members to highlight any additional studies. The questions, the study types applied, the databases searched and the years covered can be found in Appendix D.

The titles and abstracts of records retrieved by the searches were inspected for relevance, with potentially significant publications obtained in full text. These were assessed against the inclusion criteria.

During the scoping stage, a search was conducted for guidelines and reports on websites of organisations relevant to the topic. Searching for grey literature or unpublished literature was not undertaken. Searches for electronic, ahead-of-print publications were not routinely undertaken unless indicated by the committee. All references suggested by stakeholders at the scoping consultation were initially considered.

4.2.1 Health economic literature search

A global search of economic evidence relating to pancreatic cancer was undertaken in August 2015 and re-ran in April 2017. The following databases were searched:

- MEDLINE (Ovid);
- EMBASE (Ovid);
- HTA database (HTA);
- NHS Economic Evaluations Database (NHS EED).

Further to the database searches, the committee was contacted with a request for details of relevant published and unpublished studies of which they may have knowledge; reference lists of key identified studies were also reviewed for any potentially relevant studies. Finally, the NICE website was searched for any recently published guidance relating to pancreatic cancer that had not been already identified via the database searches.

The search strategy for existing economic evaluations combined terms capturing the target condition (pancreatic cancer) and, for searches undertaken in MEDLINE and EMBASE, terms to capture economic evaluations. No restrictions on language or setting were applied to any of the searches, but a standard exclusions filter was applied (letters, animals, etc.). Conference abstracts were considered for inclusion from 1st January 2014, as high-quality studies reported in abstract form before 2014 were expected to have been published in a peer-reviewed journal. Full details of the search strategies are presented in Appendix D.

The titles and abstracts of papers identified through the searches were independently assessed for inclusion using pre-defined eligibility criteria defined in Table 4.

Table 4: Inclusion and exclusion criteria for the systematic reviews of economic evaluations

Inclusion criteria
Economic evaluations that compare costs and health consequences of interventions (i.e. true cost-effectiveness analyses)
Population, interventions, comparators and outcomes match those specified in the PICO
Quality of life based outcomes were used as the measure of effectiveness in at least one of the analyses presented
Incremental results reported or enough information for incremental results to be derived
Conducted from the perspective of a healthcare system in an OECD country
Exclusion criteria
abstracts with insufficient methodological details for quality assessment
Non-English language papers

Once the screening of titles and abstracts was complete, full versions of the selected papers were acquired for assessment.

The quality of evidence was assessed using the economic evaluations checklist as specified in the NICE guidelines manual. Quality assessments of included studies and data extraction tables are provided in Appendix J.

4.3 Reviewing and synthesising research evidence

4.3.1 Systematic review process

The evidence was reviewed following these steps (See Figure 1):

- Potentially relevant studies were identified for each review question from the relevant search results by reviewing titles and abstracts. Full papers were then obtained.

- Full papers were reviewed against pre-specified inclusion and exclusion criteria in the review protocols (in Appendix C).
- Key information was extracted on the study's methods, according to the factors specified in the protocols and results. These were presented in summary tables (in each review chapter) and evidence tables (in Appendix G)
- Relevant studies were critically appraised using the appropriate checklist as specified in the NICE guidelines manual (NICE 2014).
- Summaries of evidence were generated by outcome or study where appropriate (included in the relevant review chapters) and were presented in committee meetings (details of how the evidence was appraised is described in Section 4.3.5 below):
  - Randomised studies: meta-analysis was carried out where appropriate and results were reported in GRADE profiles (for intervention reviews).
  - Observational studies: data were presented individually by study in GRADE profiles.
  - Diagnostic studies: data were presented individually by study as measures of diagnostic test accuracy (sensitivity and specificity, positive and negative likelihood ratios) and were presented in modified GRADE profiles.
  - Qualitative studies: each study was summarised by theme and meta-synthesis was carried out where appropriate to identify an overarching framework of themes and subthemes. An adapted Critical Appraisal Skills Programme Qualitative checklist (Public Health Resource Unit England 2006) was used to present quality evaluations of each study

For quality assurance of study identification, either whole study selections or a sample of the study selection results were double checked by a second reviewer. Searches related to the NMA were also double sifted.

A sample of all evidence tables, including a sample of evidence tables related to the NMA were checked by a second reviewer. All drafts of reviews were checked by a second reviewer. Any discrepancies were resolved by discussion between the 2 reviewers.

Figure 1: Step-by-step review of evidence in the guideline

4.3.2 Inclusion/exclusion criteria

The inclusion and exclusion of studies was based on the review protocols, which can be found in Appendix C. Excluded studies by review question (with the reasons for their exclusion) are listed in appendix G. In addition, the committee was consulted about any uncertainty regarding inclusion or exclusion.

4.3.3 Type of studies

Systematic reviews (SRs) with meta-analyses were considered the highest quality evidence to be selected for inclusion.

For most intervention reviews in this guideline, parallel randomised controlled trials (RCTs) were prioritised because they are considered the most robust type of study design that could produce an unbiased estimate of the intervention effects. Crossover RCTs were appropriate for some of the interventional questions. If there was limited evidence from RCTs, observational studies were included.

For diagnostic reviews, cross-sectional, retrospective or prospective observational studies were considered for inclusion. Where evidence was limited, case-control studies were also considered for inclusion.

For qualitative reviews, studies using focus groups, or structured or semi-structured interviews were considered for inclusion. Survey data or other types of questionnaires were only included if they provided analysis from open-ended questions, but not if they reported descriptive quantitative data only.

Literature reviews, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded. Conference abstracts were only considered for inclusion in the absence of full published studies.

4.3.3.1 Data synthesis for intervention studies

Pairwise meta-analysis

Meta-analysis was conducted whenever it could be robustly performed, to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software.

The generic inverse variance option in RevMan5 was used where any studies reporting solely the summary treatment effect and 95% confidence interval (95% CI) or standard error could be included.

Fixed-effect (Mantel–Haenszel) techniques were used in the first instance to calculate risk ratios (relative risk) for binary outcomes, such as rate of adverse events or rate of people with symptom improvements (Mantel & Haenszel 1959).

For continuous outcomes, measures of central tendency (mean) and variation (standard deviation) are required for meta-analysis. However, in cases where standard deviations were not reported per intervention group, the standard error (SE) for the mean difference was calculated from other reported statistics (p-values or 95% CIs): meta-analysis was then undertaken for the mean difference and SE using the generic inverse variance method in RevMan5

When the only evidence was based on studies summarising results by presenting medians (and interquartile ranges) or only p values were given, this information was assessed in terms of the study's sample size and was included in the GRADE tables without calculating the relative or absolute effects. Consequently, aspects of quality assessment, such as imprecision of effect, could not be assessed for evidence of this type. However, the limited reporting of this outcome was classified as a risk of bias in study limitations.

Stratified analyses were predefined for some review questions at the protocol stage when the committee identified that these strata are different in terms of biological and clinical characteristics and the interventions were expected to have a different effect.

Statistical heterogeneity was assessed by visually examining the forest plots (please see Appendix H) and by considering the chi-squared test for significance at $p<0.1$ or an I-squared inconsistency statistic (with an I-squared value of more than 50% indicating considerable heterogeneity). Where considerable heterogeneity was present, predefined subgroup analyses were performed.

Assessments of potential differences in effect between subgroups were based on the chi-squared tests for heterogeneity statistics between subgroups. If no sensitivity analysis was found to completely resolve statistical heterogeneity, then a random-effects (DerSimonian and Laird) model was employed to provide a more conservative estimate of the effect – (DerSimonian & Laird 1986).

Where data from observational studies were included, the committee decided that the results for each outcome should be presented separately for each study and meta-analysis was not conducted.

Network Meta-Analysis (NMA)

In some circumstances, the results of conventional pairwise meta-analyses of direct evidence does not help assess which intervention is most effective. The challenge of interpretation may arise for two main reasons:

- Relative treatment efficacies based on separate individual pairwise comparisons across multiple treatments are difficult to assess.
- Direct RCT comparison between treatments of clinical interest are not available in published literature.

To overcome these issues, NMA can be performed. The advantages of performing this type of analysis are:

- It allows the synthesis of data from direct and indirect comparisons without breaking randomisation, to produce measures of treatment effect and ranking of different interventions. If treatment A has never been compared against treatment B head to head, but these two interventions have been compared to a common comparator, then an indirect treatment comparison can use the relative effects of the two treatments versus the common comparator. This is also the case whenever there is a path linking two treatments through a set of common comparators. All the randomised evidence is considered within the same model.
- For every intervention in a connected network, a relative effect estimate (with its 95% credible intervals (95% CrI) can be estimated versus any other intervention. These estimates provide a useful clinical summary of the results and facilitate the formation of recommendations based on all of the best available evidence, whilst appropriately accounting for uncertainty. Furthermore, these estimates will be used to parameterise treatment effectiveness in the de novo cost-effectiveness modelling.

There are 3 key assumptions behind an NMA: similarity, transitivity and consistency.

Consistency is the assumption that the direct estimates are equal to the indirect estimates (i.e. that the relative effect of A versus C is equal to the relative effect of A versus B minus B versus C).

Similarity across trials is the critical rationale for the consistency assumption to be valid as, by ensuring the clinical characteristics of the trials are similar, we ensure consistency in the data analysis.

More specifically, randomisation holds only within individual trials, not across the trials. Therefore, if the trials differ in terms of patient characteristics, measurement and/or definition of outcome, length of follow-up across the direct comparisons, the similarity assumption is violated and this can bias the analysis.

Transitivity is the assumption that an intervention (A) will have the same efficacy in a study comparing A versus B as it will in a study comparing A versus C. Another way of looking at it, in terms of the study participants, is that we assume that it is equally likely that any patient in the network could have been given any of the treatments in the network and would have responded to the treatments in the same way (depending on how efficacious the treatments are). This assumption is closely related to similarity in that if participants in a study comparing A versus B are not the same as those in a study comparing A versus C.

As it is the case for ordinary pairwise meta-analysis, NMA may be conducted using either fixed or random effects models. A fixed effects model typically assumes that there is no variation in relative effects across trials for a particular pairwise comparison and any observed differences are solely due to chance. For a random effects model, it is assumed that the relative effects are different in each trial but that they are from a single common distribution. The variance reflecting heterogeneity is often assumed to be constant across trials.

In a Bayesian analysis, for each parameter the evidence distribution is weighted by a distribution of prior beliefs. Markov Chain Monte Carlo (MCMC) algorithm was used to generate a sequence of samples from a joint posterior distribution of 2 or more random variables and is particularly well adapted to sampling the treatment effects (known as posterior distribution) of a Bayesian network. A non-informative prior distribution was used to maximise the weighting given to the data and to generate the posterior distribution for each log odds ratio (OR), log rate ratio or mean difference (MD) of interest in the networks. We used the median of the distribution as our point estimate and the centiles provided the 95% Credible Intervals (CrI).Non-informative priors were used which were normally distributed with a mean of 0 and standard deviation of 100.

For the analyses, a series of 50,000 burn-in simulations were run to allow the posterior distributions to convergence and then a further 100,000 simulations were run to produce the outputs. Convergence was assessed by examining the history, autocorrelation and Brooks-Gelman-Rubin plots.

Goodness-of-fit of the model was also estimated by using the posterior mean of the sum of the deviance contributions for each item by calculating the residual deviance and deviance information criteria (DIC). If the residual deviance was close to the number of unconstrained data points (the number of trial arms in the analysis) then the model was explaining the data at a satisfactory level. The choice of a fixed or random effects model can be made by comparing their goodness-of-fit to the data.

Incoherence in NMA between direct and indirect evidence can be assessed in closed treatment loops within the network. These closed treatment loops are regions within a network where direct evidence is available on at least 3 different treatments that form a closed “circuit” of treatment comparisons (for example A versus B, B versus C, C versus A). If closed treatment loops existed then discrepancies between direct and indirect evidence was assessed for each loop using node-splitting (van Valkenhoef 2016).

The outputs of the NMA were:

- Treatment specific log HRs, log odd ratios, and MDs with their 95% CrI were generated for every possible pairs of comparisons by combining direct and indirect evidence in each network.
- The ranking of treatments (presented as median rank and its 95% CrI).

One of the main advantages of the Bayesian approach is that the method leads to a decision framework that supports decision making. The Bayesian approach also allows the probability that each intervention is best for achieving a particular outcome, as well as its ranking, to be calculated.

We adapted a model templates for continuous and dichotomous data available from NICE Decision Support UNIT (DSU) technical support document number 2. This model accounts for the within-study correlation between treatment effects induced by multi-arm trials.

NMA was considered particularly important for the review question where it was used because it allows use of indirect evidence to make comparisons between treatments that have not been compared in head-to-head RCTs. NMA allows us to estimate relative effects between all active treatments regardless of whether they had been compared directly in RCTs or not. NMA also allows all treatments to be compared to a single comparator, which is useful for health economic analysis that takes a fully incremental approach to determine the most cost-effective treatment out of all treatments under consideration. The primary motivation behind NMA for the chosen review question was that health economic analysis was prioritised for this review question.

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4.3.3.2 Data synthesis for diagnostic test accuracy and staging reviews

4.3.3.2.1 Data and outcomes

There are a number of diagnostic test accuracy measures. Sensitivity, specificity, positive and negative predictive values were used as outcomes for diagnostic reviews in this guideline. These diagnostic accuracy parameters (with 95% CI) were obtained from the studies or calculated by the technical team using data from the studies.

Sensitivity and specificity are measures of the ability of a test to correctly classify a person as having a condition or not having a condition. When Sensitivity is high, a negative test result rules out the target condition; when Specificity is high, a positive test result rules in the target condition. An ideal test would be both highly sensitive and highly specific, but this is frequently not possible and typically there is a trade-off in accuracy between the two.

The following definitions were used when summarising the levels of sensitivity or specificity for the committee:

- High: 90% and above
- Moderate: 75% to 89%
- Low: 74% or below

Predictive values are measures of the proportion of true cases relative to the total number of diagnosed cases: a positive predictive value is the probability that the target condition is present given a positive test result, whilst a negative predictive value is the probability that the target condition is not present given a negative test result.

Since predictive values are dependent on the prevalence of the target condition in the sample used, likelihood ratios were calculated from the sensitivity and specificity of the relevant studies (or the pooled sensitivity and specificity if a meta-analysis was possible) and used when presenting the evidence to the committee. Positive and negative likelihood ratios are measures of the association between a test result and the target condition. A positive likelihood ratio greater than one indicates how much more likely a person with the target condition is to have a positive test compared to a person without the target condition; a negative likelihood ratio less than one indicates how much less likely a person with the target condition is to have a negative test compared to a person without the target condition.

The following definitions were used when summarising the likelihood ratios for the committee:

- Very useful test: LR+ higher than 10; LR- lower than 0.1
- Moderately useful test: LR+ 5 to 10; LR- 0.1 to 0.2
- Not a useful test: LR+ lower than 5; LR- higher than 0.2

Table 5: '2 x 2' table for calculation of diagnostic accuracy parameters

	Reference standard positive	Reference standard negative	Total
Index test result positive	True positive (TP)	False positive (FP)	TP+FP (Total number of subjects with positive result in screening tool)
Index test result negative	False negative (FN)	True negative (TN)	FN+TN (Total number of subjects with negative results in screening tool)

	Reference standard positive	Reference standard negative	Total
Total	TP+FN (Total number of subjects with diagnosis)	FP+TN (Total number of subjects without diagnosis)	TP+FP+FN+Tn=N (Total number of subjects in study)
Note: *Sensitivity=TP/(TP+FN)* *Specificity=TN/(TN+FP)* *Positive predictive value=TP/(TP+FP)* *Negative predictive value=TN/(FN+TN)* *Positive likelihood ratio=sensitivity/(1-specificity)* *Negative likelihood ratio=(1-sensitivity)/specificity*			

4.3.3.2.2 Diagnostic meta-analysis

When data from 4 or more studies were available, a diagnostic meta-analysis was carried out. To show the differences between study results, pairs of sensitivity and specificity were plotted for each study on one receiver operating characteristics (ROC) curve in RevMan5 (for plots please see Appendix H. Study results were pooled using the bivariate method for the direct estimation of summary sensitivity and specificity using a random effects approach (in STATA® or R® software). Using the output from Stata® or R®, we constructed and plotted confidence and prediction regions and, where appropriate ROC curves. The advantage of this approach is that it produces summary estimates of sensitivity and specificity that account for the correlation between the 2 measures (sensitivity and specificity). Other advantages of this method have been described elsewhere (Reitsma et al. 2005; Van Houwelingen et al. 1993; Van Houwelingen et al. 2002). In cases where many cell counts were 0, 1 was added to that cell and 1 subtracted from the cell with the highest count to ensure the model was able to run whilst not significantly distorting the results. Likelihood ratios were calculated from either the sensitivity and specificity estimates or the raw diagnostic test accuracy data. The related 95% CIs were calculated using the log method (Altman et al. 2013); when there were zero true positives or false positives, 0.5 was added to all cells to enable calculation of the positive likelihood ratio and related 95% confidence intervals.

This model also assesses the variability by incorporating the precision by which sensitivity and specificity have been measured in each study. A 95% confidence and prediction ellipse is shown in the graph that indicates the confidence and prediction region around the pooled sensitivity or specificity point estimate a summary ROC curve is also presented. From the STATA® or R® output we report the summary estimate of sensitivity and specificity (plus their 95% confidence intervals) as well as between study variation measured as logit sensitivity and specificity as well as correlations between the 2 measures of variation.

4.3.3.3 Data synthesis for qualitative reviews

Where possible, a meta-synthesis was conducted to combine qualitative study results. The main aim of the synthesis of qualitative data was to produce a description of the topics that may influence the experience of person with pancreatic cancer, those people important to them and healthcare professionals involved in their care, rather than build new theories or reconceptualise the topic under review. Whenever studies identified a qualitative theme, this was extracted and the main characteristics were summarised. The methodologies in the majority of studies employed some form of questionnaire or interview to assess patient opinion and experience. In most cases, these were pre-existing, validated tools designed for the purpose of the study. Limitations of each study were assessed using a modified CASP Qualitative checklist

4.3.4 Appraising the quality of the evidence by outcomes

4.3.4.1 GRADE methodology

For intervention reviews, the evidence for outcomes from the included RCTs and observational studies were evaluated and presented using GRADE, which was developed by the international GRADE working group (Schünemann et al. 2013). Modified GRADE assessments were also carried out for accuracy measures in diagnostic reviews. For the appraisal of the quality of the evidence from qualitative reviews an adapted Critical Appraisal Skills Programme (CASP) Qualitative checklist was used (NICE 2015; Public Health Resource Unit England 2006).

The software developed by the GRADE working group (GRADEpro) was used to assess the quality of each outcome, taking into account individual study quality factors and the meta-analysis results. The clinical/economic evidence profile tables include details of the quality assessment and pooled outcome data, where appropriate, an absolute measure of intervention effect and the summary of quality of evidence for that outcome. In this table, the columns for intervention and control indicate summary measures of effect and measures of dispersion (such as mean and standard deviation or median and interquartile range) for continuous outcomes and frequency of events (n/N: the sum across studies of the number of patients with events divided by sum of the number of completers) for binary outcomes. Reporting or publication bias was only taken into consideration in the quality assessment and included in the clinical evidence profile tables if it was apparent.

The selection of outcomes for each review question was decided when each review protocol was discussed with the committee. However, given the nature of most of the review questions included in this guideline (driven by short- or long-term outcomes), the categorisation of outcomes as critical and important did not follow the standard GRADE approach. The outcomes selected for a review question were critical for decision-making in a specific context.

The evidence for each outcome in interventional reviews was examined separately for the quality elements listed and defined in Table 6.

Table 6: Description of quality elements in GRADE for intervention studies

Quality element	Description
Risk of bias (study limitations)	Limitations in the study design and implementation may bias the estimates of the treatment effect. High risk of bias for the majority of the evidence decreases confidence in the estimate of the effect.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results or findings.
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question, or recommendation made, such that the effect estimate is changed. This is also related to applicability or generalisability of findings.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect. Imprecision results if the confidence interval includes the clinically important threshold. For qualitative research this can relate to the sufficiency of data within each theme.
Publication bias	Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.

The GRADE toolbox is designed only for RCTs and observational studies. For diagnostic test accuracy and staging reviews, the QUADAS-2 checklist risk of bias and applicability items

were used for evaluating the risk of bias and indirectness, respectively, of the studies. The quality assessment of inconsistency and imprecision were adapted as detailed below in Sections 4.3.4.4 and 4.3.4.6.

Table 7: Description of the elements in GRADE and how they are used to assess the quality for diagnostic accuracy reviews

Quality element	Description
Risk of bias ('Study limitations')	Limitations in the study design and implementation may bias the estimates of the diagnostic accuracy. High risk of bias for the majority of the evidence decreases confidence in the estimate of the effect. Diagnostic accuracy studies are not usually randomised and therefore would not be downgraded for study design from the outset and start as high level evidence. Evaluated using QUADAS-2 risk of bias items.
Inconsistency	Inconsistency refers to unexplained heterogeneity of test accuracy measures such as sensitivity and specificity between studies.
Indirectness	Indirectness refers to differences in study population, differences in index tests across studies, reference standards and outcomes between the available evidence and the review question. Evaluated using QUADAS-2 applicability items.
Imprecision	Results are considered not imprecise, seriously imprecise, or very seriously imprecise according to how wide the confidence intervals of the primary measure of sensitivity were.

The main criteria considered in the rating of these elements are discussed below (see section 4.3.4.1). Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems. The ratings for each component were summed to obtain an overall assessment for each outcome.

The main criteria considered in the rating of these elements are discussed below. Footnotes beneath GRADE tables were used to describe reasons for grading a quality element as having serious or very serious limitations. The ratings for each component were summed to obtain an overall assessment for each outcome (See Table 10).

4.3.4.2 Grading the quality of clinical evidence

After results were pooled using data synthesis methods, the overall quality of evidence for each outcome was considered. The following procedure was adopted when using the GRADE approach:

- An initial quality rating was assigned, based on the study design. RCTs start as 'High' in intervention reviews and observational studies as 'Low'. In diagnostic and qualitative reviews, evidence from non-randomised studies start as 'High'.
- The rating was then downgraded for the specified criteria: risk of bias (study limitations); inconsistency; indirectness; imprecision; and publication bias. These criteria are detailed below. Evidence from observational studies (which had not previously been downgraded) was upgraded if there was a large magnitude of effect or a dose-response gradient, and if all plausible confounding would reduce a demonstrated effect, or suggest a spurious effect when results showed no effect.

Each quality element considered to have 'serious' or 'very serious' issues was rated down by 1 or 2 points respectively. Value based judgements for relevant interpretation of the levels of quality elements were informed by discussion with the committee for each review to balance consistency of approach across the guideline and clinical relevance within each review (see Table 8). The downgraded/upgraded ratings were then summed and the overall quality rating was revised, taking into account the relative contributions from the individual studies within a meta-analyses, where performed. For example, RCTs start as high and the overall quality

becomes moderate, low or very low if 1, 2 or 3 points are deducted respectively. The reasons or criteria used for downgrading were specified in the footnotes.

For qualitative reviews, each quality element considered to have 'minor or 'serious' limitations was rated down by 1 or 2 points respectively. A quality assessment of 'Unclear' was added to the list of possible GRADE-CERQual levels. Together with the committee, it was decided that in qualitative reviews 1 'Unclear' rating did not mean an automatic downgrade of the evidence for this theme. However, 2 'Unclear' ratings were downgraded by 1. Footnotes were not used for the CERQual tables (See Table 9).

Table 8: Levels of quality elements in GRADE for intervention and diagnostic reviews

Level	Description
None	There are no serious issues with the evidence.
Serious	The issues are serious enough to downgrade the outcome evidence by 1 level.
Very serious	The issues are serious enough to downgrade the outcome evidence by 2 levels.

Table 9: Levels of quality elements in GRADE for qualitative reviews

Level	Description
No limitations	There are no serious issues with the evidence.
Minor limitations	The issues are serious enough to downgrade the outcome evidence by 1 level.
Serious limitations	The issues are serious enough to downgrade the outcome evidence by 2 levels.
Unclear	There is no enough information available to assess the domain.

Table 10: Overall quality of outcome evidence in GRADE

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

The details of the criteria used for each of the main quality elements are discussed further in Sections 4.3.5.2.1 to 4.3.5.3.4 below.

4.3.4.3 Risk of bias / methodological limitations

Intervention studies

For intervention studies, the Cochrane Risk of Bias tool was used for randomised control trials (Higgins & Green 2011; NICE 2015).

Bias can be defined as anything that causes a consistent deviation from the truth. Bias can be perceived as a systematic error. The risk of bias for a given study and outcome is associated with the risk of over or underestimation of the true effect. Sources of bias in randomised controlled trials are listed in Table 11).

A study with a poor methodological design does not automatically imply high risk of bias; the bias is considered individually for each outcome and it is assessed whether this poor design will impact on the estimation of the intervention effect.

Table 11: Summary of Cochrane risk of bias tool

Risk of bias	Explanation
Allocation concealment	Those enrolling patients are aware of the group to which the next enrolled patient will be allocated (this is a major problem in 'pseudo' or 'quasi' randomised trials with allocation by, for example, day of week, birth date, chart number).
Lack of blinding	Patient, caregivers, those recording outcomes, those adjudicating outcomes or data analysts are aware of the arm to which patients are allocated.
Incomplete accounting of patients and outcome events	Missing data not accounted for and failure of the investigators to adhere to the intention to treat principle when indicated.
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results.
Other risks of bias	For example: • stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules • use of unvalidated patient-reported outcomes • recruitment bias in cluster randomised trials.

For observational studies, quality was assessed using the Newcastle-Ottawa Scale (Wells et al. 2008; NICE 2015).

The risk of bias was derived by assessing the risk of bias across 3 domains – selection, comparability and outcome. Studies are given a rating depending on how they perform on each of the domains. More details about the quality assessment items for observational studies are shown in Table 12.

Table 12: Summary of Newcastle and Ottawa scale

Risk of bias category	Quality assessment item
Selection	Representativeness of the cohort
	Selection of the non-exposed cohort
	Ascertainment of exposure
	Demonstration that the outcome of interest was not present at the start of the study
Comparability	Comparability of cohorts on the basis of the design or analysis
Outcome	Assessment of outcome
	Was follow-up long enough for outcomes to occur
	Adequacy of follow-up of cohorts

Diagnostic studies

For diagnostic accuracy studies, the Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS- 2) checklist was used (Whiting et al. 2011).

Evaluating risk of bias in primary diagnostic accuracy and staging studies in QUADAS- 2 consists of assessing patient selection, the index test, the reference standard, and patient flow and timing of the tests. More details about the quality assessment of diagnostic studies are shown in Table 13.

Table 13: Summary of QUADAS-2 risk of bias items

Domain	Patient Selection	Index text	Reference standard	Flow and timing
Description	Describe methods of patient selection: Describe included patients (prior testing, presentation, intended use of index test and setting):	Describe the index test and how it was conducted and interpreted:	Describe the reference standard and how it was conducted and interpreted:	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table: Describe the time interval and any interventions between index test(s) and reference standard:
Signalling questions (yes/no/unclear)	Was a consecutive or random sample of patients enrolled?	Were the index test results interpreted without knowledge of the results of the reference standard?	Is the reference standard likely to correctly classify the target condition?	Was there an appropriate interval between index test(s) and reference standard?
	Was a case-control design avoided?	If a threshold was used, was it pre-specified?	Were the reference standard results interpreted without knowledge of the results of the index test?	Did all patients receive a reference standard?
	Did the study avoid inappropriate exclusions?			Did all patients receive the same reference standard?
				Were all patients included in the analysis?
Risk of bias: (high/low/unclear)	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct, or its interpretation have introduced bias?	Could the patient flow have introduced bias?
Concerns regarding applicability: (high/low/unclear)	Are there concerns that the included patients do not match the review question?	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Are there concerns that the target condition as defined by the reference standard does not match the review question?	

Qualitative studies

For qualitative studies, quality was assessed using a checklist for qualitative studies (NICE 2015). This was based on the Critical Appraisal Skills Programme (CASP) checklist for qualitative studies (Public Health Resource Unit England 2006). The quality rating for risk of bias (low, high and unclear) was derived by assessing the risk of bias across 6 domains.

The evidence was then assessed by theme using a modified CASP approach for each study as described above (see Table 14).

Table 14: Summary of CASP tool for qualitative studies

Risk of bias	Explanation
Aim and appropriateness of qualitative evidence.	This refers to an assessment of whether the aims and relevance of the study were clearly described and whether qualitative research methods were appropriate for investigating the research question.
Rigour in study design or validity of theoretical approach	This domain assesses whether the study approach has been clearly described and is based on a theoretical framework (for example ethnography or grounded theory). This does not necessarily mean that the framework has to be explicitly stated, but that at least a detailed description is provided which makes it transparent and reproducible.
Sample selection	The background, the procedure and reasons for the chosen method of selecting participants should be stated. It should also be assessed whether there was a relationship between the researcher and the informant and if so, how this may have influenced the findings that were described.
Data collection	Consideration was given to how well the method of data collection (in-depth interviews, semi-structured interviews, focus groups or observations) was described, whether details were provided and how the data were collected (who conducted the interviews, how long did they last and where did they take place).
Data analysis	For this criterion it is assessed whether sufficient detail is provided about the analytical process and whether it is in accordance with the theoretical approach. For instance, if a thematic analysis was used, it is assessed whether there was a clear description of how the theme was arrived at. Data saturation is also part of this section. This refers to whether a theoretical point of theme saturation was achieved at which point no further citations or observations would provide more insight or suggest a different interpretation of this theme. This could be explicitly stated, or it may be clear from the citations presented that it may have been possible to find more themes.
Results	In relation to this section the reasoning about the results are important, for instance whether a theoretical proposal or framework is provided rather than being restricted to citations / presentation of data.

4.3.4.4 Inconsistency / coherence of findings

Inconsistency refers to unexplained heterogeneity of results. When estimates of treatment effect measures vary widely across studies (that is, there is heterogeneity or variability in results between studies), this suggests that there are true differences in underlying effects.

Heterogeneity in meta-analyses was evaluated. If present, sensitivity and subgroup analyses were performed as pre-specified in the protocols (Appendix C).

If there was heterogeneity (chi-squared probability less than 0.1, I-squared inconsistency statistic of greater than 50%, or from visually examining forest plots), but no plausible explanation (for example duration of intervention or different follow-up periods) could be found, the quality of the evidence was downgraded in GRADE by 1 or 2 levels, depending on the extent of inconsistency in the results. When outcomes were derived from a single trial, inconsistency is not applicable. However, 'no inconsistency' is nevertheless used to describe

this quality assessment in the GRADE profiles as this is the default option in the GRADEpro software used.

For diagnostic test accuracy and staging reviews, inconsistency in the studies was assessed by visual inspection of the sensitivity and specificity forest plots.

For qualitative research, a similar concept to inconsistency is coherence, which refers to the way findings within themes are described and whether they make sense. This concept was used in the quality assessment across studies for individual themes. This does not mean that contradictory data was downgraded automatically, but that it was highlighted and presented, and that reasoning was provided. As long as the themes, or components of themes, from individual studies fit into a theoretical framework, they do not necessarily have to have the same perspective. It should, however, be possible to explain these by differences in context (for example, the views of healthcare professionals might not be the same as those of family members, but they could contribute to the same overarching theme). Coherence was graded across studies with the following labels: coherent, incoherent or unclear.

4.3.4.5 Indirectness / applicability or relevance of findings

For quantitative reviews, directness refers to the extent to which the populations, intervention, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention.

For the reviews on diagnostic test accuracy and staging, the applicability items of the QUADAS-2 checklist (Whiting et al. 2011) covering patient selection, the index test and the reference standard were used. More details about the quality assessment of diagnostic studies are shown in Table 15.

Table 15: Summary of QUADAS-2 applicability items

Domain	Patient Selection	Index text	Reference standard	Flow and timing
Concerns regarding applicability: (high/low/unclear)	Are there concerns that the included patients do not match the review question?	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Are there concerns that the target condition as defined by the reference standard does not match the review question?	Not applicable

Relevance of findings in qualitative research is the equivalent of indirectness for quantitative outcomes and refers to how closely the aims and context of the studies contributing to a theme reflect the objectives outlined in the review protocol of the guideline question.

4.3.4.6 Imprecision / theme saturation or sufficiency

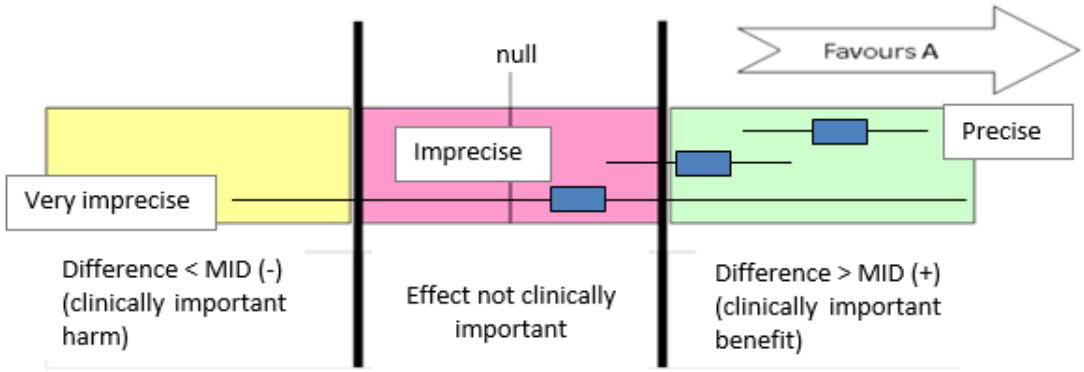
For quantitative reviews, imprecision in guidelines concerns whether the uncertainty (confidence interval) around the effect estimate means that it is not clear whether there is a clinically important difference between interventions or not (that is, whether the evidence would clearly support one recommendation or appear to be consistent with several different types of recommendations). Therefore, imprecision differs from the other aspects of evidence quality because it is not really concerned with whether the point estimate is accurate or correct (has internal or external validity). Instead, it is concerned with the uncertainty about

what the point estimate actually is. This uncertainty is reflected in the width of the confidence interval.

The 95% confidence interval (95% CI) is defined as the range of values within which the population value will fall on 95% of repeated samples, were this procedure to be repeated. The larger the trial, the smaller the 95% CI and the more certain the effect estimate.

Imprecision in the evidence reviews was assessed by considering whether the width of the 95% CI of the effect estimate was relevant to decision-making, taking each outcome in isolation. This is explained in Figure 2, which considers a positive outcome for the comparison of treatment A versus treatment B. Three decision-making zones can be identified, bounded by the thresholds for clinical importance (minimal important difference, MID) for benefit and for harm. The MID for harm for a positive outcome means the threshold at which drug A is less effective than drug B by an amount that is clinically important to patients (favours B).

Figure 2: Illustration of precise, imprecise and very imprecise evidence based on the confidence interval of outcomes in forest plots



When the confidence interval of the effect estimate is wholly contained in 1 of the 3 zones (for example clinically important benefit), we are not uncertain about the size and direction of effect (whether there is a clinically important benefit, or the effect is not clinically important, or there is a clinically important harm), so there is no imprecision.

When a wide confidence interval lies partly in each of 2 zones, it is uncertain in which zone the true value of effect estimate lies and therefore there is uncertainty over which decision to make (based on this outcome alone). The confidence interval is consistent with 2 possible decisions and so this is considered to be imprecise in the GRADE analysis and the evidence is downgraded by 1 level ('serious imprecision').

If the confidence interval of the effect estimate crosses into 3 zones, this is considered to be very imprecise evidence because the confidence interval is consistent with 3 possible clinical decisions and there is therefore a considerable lack of confidence in the results. The evidence is therefore downgraded by 2 levels in the GRADE analysis ('very serious imprecision').

Implicitly, assessing whether the confidence interval is in, or partially in, a clinically important zone, requires the committee to estimate an MID or to say whether they would make different decisions for the 2 confidence limits.

Minimally Important Differences

The literature was searched for established minimally important differences (MIDs) for the selected outcomes in the evidence reviews, such as symptom measurement tools. The following MIDs were used consistently throughout the guideline:

- For survival outcomes (e.g. overall survival, disease-free survival), any statistically significant change was considered by the committee to be clinically important.
- For adverse events, the default MIDs of 0.8 and 1.25 were used.
- For EORTC QLQ-C30, a published MID of 5 points was used (Osoba et al. 1998).
- For all other quality of life measures, the default MIDs were assumed.

Finally, if no published or acceptable MIDs were identified, the committee considered whether it was clinically acceptable to use the GRADE default MID to assess imprecision. For binary outcomes clinically important thresholds for a risk ratio of 0.8 and 1.25 respectively were used (due to the statistical distribution of this measure this means that this is not a symmetrical interval). This default MID was used for all the binary outcomes in the interventions' evidence reviews as a starting point and decisions on clinical importance were then considered based on the absolute risk difference. For continuous outcomes, the GRADE default MIDs were assumed to be half of the standard deviation of the control group at baseline.

In evaluating diagnostic accuracy and staging measures, imprecision was assessed using the 95% CI of sensitivity as the primary measure of interest as the harmful consequences of false negatives (e.g. death caused by malignant tumours not identified as such) were considered to be worse than the harmful consequences of false positives (e.g. unnecessary surgery or treatment on benign tumour).

- Sensitivity and specificity
  - Not serious: both upper and lower 95% CI >0.9
  - Serious: 95% CI crosses 0.75 or 0.9
  - Very serious: 95% CI crosses both 0.75 and 1.0 or difference between upper and lower 95% CI $\geq$0.25
- Positive likelihood ratio:
  - Very useful test: >10
  - Moderately useful test: 5-10
  - Not a useful test: <5
- Negative likelihood ratio:
  - Very useful test: <0.1
  - Moderately useful test: 0.1 to 0.2
  - Not a useful test: >0.2

Theme saturation or sufficiency refers to a similar concept in qualitative research. This refers to whether a theoretical point of theme saturation was achieved, at which point no further citations or observations would provide more insight or suggest a different interpretation of this theme. As already highlighted in a previous section on qualitative reviewing methods, it is not equivalent to the number of studies contributing to a theme, but rather to the depth of data and whether sufficient quotes or observations were provided that could underpin these findings.

4.3.4.7 NMA quality appraisal

The use of GRADE to assess the quality of studies addressing a particular review question for pairwise comparisons of interventions is relatively established. However, the use of GRADE to assess the quality of evidence across a NMA is still a developing methodology. Therefore the ISPOR checklist was used to appraise the risk of bias of NMAs (Jansen et al. 2014).

Table 16: Rationale for downgrading quality of evidence in NMAs

GRADE criteria	Example reasons for downgrading quality
Risk of bias	Risk of bias was assessed in accordance with the 26-item checklist developed by the ISPOR Good Research Practices. This includes (22 items of the checklist) limitations in the design or execution of the study, including 1) the used evidence base, 2) analysis methods, 3) reporting quality and transparency, 4) interpretation of findings, and 5) conflicts of interest.
Inconsistency	Evidence of any inconsistency between the direct and indirect estimates of effect was assessed using the residual deviance, deviance information criterion and the statistic tau; outcome was downgraded if tau > 0.5
Indirectness	The extent to which the available evidence fails to address the specific review question (this can reduce the quality rating). This may be in relation to the setting, population, outcomes, interventions or study designs used in the evidence base. Indirectness was assessed in accordance with the 26-item checklist developed by the ISPOR Good Research Practices. This includes (4 items of the checklist) assessments about the applicability of network meta-analysis results to the setting of interest.
Imprecision	This is considered to be present when there is uncertainty around the estimate of effect, and reflects the confidence in, or 'credibility' of, the estimate of effect. It is assessed based on the overall distribution of the rankings, such that evidence was downgraded if no interventions had rank credible intervals ≤33% of total distribution of comparators.

4.3.4.8 Assessing clinical significance

Intervention reviews

The committee assessed the evidence by outcome. To facilitate this, where possible, binary outcomes were converted into absolute risk differences (ARDs) using GRADEpro software: the median control group risk across studies was used to calculate the ARD and its 95% CI from the pooled risk ratio. For continuous outcomes, the mean difference between the intervention and control arm of the trail was calculated. This was then assessed in relation to a published MID (if available) or the default MID (0.5 times the median control group standard deviation at baseline or if not available, follow up).

The clinical significance of a treatment effect was evaluated as a combination of the minimally / clinically important difference (MID) thresholds and statistical significance / the null hypothesis value (zero for continuous outcomes and 1 for RRs, ORs and HRs):

- If the point estimate for a treatment effect exceeded the MID and the 95% CI did not include the null hypothesis value then the result was considered to be "clinically significant"
- If the point estimate for a treatment effect did not exceed the MID then the result was not considered to be "clinically significant"

Diagnostic reviews

The clinical usefulness of a test for diagnosis was determined based on either sensitivity, specificity, positive likelihood ratio or negative likelihood ratio, depending on what the committee believed was the most important – correctly identifying if a patient had the target condition (ruling in) or correctly identifying if a patient did not have the target condition (ruling out).

The value of the point estimate within the different MID thresholds for sensitivity, specificity, positive likelihood ratio or negative likelihood ratio were used to determine clinical usefulness.

Qualitative reviews

For themes stemming from qualitative findings, clinical significance was decided upon by the committee taking into account the generalisability of the context from which the theme was derived and whether it was convincing enough to support or warrant a change in current practice, as well as the evidence quality.

4.3.5 Evidence statements

Evidence statements are summary statements that are presented after the GRADE profiles, summarising the key features of the clinical evidence presented. The wording of the evidence statements reflects the certainty or uncertainty in the estimate of effect. The evidence statements are presented by outcome or theme and encompass the following key features of the evidence:

- the quality of the evidence (GRADE rating)
- the number of studies and the number of participants for a particular outcome
- a brief description of the participants
- the clinical significance of the effect and an indication of its direction (for example, if a treatment is clinically important [beneficial or harmful] compared with another, or whether there is no clinically important difference between the tested treatments).

4.3.6 Evidence of cost effectiveness

The aims of the health economic input to the guideline were to inform the committee of potential economic issues related to the diagnosis and management of pancreatic cancer to ensure that recommendations represented a cost-effective use of healthcare resources. Health economic evaluations aim to integrate data on healthcare benefits (ideally in terms of quality-adjusted life-years (QALYs) with the costs of different care options. In addition, the health economic input aimed to identify areas of high resource impact; recommendations which – while nevertheless cost-effect – might have a large impact on CCG or Trust finances and so need special attention.

4.3.6.1 Undertaking new health economic analysis

As well as reviewing the published economic literature, as described above, new economic analysis was undertaken by the Health Economist in selected areas. The following priority areas for de novo economic analysis were agreed by the committee after formation of the review questions and consideration of the available health economic evidence:

- management of biliary obstruction
- management of locally advanced non-metastatic pancreatic cancer

A costing tool was also developed for the review question relating to models of care, where little clinical evidence was uncovered. It was thought that the committee may wish to make recommendations that would lead to a high resource impact, although current practice was recommended.

The methods and results of de novo economic analyses are reported in Chapters 12 and 13. When new economic analysis was not prioritised, the committee made a qualitative judgement regarding cost effectiveness by considering expected differences in resource and cost use between options, alongside clinical effectiveness evidence identified from the clinical evidence review.

4.3.6.2 Cost effectiveness criteria

NICE's report Social value judgements: principles for the development of NICE guidance sets out the principles that committees should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- the intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or;
- the intervention cost less than £20,000 per QALY gained compared with the next best strategy, or;
- the intervention provided clinically significant benefits at an acceptable additional cost when compared with the next best strategy.

The committee's considerations of cost-effectiveness are discussed explicitly in the 'Consideration of economic benefits and harms' section of the relevant chapters.

4.4 Developing recommendations

4.4.1 Guideline recommendations

Over the course of the guideline development process, the committee was presented with:

- evidence tables of the clinical and economic evidence reviewed from the literature: all evidence tables are in Appendix F and economic evidence tables are in Appendix J
- summary of clinical and economic evidence and quality assessment (as presented in Chapters 5 to 11)
- forest plots (Appendix H)
- a description of the methods and results of the cost-effectiveness analysis undertaken for the guideline (Chapters 12 & 13).

Recommendations were drafted on the basis of the group's interpretation of the available evidence, taking into account the balance of benefits, harms and costs between different courses of action. This was either done formally, in an economic model, or informally. Firstly, the net benefit over harm (clinical effectiveness) was considered, focusing on the critical outcomes, although most of the reviews in the guideline were outcome driven. When this was done informally, the group took into account the clinical benefits and harms when one intervention was compared with another. The assessment of net benefit was moderated by the importance placed on the outcomes (the group's values and preferences) and the confidence the group had in the evidence (evidence quality). Secondly, the group assessed whether the net benefit justified any differences in costs.

When clinical and economic evidence was of poor quality, conflicting or absent, the group drafted recommendations based on their expert opinion. The considerations for making consensus-based recommendations include the balance between potential harms and benefits, the economic costs or implications compared with the economic benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The group also considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation.

The wording of recommendations was agreed by the group and focused on the following factors:

- the actions healthcare professionals need to take,
- the information readers of the guideline need to know,

- the strength of the recommendation (for example the word 'offer' was used for strong recommendations and 'consider' for weak recommendations),
- the involvement of patients (and their carers if needed) in decisions about treatment and care,
- consistency with NICE's standard advice on recommendations about drugs, waiting times and ineffective intervention.

The main considerations specific to each recommendation are outlined in the 'Recommendations and link to evidence' sections within each chapter.

4.4.2 Research recommendations

When areas were identified for which good evidence was lacking, the committee considered making recommendations for future research. Decisions about inclusion were based on factors such as:

- the importance to patients or the population,
- national priorities,
- potential impact on the NHS and future NICE guidance,
- ethical and technical feasibility.

4.5 Validation process

This guidance is subject to a 6-week public consultation and feedback as part of the quality assurance and peer review of the document. All comments received from registered stakeholders are responded to in turn and posted on the NICE website at publication.

4.6 Updating the guideline

Following publication, and in accordance with the NICE guidelines manual, NICE will undertake a review of whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

4.7 Disclaimer

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The NGA disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

4.8 Funding

The NGA was commissioned by the National Institute for Health and Care Excellence (NICE) to undertake the work on this guideline.

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5 Diagnosis

5.1 People with jaundice

Review question: What is the most effective diagnostic pathway (imaging +/-CA 19–9, biopsy (cytology or histology)) for adults with suspected pancreatic cancer in secondary care who have jaundice?

5.1.1 Introduction

Obstructive jaundice is the most common presenting symptom in people with pancreatic cancer, although it is to be noted that most people presenting with jaundice do not actually have pancreatic cancer.

There is currently uncertainty about the most accurate technique for diagnosing the disease in people with obstructive jaundice. CT scans are commonly used to diagnose pancreatic cancer in this group of people, however it is not always possible for the CT scan to visualise the cancer that is causing the obstruction. Ultrasound is another technique which can identify pancreatic cancer. MRI and PET-CT are both increasingly being used but their diagnostic accuracy in this group of people is not clearly understood. Whether histology and cytology are needed to make the diagnosis of pancreatic cancer in someone with obstructive jaundice is uncertain, with some centres operating on imaging alone. There is also variation in practice as to how the histology and cytology are obtained. The role of CA 19-9 in combination with imaging is not defined.

In the group of people thought not suitable for resection based on imaging, brushing the duct (for cytology) at the time of ERCP and stenting is common. Where this does not confirm a diagnosis, EUS and fine needle aspiration (FNA) is usually done. However there are still a small group of people in whom the imaging is highly suggestive of malignancy but the cytology/histology does not confirm, leaving the question of what to do next.

Guidance is needed on the most effective diagnostic pathway to identify pancreatic cancer in people who have jaundice.

5.1.1.1 Review protocol summary

The review protocol summary used for this question can be found in Table 17. Full details of the review protocol can be found in Appendix C.

Table 17: Clinical review protocol summary for the review of most effective diagnostic pathway for people with suspected pancreatic cancer who have jaundice

Population	Adults suspected of having pancreatic cancer who have jaundice
Index Test	Imaging +/- CA 19–9 (Ultrasound , CT, MRI, PET-CT) Biopsy (cytology or histology) • endoscopic ultrasound +/- FNA • ERCP+/- biliary brushings, • EUS +/- core biopsy • Percutaneous liver biopsy • laparoscopy + biopsy • percutaneous pancreatic biopsy
Reference standard	• Definitive diagnosis (preferably Pathological diagnosis) • Each other

.

Outcome	• Diagnostic Accuracy including: • Sensitivity • Specificity • Positive Predictive Value • Negative Predictive Value • Adverse events

5.1.2 Description of Clinical Evidence

Five single-centre retrospective cohort studies (n=647) were included in the review. A summary of the included studies is presented in Table 18.

One study (n=47) reported on the diagnostic accuracy of spiral CT. This study was carried out in the USA and included patients with obstructive jaundice with a suspicion of pancreatic cancer (Agarwal et al. 2004).

One study (n=47) reported on the diagnostic accuracy of EUS. This study was carried out in the USA and included patients with obstructive jaundice with a suspicion of pancreatic cancer (Agarwal et al. 2004).

Five studies (n=691) reported on the diagnostic accuracy of EUS-FNA based cytology (Agarwal et al. 2004; Kim et al. 2015; Oppong et al. 2010; Ross et al. 2008; Tummala et al. 2013). All studies included patients with obstructive jaundice with a suspicion of pancreatic cancer. One study was conducted in the UK (Oppong et al. 2010), whilst the remaining 4 studies were conducted in the USA.

Two studies (n=89) reported on the diagnostic accuracy of ERCP + brushings of biliary strictures (Oppong et al. 2010; Ross et al. 2008). Both studies included patients with obstructive jaundice with a suspicion of pancreatic. One study was conducted in the UK (Oppong et al. 2010), with the other study conducted in the USA (Ross et al. 2008).

All included studies reported on diagnostic accuracy outcome measures, whilst only one study reported adverse effects or complications. Positive and likelihood ratios were calculated, where appropriate, from the sensitivity and specificity of the studies to enable evaluation of the relevant tests. The QUADAS-2 checklist was used to evaluate the risk of bias and indirectness (applicability) of the studies.

Further information about the search strategy can be found in Appendix D. See study selection flow chart in Appendix E, single and multiple test ROC curves and forest plots in Appendix H, summary of Risk of Bias in Appendix J, study evidence tables in Appendix F and list of excluded studies in Appendix G.

5.1.3 Summary of included studies

A summary of the studies that were included in this review is presented in Table 18.

Table 18: Summary of included studies

Study	Population	Study design Country	Index test (s)	Reference standard*	Outcomes	Overall risk of bias
Agarwal et al., 2004	Sample size N= 47 Characteristics M/F (n): not reported Median age (range): not reported Final diagnosis: malignant(n): 45 benign(n): 2	Retrospective single-centre study USA	Index test 1 (n=47): EUS Index test 2 (n=47): EUS-FNA cytology Index test 3 (n=47): Spiral CT	The final diagnosis was based on: definitive cytology, surgical pathology or the development of metastatic disease. Number of patients by reference standard test are not reported	Diagnostic accuracy Sensitivity Specificity NPV PPV	Serious risk of bias Potential risk of verification bias: as the reference standard used for is different across the study sample Unclear of review bias (lack of blinding) * 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.
Kim et al., 2015	Sample size N= 180 Characteristics M/F (n): 108 / 72 Mean age (SD): 65 (12) years Final diagnosis: malignant(n): 172 benign(n): 8	Retrospective single-centre study USA	Index test (n=180): EUS-FNA cytology	The final diagnosis was based on: histologic diagnosis of malignancy on EUS-FNA CYTOLOGY (n=166) surgically resected specimen (number not reported) and/or other tissue acquisition from endoscopic or percutaneous modalities (n=6)	Diagnostic accuracy Sensitivity Specificity NPV PPV	Very serious risk of bias Potential risk of verification bias: as the reference standard used for is different across the study sample Unclear of review bias (lack of blinding) High Incorporation bias: as the test that is being evaluated is included in the reference standard, there can be an overestimation of test accuracy

Study	Population	Study design Country	Index test (s)	Reference standard*	Outcomes	Overall risk of bias
Oppong et al., 2010	Sample size N= 37 (39 procedures) Characteristics M/F (n): 21 / 17 Mean age (range): 62.4 (26- 87) years Final diagnosis: malignant(n): 32 benign(n): 5	Retrospective single-centre study UK	Index test 1 (n=39): EUS-FNA cytology Index test 2 (n=39): ERCP + Brushings of biliary strictures A cytopathologist was not present in the endoscopy suite for any of the procedures.	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).	Diagnostic accuracy Sensitivity Specificity NPV PPV	Serious risk of bias Potential risk of verification bias: as the reference standard used for is different across the study sample Unclear of review bias (lack of blinding)
Ross et al., 2008	Sample size N= 114 Characteristics M/F (n): 66 / 48 Mean age (SD): 62.6 (11.8) years Final diagnosis: malignant(n): 80 benign(n): 34	Retrospective single-centre study USA	Index test 1 (n=83): EUS-FNA cytology Index test 2 (n=50): ERCP + Brushings of biliary strictures	The final diagnosis was based on: tissue acquisition (n=78) or clinical course (n=2)	Diagnostic accuracy Sensitivity Specificity NPV PPV	Very serious risk of bias Potential risk of verification bias: as the reference standard used for is different across the study sample Unclear of review bias (lack of blinding) High risk of bias due to bias due to inappropriate exclusions (4 cases of suspicious aspirates are excluded from analysis and not considered as either diagnostic or false negative)
Tummala et al., 2013	Sample size N= 348 Characteristics	Retrospective single-centre study USA	Index test (n=342): EUS-FNA cytology	The final diagnosis was based on: surgical pathology	Diagnostic accuracy Sensitivity	Serious risk of bias Potential risk of verification bias: as the reference

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Study	Population	Study design Country	Index test (s)	Reference standard*	Outcomes	Overall risk of bias
	M/F (n): 176 / 166 Mean age (range): 68 (12.5) years Final diagnosis: malignant(n): 248 benign(n): 9			or definitive cytology and clinical follow-up of >=12 months	Specificity NPV PPV Adverse events/complications	standard used for is different across the study sample Unclear of review bias (lack of blinding)

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

5.1.4 Clinical evidence profile

The clinical evidence profiles for this review question are presented in Table 19 to Table 22.

Table 19: Summary of clinical evidence for spiral CT to detect malignancy in people with jaundice

Study	N	Risk of bias[1]	Inconsistency[2]	Indirectness[3]	Imprecision[4]	Point estimates of sensitivity (95% CI)	Point estimates of specificity (95% CI)	Positive likelihood ratio (95% CI)[5]	Negative likelihood ratio (95% CI)[5]	Quality
Agarwal et al. 2004	47	Serious[6]	Not applicable	Not serious	Serious[7]	0.67 (0.51-0.8)	1.0 (0.16-1.0)	3.98 (0.31-50.4)[8]	0.33 (0.22-0.5)	LOW

[1], Risk of bias was assessed using the QUADAS-2 checklist

[2], Inconsistency was assessed by inspection of the 95% prediction region in a summary ROC plot if a diagnostic meta-analysis was conducted. If between 2 and 3 studies, inconsistency was assessed by visual inspection of the point estimates of sensitivity and specificity. If only one study, then inconsistency is not applicable

[3], Indirectness was assessed using the QUADAS-2 checklist items referring to applicability

[4], The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest as a false negative - missing malignancy - risks a potentially avoidable death, whilst a false positive - indicating malignancy when there is none - risks potentially avoidable surgery or other treatment such as chemotherapy. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for

the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise

[5], positive and negative likelihood ratios calculated from raw diagnostic test accuracy data if not already reported; 95% CIs calculated using log method (see Chapter 4.3.3.2.2 for details).

[6], Unclear risk of review bias (lack of blinding in the interpretation both of the index test and reference standard – no details are given in the text), unclear risk of verification bias (not all patients received the same reference test)

[7] 95% CI of sensitivity crosses 0.75

[8], since the specificity was 1, a continuity correction of 0.5 was added to all cells to enable calculation of the positive likelihood ratio and related 95% CIs.

Table 20: Summary of clinical evidence for EUS to detect malignancy in people with jaundice

Study	N	Risk of bias[1]	Inconsistency[2]	Indirectness[3]	Imprecision[4]	Point estimates of sensitivity (95% CI)	Point estimates of specificity (95% CI)	Positive likelihood ratio (95% CI)[5]	Negative likelihood ratio (95% CI)[5]	Quality
Agarwal et al. 2004	47	Serious risk of bias[6]	Not applicable	Not serious	Not serious	1.0 (0.92-1.0)	0.5 (0.1-0.99)	2.0 (0.5-8.0)	0	MODERATE

[1] Risk of bias was assessed using the QUADAS-2 checklist

[2], Inconsistency was assessed by inspection of the 95% prediction region in a summary ROC plot if a diagnostic meta-analysis was conducted. If between 2 and 3 studies, inconsistency was assessed by visual inspection of the point estimates of sensitivity and specificity. If only one study, then inconsistency is not applicable

[3], Indirectness was assessed using the QUADAS-2 checklist items referring to applicability

[4], The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest as a false negative - missing malignancy - risks a potentially avoidable death, whilst a false positive - indicating malignancy when there is none - risks potentially avoidable surgery or other treatment such as chemotherapy. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise

[5], positive and negative likelihood ratios calculated from raw diagnostic test accuracy data if not already reported; 95% CIs calculated using log method (see Chapter 4.3.3.2.2 for details).

[6] Unclear risk of review bias (lack of blinding in the interpretation both of the index test and reference standard – no details are given in the text), unclear risk of verification bias (not all patients received the same reference test).

Table 21: Summary of clinical evidence for EUS-FNA cytology to detect malignancy in people with jaundice

Studies	N	Risk of bias[1]	Inconsistency[2]	Indirectness[3]	Imprecision[4]	Point estimates of sensitivity (95% CI)	Point estimates of specificity (95% CI)	Positive likelihood ratio (95% CI)[5]	Negative likelihood ratio (95% CI)[5]	Quality
Diagnostic test accuracy										
5 retrospective cohort studies	691	Serious[6]	Serious[7]	Not serious	Not serious	0.85 (0.79-0.90)	0.96 (0.86-0.99)	22.0 (5.81-84.75)	0.15 (0.11-0.22)	LOW
Procedure-related complications						Details of complications				
Tummala et al. 2013	342	Very serious[8]	Not serious	Not serious	Not serious	1 case of acute pancreatitis requiring hospitalization for 3 days; 1 case aspiration pneumonia requiring oral antibiotics				LOW

[1] *Risk of bias was assessed using the QUADAS-2 checklist;*

[2], *Inconsistency was assessed by inspection of the 95% prediction region in a summary ROC plot if a diagnostic meta-analysis was conducted. If between 2 and 3 studies, inconsistency was assessed by visual inspection of the point estimates of sensitivity and specificity. If only one study, then inconsistency is not applicable*

[3], *Indirectness was assessed using the QUADAS-2 checklist items referring to applicability;*

[4], *The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest as a false negative - missing malignancy - risks a potentially avoidable death, whilst a false positive - indicating malignancy when there is none - risks potentially avoidable surgery or other treatment such as chemotherapy. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise;*

[5], *positive and negative likelihood ratios from meta-analysis.*

[6], *There were 4 suspicious exclusions in one study (Ross et al., 2008). Furthermore there was potential risk review bias (lack of blinding in the interpretation both of the index test and reference standard) and unclear risk of verification bias in all studies;*

[7] *95% prediction region was very wide and ranged from 0 to 1.0 along the sensitivity axis and from 0.2 to 1.0 along the specificity axis (i.e. if the model is correct, there is probability of 0.95 that a future study will have sensitivity and specificity within these regions);*

[8], *Very high risk of selection and performance bias.*

Table 22: Summary of clinical evidence for ERCP + brushings of biliary strictures to detect malignancy in people with jaundice

Studies	N	Risk of bias[1]	Inconsistency[2]	Indirectness[3]	Imprecision[4]	Point estimates of sensitivity (95% CI)	Point estimates of specificity (95% CI)	Positive likelihood ratio (95% CI)[5]	Negative likelihood ratio (95% CI)[5]	Quality
Oppong et al. 2010	39	Serious [6]	Not applicable	Not serious	Serious[7]	0.65 (0.46-0.80)	1.0 (0.48- 1.0)	7.71 (0.54-110.87)[8]	0.35 (0.22-0.56)	LOW
Ross et al. 2008	50	Very serious[9]	Not applicable	Not serious	Not serious	0.13 (0.04-0.31)	1.0 (0.83- 1.0)	6.1 (0.35-107.4)	0.87 (0.75-1.0)	LOW
Overall	89	Very serious [10]	Serious[11]	Not serious	Serious					VERY LOW

[1] Risk of bias was assessed using the QUADAS-2 checklist;

[2], Inconsistency was assessed by inspection of the 95% prediction region in a summary ROC plot if a diagnostic meta-analysis was conducted. If between 2 and 3 studies, inconsistency was assessed by visual inspection of the point estimates of sensitivity and specificity. If only one study, then inconsistency is not applicable;

[3], Indirectness was assessed using the QUADAS-2 checklist items referring to applicability;

[4], The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest as a false negative - missing malignancy - risks a potentially avoidable death, whilst a false positive - indicating malignancy when there is none - risks potentially avoidable surgery or other treatment such as chemotherapy. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise;

[5], positive and negative likelihood ratios calculated from raw diagnostic test accuracy data if not already reported; 95% CIs calculated using log method (see Chapter 4.3.3.2.2 for details).

[6], Unclear risk of review bias (lack of blinding in the interpretation both of the index test and reference standard – no details are given in the text), unclear risk of verification bias (not all patients received the same reference test); g, 95% CI of sensitivity crosses 0.75;

[7], 95% CI of sensitivity crosses 0.75

[8], since the specificity was 1, a continuity correction of 0.5 was added to all cells to enable calculation of the positive likelihood ratio and related 95% CIs.

[9], There were 4 suspicious aspirates that were excluded from analysis and not considered as either diagnostic or false negative. Furthermore there was potential risk review bias (lack of blinding in the interpretation both of the index test and reference standard), and unclear risk of verification bias (not all patients received the same reference test);

[10], Ross et al. 2008 contributes more than 50% of the sample;

[11], *sensitivity estimates range from 0.13 to 0.65.*

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5.1.5 Economic evidence

A literature review of published cost effectiveness analyses did not identify any relevant studies for this topic. Although there were potential implications for resource use associated with making recommendations in this area, other topics in the guideline were agreed as a higher economic priority. Consequently, bespoke economic modelling was not done for this topic.

5.1.6 Evidence Statements

5.1.6.1 Spiral CT

Diagnostic accuracy

Low quality evidence from 1 retrospective observational study (n=47) found that spiral CT had a low sensitivity of 0.67 (95% CI, 0.51-0.8) and high specificity of 1.0 (95% CI, 0.16-1.0) in detecting malignancy in pancreatic cancer patients with obstructive jaundice. The positive likelihood ratio of 3.98 (95% CI, 0.31-50.34) suggests that a positive result for malignancy is not particularly useful for ruling it in, though there is uncertainty in the estimate. The negative likelihood ratio of 0.33 (95% CI, 0.22-0.50) suggests that a negative result for malignancy is not particularly useful for and ruling it out.

Adverse events

No evidence was identified to inform this outcome

5.1.6.2 EUS

Diagnostic accuracy

Moderate quality evidence from 1 retrospective observational study (n=47) people found that EUS had high sensitivity of 1.0 (95% CI, 0.92-1.0) and low specificity of 0.5 (95%CI, 0.01-0.99) in detecting malignancy in pancreatic cancer patients with obstructive jaundice. The positive likelihood ratio of 2.0 (95% CI, 0.5-8.0) suggests that a positive result for malignancy is not particularly useful for ruling it in, though there is uncertainty in the estimate. The negative likelihood ratio of 0 suggests that a negative result for malignancy is very useful for ruling it out.

Adverse events

No evidence was identified to inform this outcome

5.1.6.3 EUS-FNA cytology

Diagnostic accuracy

Low quality evidence from a meta-analysis of 5 retrospective observational studies (n=691) found that EUS-FNA-based cytology had a moderate sensitivity of 0.85 (95% CI, 0.79-0.9) and a high specificity of 0.96 (95% CI, 0.86-0.99) in detecting malignancy in pancreatic cancer patients with obstructive jaundice. The positive likelihood ratio of 22.2 (95% CI, 5.81-84.75) suggests that a positive result for malignancy is very useful for ruling it in, though there is uncertainty in the estimate. The negative likelihood ratio of 0.15 (95% CI, 0.11-0.22) suggests that a negative result for malignancy is moderately useful for ruling it out, though there is uncertainty in the estimate.

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Adverse events

Low quality evidence from 1 retrospective observational study (n=342 with resectable pancreatic cancer) found that there were 2 overall complications related to the EUS-FNA procedure: 1 patient had acute pancreatitis requiring hospitalization for 3 days and another patient had aspiration pneumonia requiring oral antibiotics.

5.1.6.4 ERCP + Brushings of biliary strictures

Diagnostic accuracy

Low to very low quality evidence from 2 retrospective observational studies with (n=39; n=50) found that ERCP plus brushings of biliary strictures had a low sensitivity, ranging from 0.13 to 0.65 and a high specificity of 1.0 (in both studies) in detecting malignancy in pancreatic cancer patients with obstructive jaundice. The positive likelihood ratios ranged from 7.71 (95% CI, 0.54-110.87) to 6.1 (95% CI, 0.35-107.4) suggesting that a positive result for malignancy is moderately useful for ruling it in, though there is uncertainty in the estimates. The negative likelihood ratios ranged from 0.35 (95% CI, 0.22-0.56) to 0.87 (95% CI, 0.75-1.0) suggesting that a negative result for malignancy is not particularly useful for ruling it out.

Adverse events

No evidence was identified to inform this outcome

5.1.7 Recommendations

1. **For people with obstructive jaundice and suspected pancreatic cancer, use a pancreatic protocol CT scan before draining the bile duct.**

2. **If the diagnosis is still unclear, offer endoscopic ultrasound (EUS) and EUS-guided tissue sampling.**

3. **Take a biliary brushing for cytology if:**
   - endoscopic retrograde cholangiopancreatography (ERCP) is being used to relieve the biliary obstruction and
   - there is no tissue diagnosis.

5.1.8 Evidence to recommendations

5.1.8.1 Relative value placed on the outcomes considered

Diagnostic accuracy (sensitivity, specificity, positive predictive value and negative predictive value) and adverse events were considered the critical outcomes for this question. Diagnostic accuracy was reported for all comparisons of interest. Adverse events were only reported for EUS-FNA.

5.1.8.2 Quality of evidence

Evidence was identified on the diagnostic accuracy of spiral CT, EUS, EUS-FNA cytology and ERCP plus brushings of biliary strictures. The quality of the evidence for ERCP plus brushings of biliary strictures ranged from very low to low, for spiral CT and EUS-FNA cytology was low and for EUS was moderate.

The committee noted that all studies had either a serious or a very serious risk of bias due to different reference standards being used across the study sample; a lack of blinding; the test

being evaluated being included in the reference standard (potentially leading to an overestimation of test accuracy); people inappropriately excluded from the analysis.

The committee also noted that all patients had either imaging or ERCP in order to get into these studies –the quality of this imaging could have had an effect on the accuracy results. In addition the data for spiral CT were very old as the paper was from 2004. The committee considered that the accuracy of CT was likely to be better than reported by these data as the technology has advanced significantly since that time. They also agreed that CT was able to image the entire body which would be beneficial in these patients and therefore made a strongly worded recommendation.

The committee noted that adverse event data were only found for EUS-FNA. Based on their clinical knowledge and experience, that there is a relatively low occurrence of adverse events with this procedure, the committee did not apply much weight to this data when making recommendations.

No evidence was found on the diagnostic accuracy of CA19-9 or CT-guided biopsy in diagnosing pancreatic cancer in people with jaundice. Therefore no recommendations were made about these investigations. No further research was recommended since these were not considered high priorities for research funding.

5.1.8.3 Consideration of clinical benefits and harms

The evidence showed that CT had high specificity for detecting pancreatic cancer but low sensitivity whilst EUS had low specificity but high sensitivity. Based on their clinical experience and knowledge the committee noted that a CT scan was a less invasive technique and was able to identify metastases, which EUS could not do. They therefore recommended CT as the first investigation to diagnose pancreatic cancer in someone with obstructive jaundice.

Based on their clinical knowledge and experience, the committee noted that if a CT scan is used pancreatic protocol CT scan would be needed to ensure good visualisation of any pathology in the pancreas. They also noted, based on their knowledge and experience, that if biliary drainage was performed to relieve the jaundice before the CT scan was conducted, this would detrimentally affect the interpretation of the CT scan. They therefore agreed that the CT scan should be conducted before biliary drainage.

The committee agreed that EUS was the next best test if the diagnosis remains unclear after CT scan. They recommended EUS with tissue sampling as the tissue sample would be needed to confirm the diagnosis and taking it at the same time would reduce the need for repeated tests which would be more acceptable to patients.

The committee noted that the evidence for ERCP plus brushings of biliary strictures showed high specificity but relatively low sensitivity and was of very low or low quality. They therefore agreed not to make any recommendation about whether ERCP should be performed or not. However, the committee noted, based on their knowledge and experience, that some people who are deeply jaundiced or who are unfit for surgery will have an ERCP to relieve the obstruction that is causing the jaundice before they have a tissue diagnosis. Brushings of biliary strictures taken during the ERCP will give further diagnostic information which will inform treatment. They therefore agreed to recommend biliary brushing to obtain cytology if an ERCP is being performed and there is no tissue diagnosis. The committee agreed that despite the low quality of the evidence, this should be a strong recommendation because having the diagnostic information provided by the brushings was essential, and in this group it could only be obtained by biliary brushings.

The potential benefits of the recommendations made were considered to be a more efficient pathway to diagnosis for people with obstructive jaundice which optimises non-invasive investigations and a reduction in the need for multiple diagnostic investigations. The potential

harms were complications associated with the use of EUS and ERCP. However, as these complication rates are low the potential benefits were considered to outweigh the potential harms.

5.1.8.4 Consideration of economic benefits and harms

The committee noted that no relevant published economic evaluations had been identified and no additional economic analysis had been undertaken in this area.

The tests recommended are already being done as part of current practice so there are unlikely to be any significant resource implications associated with these recommendations. There may be some cost savings from refining the diagnostic pathway and reducing the requirement for repeat investigations.

5.1.8.5 Other considerations

The committee were aware that an HTA report was likely to include evidence relevant to this section of the guideline. However, the final report was not published when this guideline went out for consultation. It was agreed that if the report was published in time, the committee would review it after the guideline consultation, and amend the recommendations if needed.

5.1.9 References

Agarwal B, Abu-Hamda E, Molke KL et al. (2004) Endoscopic ultrasound-guided fine needle aspiration and multidetector spiral CT in the diagnosis of pancreatic cancer. American Journal of Gastroenterology 99(5): 844-50

Kim JJ, Walia S, Lee SH et al. (2015) Lower yield of endoscopic ultrasound-guided fine-needle aspiration in patients with pancreatic head mass with a biliary stent. Digestive diseases and sciences 60(2): 543-549

Oppong K, Raine D, Nayar M et al. (2010) EUS-FNA versus biliary brushings and assessment of simultaneous performance in jaundiced patients with suspected malignant obstruction. Journal of the Pancreas 11(6): 560-567

Ross WA, Wasan SM, Evans DB et al. (2008) Combined EUS with FNA and ERCP for the evaluation of patients with obstructive jaundice from presumed pancreatic malignancy. Gastrointestinal endoscopy 68(3): 461-466

Tummala P, Munigala S, Eloubeidi MA et al. (2013) Patients with obstructive jaundice and biliary stricture±mass lesion on imaging: prevalence of malignancy and potential role of EUS-FNA. Journal of clinical gastroenterology 47(6): 532-537

5.2 People without jaundice but with a pancreatic abnormality

Review question: What is the most effective diagnostic pathway (imaging +/-CA 19–9, biopsy (cytology or histology)) for adults with suspected pancreatic cancer in secondary care who do not have jaundice but have a pancreatic abnormality on imaging?

5.2.1 Introduction

The availability and use of imaging, both ultrasound and CT, continues to increase in clinical practice and, as a consequence, incidental lesions are detected with increasing frequency. Incidental lesions in the pancreas, both solid and cystic, in asymptomatic people are a common finding. There is no consensus as to the most appropriate pathway to establish an accurate diagnosis in this patient group.

Pancreatic CT scanning is regarded as the mainstay of the imaging pathway, but the role of pancreatic MRI and CT-PET, although not well defined, is increasing.

In addition, the role of both cytology and histology and the best method of obtaining tissue to confirm the diagnosis has not been established. Imaging may also reveal metastatic disease, which could be sampled to help establish the diagnosis.

Guidance is needed on the most effective diagnostic pathway to identify pancreatic cancer in people who have a pancreatic abnormality on imaging.

5.2.1.1 Review protocol summary

The review protocol summary used for this question can be found in Table 23. Full details of the review protocol can be found in Appendix C.

Table 23: Clinical review protocol summary for the review of the most effective diagnostic pathway for people with suspected pancreatic cancer who do not have jaundice but have a pancreatic abnormality on imaging

Population	Adults suspected of having pancreatic cancer who do not have jaundice but have a pancreatic abnormality on imaging
Index Test	• Imaging +/- CA 19–9 • Ultrasound • CT • MRI • PET-CT • Biopsy (cytology or histology) • EUS +/- FNA • EUS +/- Core biopsy • Percutaneous liver biopsy • Laparoscopy + biopsy • Percutaneous pancreatic biopsy
Reference Standard	• Definitive diagnosis (preferably Pathological diagnosis) • Each other
Outcomes	• Diagnostic Accuracy including: • Sensitivity • Specificity • Positive Predictive Value • Negative Predictive Value • Adverse events

5.2.2 Description of clinical evidence

Twenty-one articles reporting a total of 32 datasets were identified: 3 of these were RCTs (Bang et al. 2012; Lee et al. 2014; Ramesh et al. 2015), 13 were prospective cohort studies (Bournet et al. 2015; Bournet et al. 2009; Fabbri et al. 2011; Harewood & Wiersema 2002; Iglesias-Garcia et al. 2007; Kliment et al. 2010; Krishna et al. 2009; Mishra et al. 2006; Seicean et al. 2016; Strand et al. 2014; Touchefeu et al. 2009; Wakatsuki et al. 2005; Wittman et al. 2006) and 5 were retrospective cohort studies (Fritscher-Ravens et al. 2002; Hikichi et al. 2009; Tamm et al. 2007; Yang et al. 2015; Yusuf et al. 2009). A summary of the included studies is presented in Table 24.

The majority of the studies examined the diagnostic test accuracy of EUS-FNA for detecting malignancy in patients with suspected pancreatic cancer due to a solid lesion identified through previous imaging (e.g. EUS, CT, MRI, ERCP). The majority of the studies reported

sensitivity and specificity, as well as positive/negative predictive value. Three articles (Hikichi et al. 2009; Ramesh et al. 2015; Yusuf et al. 2009) contributed two sets of data to the review on EUS-FNA. The majority of the studies also used a composite 'gold standard' reference test generally comprised of histo-/cyto-pathology from surgery, and subsequent clinical and imaging follow-up results. The majority of the studies also reported that there were no procedure-related adverse events, serious or otherwise. No studies were found that examined percutaneous liver biopsy, laparoscopy + biopsy.

One single centre retrospective cohort study (n=117) examined the diagnostic accuracy of multidetector CT (Tamm et al. 2007) in detecting malignancy in solid lesions initially identified through imaging.

Two single centre cohort studies (n=330) – one prospective (n=213; Krishna et al. 2009) and one retrospective (n=117; Tamm et al. 2007) - examined the diagnostic accuracy of EUS in detecting malignancy in solid lesions initially identified through imaging. The sample in Krishna et al. (2009) had a low prevalence of malignant lesions (0.52) and included 15% patients whose lesions were revealed to be cystic by EUS-FNA.

Twenty-two datasets (n=2869) from 19 studies - 3 RCTs (Bang et al. 2012; Lee et al. 2014; Ramesh et al. 2015) and 16 (11 prospective and 5 retrospective) cohort studies - examined the diagnostic accuracy of EUS-FNA in detecting malignancy in solid lesions initially identified through imaging (Bournet et al. 2009, 2015; Fabbri et al. 2011; Fritscher-Ravens et al. 2002; Harewood & Wiersema 2002; Hikichi et al. 2009; Iglesias-Garcia et al. 2007; Kliment et al. 2010; Krishna et al. 2009; Mishra et al. 2006; Seicean et al. 2016; Tamm et al. 2007; Touchefeu et al. 2009; Wakatsuki et al. 2005; Wittman et al. 2006; Yusuf et al. 2009). The majority of these studies used a 22-gauge needle to extract a cytological specimen. The number of included studies (≥4) allowed a meta-analysis of the diagnostic test accuracy data to be performed, which produces a summary point estimate of the sensitivity and specificity of EUS-FNA. Although there was not sufficient data to examine heterogeneity for covariates such as needle type and type of reference test, a subgroup analysis by type of study (RCT/prospective cohort vs retrospective cohort) was conducted.

Four studies (n=158) - 2 RCTs (Bang et al. 2012; Lee et al. 2014) and two prospective cohort studies (Strand et al. 2014; Wittman et al. 2006) - examined the diagnostic accuracy of EUS-core biopsy in detecting malignancy in solid lesions initially identified through imaging. The number of included studies (≥4) allowed a meta-analysis of the diagnostic test accuracy data to be performed, which produces a summary point estimate of the sensitivity and specificity of EUS-core biopsy. The two RCTs, which randomised participants to receive either EUS-FNA or EUS-core, both used fine biopsy (ProCore) needles (EUS-FNB), whilst the cohort studies used either FNB (Strand et al. 2014) or trucut (Wittman et al. 2006) biopsy needles (EUS-TNB).

One prospective cohort study (n=36) examined the diagnostic accuracy of combining EUS-FNA with EUS-Core (Wittman et al. 2006).

One multicentre retrospective cohort study (n=60) examined the diagnostic accuracy of percutaneous US-guided core in detecting malignancy in solid lesions initially identified through imaging (Yang et al. 2015).

One multicentre retrospective cohort study (n=15) examined the diagnostic accuracy of percutaneous US-guided FNA + core in detecting malignancy in solid lesions initially identified through imaging (Yang et al. 2015).

Positive and likelihood ratios were calculated, where appropriate, from the sensitivity and specificity of the studies to enable evaluation of the relevant tests. The QUADAS-2 checklist was used to evaluate the risk of bias and indirectness (applicability) of the studies.

5.2.3 Summary of included studies

A summary of the studies that were included in this review is presented in Table 24.

Table 24: Summary of included studies

Study ID	Population	Study design Country	Index test	Reference standard	Outcomes	Overall risk of bias (ROB)/ Indirectness (ROA) (High/Low/Unclear)
Bang et al. 2012	56 consecutive patients with solid lesion	RCT USA	EUS-FNA EUS-Core (FNB)	Histology	Sensitivity Specificity	ROB: LOW ROA: LOW
Bournet, Selves et al. 2015	186 consecutive patients with suspected solid lesion	Prospective cohort France	EUS-FNA	Clinical follow up (including subsequent imaging and surgery)	Sensitivity Specificity	ROB: LOW ROA: LOW
Bournet, Souque et al. 2009	178 consecutive patients with suspected solid lesion	Prospective cohort France	EUS-FNA	Clinical follow up (including subsequent imaging and cytopathology)	Sensitivity Specificity	ROB: LOW ROA: LOW
Fabbri et al. 2011	50 consecutive patients with solid lesion	Prospective cohort Italy	EUS-FNA	Surgery, death from disease or clinical/imaging follow up	Sensitivity Specificity	ROB: HIGH ROA: LOW
Fritscher-Ravens et al. 2002	207 consecutive patients with solid lesion	Retrospective cohort Germany	EUS-FNA	Histology, bacteriology, or clinical follow up	Sensitivity Specificity	ROB: LOW ROA: LOW
Harewood et al. 2002	185 consecutive patients with suspected or known solid lesion	Prospective cohort USA	EUS-FNA	Surgical pathology, cytology, and clinical course + sequential radiological imaging	Sensitivity Specificity	ROB: LOW ROA: LOW
Hikichi et al. 2009	73 consecutive patients with solid lesion	Retrospective cohort Japan	EUS-FNA	Surgery, autopsy, or >12 months clinical follow up	Sensitivity Specificity	ROB: LOW ROA: LOW

Study ID	Population	Study design Country	Index test	Reference standard	Outcomes	Overall risk of bias (ROB)/ Indirectness (ROA) (High/Low/Unclear)
Iglesias-Garcia et al. 2007	62 consecutive patients with solid lesion	Prospective cohort Spain	EUS-FNA	Surgery or clinical follow up (including subsequent imaging and biochemical evaluation)	Sensitivity Specificity	ROB: LOW ROA: LOW
Kliment et al. 2010	207 consecutive patients with solid lesion	Prospective cohort Czech Republic	EUS-FNA	Histology from resection, or clinical/imaging follow up >6 months	Sensitivity Specificity	ROB: LOW ROA: LOW
Krishna et al. 2009	213 consecutive patients with solid lesion	Prospective cohort USA	EUS EUS-FNA	Definitive cytology, surgical pathology, and >12 months follow up.	Sensitivity Specificity	ROB: LOW ROA: LOW
Lee et al. 2014	118 consecutive patients with solid lesion	RCT South Korea	EUS-FNA EUS-Core (FNB)	Surgery or clinical/imaging follow up	Sensitivity Specificity	ROB: LOW ROA: LOW
Mishra et al. 2006	52 consecutive patients with solid lesion	Prospective cohort USA	EUS-FNA	Cytology on EUS-FNA or CT-guided biopsy and clinical follow up, or surgical exploration with intraoperative biopsy	Sensitivity Specificity	ROB: LOW ROA: LOW
Ramesh et al. 2015	100 consecutive patients with suspected solid lesion	Multicentre RCT USA	EUS-FNA with 19-gauge needle EUS-FNA with 22-gauge needle	Histology	Sensitivity Specificity	ROB: LOW ROA: LOW
Seicean et al. 2016	118 consecutive patients with solid lesion	Prospective cohort Romania	EUS-FNA	EUS-FNA core biopsy (follow up EUS-FNA if inconclusive), hepatic biopsy, or >6 months clinical follow up (including repeated CT-EUS if needed)	Sensitivity Specificity	ROB: LOW ROA: LOW

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Study ID	Population	Study design Country	Index test	Reference standard	Outcomes	Overall risk of bias (ROB)/ Indirectness (ROA) (High/Low/Unclear)
Strand et al. 2014	32 consecutive patients with suspected solid lesion	Prospective cohort USA	EUS-FNB	EUS-FNA cytology	Sensitivity Specificity	ROB: UNCLEAR ROA: HIGH
Tamm et al. 2007	117 consecutive patients with solid lesion	Retrospective cohort USA	MDCT EUS EUS-FNA	Histopathology on biopsy or surgery samples, or >9 months clinical follow up	Sensitivity Specificity	ROB: LOW ROA: LOW
Touchefeu et al. 2009	90 consecutive patients with solid lesion	Prospective cohort France	EUS-FNA	Histology on surgery samples or clinical/imaging follow up	Sensitivity Specificity	ROB: HIGH ROA: LOW
Wakatsuki et al. 2005	83 consecutive patients with solid lesion	Retrospective cohort Japan	EUS-FNA	Surgery, autopsy or >6 months follow up	Sensitivity Specificity	ROB: LOW ROA: LOW
Wittman et al. 2006	83 consecutive patients with solid lesion	Prospective cohort UK	EUS-FNA EUS-Core (Trucut needle) EUS-FNA+Core	Cytology, histology, surgery, or clinical follow up	Sensitivity Specificity	ROB: LOW ROA: LOW
Yang et al. 2015	88 consecutive patients with solid lesion	Retrospective cohort Canada	Percutaneous US-guided Core Percutaneous US-guided FNA Percutaneous US-guided Core + FNA	Surgical pathology or clinical follow up	Sensitivity Specificity	ROB: LOW ROA: LOW
Yusuf et al. 2009	N=540 consecutive patients with suspected PC due to	Retrospective cohort USA	EUS-FNA with 22-gauge needle	Surgical histopathology or long-term follow up	Sensitivity Specificity	ROB: LOW ROA: LOW

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Study ID	Population	Study design Country	Index test	Reference standard	Outcomes	Overall risk of bias (ROB)/ Indirectness (ROA) (High/Low/Unclear)
	solid mass (22-gauge needle) N=302 consecutive patients with suspected PC due to solid mass (25-gauge needle)		EUS-FNA with 25-gauge needle			

5.2.4 Clinical evidence profile

The clinical evidence profiles for this review question are presented in Table 25 to Table 32.

5.2.4.1 Computed tomography

Table 25: Summary of clinical evidence for computed tomography to detect malignancy in people without jaundice but who have a pancreatic abnormality on imaging

Study	N	Risk of bias[1]	Inconsistency[2]	Indirectness[3]	Imprecision[4]	Point estimates of sensitivity (95% CI)	Point estimates of specificity (95% CI)	Positive likelihood ratio (95% CI)[5]	Negative likelihood ratio (95% CI)[5]	Quality
Tamm et al. 2007	117	Not serious	Not applicable	Not serious	Not serious	0.97 (0.91-0.99)	0.72 (0.46-0.89)	3.49 (1.66-7.36)	0.04 (0.01-0.13)	HIGH

[1] *risk of bias evaluated using risk of bias items of QUADAS-2 checklist;*

[2], *Inconsistency was assessed by inspection of the 95% prediction region in a summary ROC plot if a diagnostic meta-analysis was conducted. If between 2 and 3 studies, inconsistency was assessed by visual inspection of the point estimates of sensitivity and specificity. If only one study, then inconsistency is not applicable;*

[3], *indirectness was evaluated using the applicability items of QUADAS-2;*

[4], *judgement of imprecision was based on consideration of the 95% CIs of test sensitivity as this was considered to be the primary measure of interest as a false negative - missing malignancy - risks a potentially avoidable death, whilst a false positive - indicating malignancy when there is none - risks potentially avoidable surgery or other treatment such as chemotherapy. Studies were considered to be of high sensitivity (and not imprecise) if the 95% CI was above 0.9 or of low sensitivity if it was below 0.75. Studies were assessed as subject to serious imprecision if the 95% CI crossed either 0.75 or 0.9, or subject to very serious imprecision if it crossed both 0.75 and 0.9.*

[5], positive and negative likelihood ratios calculated from raw diagnostic test accuracy data if not already reported; 95% CIs calculated using log method (see Chapter 4.3.3.2.2 for details).

5.2.4.2 Endoscopic ultrasonography (EUS)

5.2.4.2.1 EUS

Table 26: Summary of clinical evidence for EUS to detect malignancy in people without jaundice but who have a pancreatic abnormality on imaging

Study	N	Risk of bias[1]	Inconsistency[2]	Indirectness[3]	Imprecision[4]	Point estimates of sensitivity (95% CI)	Point estimates of specificity (95% CI)	Positive likelihood ratio (95% CI)[5]	Negative likelihood ratio (95% CI)[5]	Quality
Krishna et al. 2009	213	Not serious	Not serious	Serious[6]	Not serious	1.0 (0.97-1.0)	0.66 (0.57-0.75)	2.94 (2.25-3.85)	0	MODERATE
Tamm et al. 2007	117	Not serious	Not serious	Not serious	Not serious	0.99 (0.94-0.99)	0.5 (0.27-0.73)	1.98 (1.25-3.14)	0.02 (0-0.15)	HIGH
Overall	330	Not serious	Not serious	Serious[7]	Not serious					MODERATE

[1] risk of bias evaluated using risk of bias items of QUADAS-2 checklist;

[2], Inconsistency was assessed by inspection of the 95% prediction region in a summary ROC plot if a diagnostic meta-analysis was conducted. If between 2 and 3 studies, inconsistency was assessed by visual inspection of the point estimates of sensitivity and specificity. If only one study, then inconsistency is not applicable;

[3], indirectness was evaluated using the applicability items of QUADAS-2;

[4], judgement of imprecision was based on consideration of the 95% CIs of test sensitivity as this was considered to be the primary measure of interest as a false negative - missing malignancy - risks a potentially avoidable death, whilst a false positive - indicating malignancy when there is none - risks potentially avoidable surgery or other treatment such as chemotherapy. Studies were considered to be of high sensitivity (and not imprecise) if the 95% CI was above 0.9 or of low sensitivity if it was below 0.75. Studies were assessed as subject to serious imprecision if the 95% CI crossed either 0.75 or 0.9, or subject to very serious imprecision if it crossed both 0.75 and 0.9;

[5], positive and negative likelihood ratios calculated from raw diagnostic test accuracy data if not already reported; 95% CIs calculated using log method (see Chapter 4.3.3.2.2 for details).

[6], although Krishna et al. 2009 excluded patients whose lesions appeared to be cystic on CT or MRI, the sample included 33 participants (15% of analysed sample) whose focal lesions were found to be cystic by EUS-FNA;

[7], Krishna et al. 2009 contributes more than 50% of the total sample.

1*5.2.4.2.2 EUS-FNA*

Table 27: Summary of clinical evidence for EUS-FNA to detect malignancy in people without jaundice but who have a pancreatic abnormality on imaging

Studies	N	Risk of bias[1]	Inconsistency[2]	Indirectness[3]	Imprecision[4]	Pooled Sensitivity (95% CI)	Pooled Specificity (95% CI)	Positive likelihood ratio (95% CI)[5]	Negative likelihood ratio (95% CI)[5]	Quality
22 datasets (3 RCTs and 16 observational cohort)[6]	2869	Not serious[7]	Serious[8]	Not serious	Not serious	0.89 (0.85-0.92)	0.99 (0.96-1.0)	121.03 (20.64-709.55)	0.11 (0.08-0.15)	MODERATE

[1], risk of bias evaluated using QUADAS-2 checklist;

[2], Inconsistency was assessed by inspection of the 95% prediction region in a summary ROC plot if a diagnostic meta-analysis was conducted. If between 2 and 3 studies, inconsistency was assessed by visual inspection of the point estimates of sensitivity and specificity. If only one study, then inconsistency is not applicable;

[3], indirectness was evaluated using the applicability items of QUADAS-2;

[4], judgement of imprecision was based on consideration of the 95% CIs of test sensitivity as this was considered to be the primary measure of interest as a false negative - missing malignancy - risks a potentially avoidable death, whilst a false positive - indicating malignancy when there is none - risks potentially avoidable surgery or other treatment such as chemotherapy. Studies were considered to be of high sensitivity (and not imprecise) if the 95% CI was above 0.9 or of low sensitivity if it was below 0.75. Studies were assessed as subject to serious imprecision if the 95% CI crossed either 0.75 or 0.9, or subject to very serious imprecision if it crossed both 0.75 and 0.9;

[5], positive and negative likelihood ratios calculated from meta-analysis;

[6], 11 prospective, and 7 retrospective, cohort studies;

[7], note that risk of bias for patient selection, index test, and flow and timing was low in all studies except for Fabbri et al. (2011) and Touchefeu et al. (2009), which both had high risk of bias for flow and timing; also, in all the studies it was unclear how long the period was between initial index and subsequent reference test, whilst in the majority of included studies, the same reference standard was not used;

[8], the 95% prediction region was very wide and ranged from approximately 0.58 to 0.97 along the sensitivity axis and approximately 0.2 to 1.0 along the specificity axis (i.e. if the model is correct, there is probability of 0.95 that a future study will have sensitivity and specificity within these regions).

Table 28: Pooled sensitivity and specificity of EUS-FNA by type of study

Parameter	Type of study		Significant difference between subgroups (t-value, p-value)[1]
	RCTs/prospective cohort (15 studies, n=1612)	Retrospective cohort (7 studies, n=1285)	
Pooled sensitivity (95% CI)	0.89	0.88	t=0.02, p=0.99

Parameter	Type of study		Significant difference between subgroups (t-value, p-value)[1]
	RCTs/prospective cohort (15 studies, n=1612)	Retrospective cohort (7 studies, n=1285)	
	(0.84-0.93)	(0.84-0.91)	
Pooled specificity (95% CI)	0.99 (0.91-1.0)	0.99 (0.97-1.0)	t=0, p=1.0
Positive likelihood ratio (95% CI)[2]	92.82 (9.29-927.71)	109.95 (25.14-480.83)	
Negative likelihood ratio (95% CI)[2]	0.11 (0.07-0.17)	0.12 (0.09-0.16)	

[1], Unpaired t-test to compare pooled estimates of RCTs and prospective cohort studies with retrospective cohort studies. Standard errors for each subgroup used to conduct t-test calculated from 95% confidence intervals;

[2], positive and negative likelihood ratios calculated from meta-analysis.

5.2.4.2.3 EUS-Core (FNB or TNB)

Table 29: Summary of clinical evidence for EUS-guided core biopsy (FNB or trucut) to detect malignancy in people without jaundice but who have a pancreatic abnormality on imaging

Study	N	Risk of bias[1]	Inconsistency[2]	Indirectness[3]	Imprecision[4]	Pooled Sensitivity (95% CI)	Pooled Specificity (95% CI)	Positive likelihood ratio (95% CI)[5]	Negative likelihood ratio (95% CI)[5]	Quality
4 studies (2 RCTs and 2 prospective cohort)	154	Not serious	Very serious[6]	Not serious	Very serious[7]	0.70 (0.3-0.93)	1.0 (0.03-1.0)	176.61 (0.02-1867693)[8]	0.3 (0.09-1.02)	VERY LOW

[1] risk of bias evaluated using QUADAS-2 checklist;

[2], Inconsistency was assessed by inspection of the 95% prediction region in a summary ROC plot if a diagnostic meta-analysis was conducted. If between 2 and 3 studies, inconsistency was assessed by visual inspection of the point estimates of sensitivity and specificity. If only one study, then inconsistency is not applicable;

[3], indirectness was evaluated using the applicability items of QUADAS-2;

[4], judgement of imprecision was based on consideration of the 95% CIs of test sensitivity as this was considered to be the primary measure of interest as a false negative - missing malignancy - risks a potentially avoidable death, whilst a false positive - indicating malignancy when there is none - risks potentially avoidable surgery or other treatment such as chemotherapy. Studies were considered to be of high sensitivity (and not imprecise) if the 95% CI was above 0.9 or of low sensitivity if it was below

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0.75. Studies were assessed as subject to serious imprecision if the 95% CI crossed either 0.75 or 0.9, or subject to very serious imprecision if it crossed both 0.75 and 0.9;

[5], positive and negative likelihood ratios calculated from meta-analysis

[6], the 95% prediction region was extremely wide and ranged from 0 to 1.0 along both the sensitivity and specificity axes. Note that the 2 RCTs have a much higher sensitivity and specificity than the 2 prospective cohort studies;

[7], 95% CI of sensitivity crosses both 0.75 and 1.0;

[8], since the specificity was 1, a continuity correction of 0.5 was added to all cells to enable calculation of the positive likelihood ratio and related 95% CIs.

5.2.4.2.4 EUS-FNA + Core

Table 30: Summary of clinical evidence for EUS-FNA + Core to detect malignancy in people without jaundice but who have a pancreatic abnormality on imaging

Study	N	Risk of bias[1]	Inconsistency[2]	Indirectness[3]	Imprecision[4]	Point estimates of sensitivity (95% CI)	Point estimates of specificity (95% CI)	Positive likelihood ratio (95% CI)[5]	Negative likelihood ratio (95% CI)[5]	Quality
Wittmann et al. 2006	36	Not serious	Not applicable	Not serious	Very serious[6]	0.76 (0.55-0.91)	1.0 (0.72-1.0)	18 (1.18-273.95)[7]	0.24 (0.12-0.48)	LOW

[1] risk of bias evaluated using risk of bias items of QUADAS-2 checklist;

[2], Inconsistency was assessed by inspection of the 95% prediction region in a summary ROC plot if a diagnostic meta-analysis was conducted. If between 2 and 3 studies, inconsistency was assessed by visual inspection of the point estimates of sensitivity and specificity. If only one study, then inconsistency is not applicable;

[3], indirectness was evaluated using the applicability items of QUADAS-2;

[4], judgement of imprecision was based on consideration of the 95% CIs of test sensitivity as this was considered to be the primary measure of interest as a false negative - missing malignancy - risks a potentially avoidable death, whilst a false positive - indicating malignancy when there is none - risks potentially avoidable surgery or other treatment such as chemotherapy. Studies were considered to be of high sensitivity (and not imprecise) if the 95% CI was above 0.9 or of low sensitivity if it was below 0.75. Studies were assessed as subject to serious imprecision if the 95% CI crossed either 0.75 or 0.9, or subject to very serious imprecision if it crossed both 0.75 and 0.9;

[5], positive and negative likelihood ratios calculated from raw diagnostic test accuracy data if not already reported; 95% CIs calculated using log method (see Chapter 4.3.3.2.2 for details).

[6], 95% CI of specificity crosses both 0.75 and 0.9 thresholds;

[7], since the specificity was 1, a continuity correction of 0.5 was added to all cells to enable calculation of the positive likelihood ratio and related 95% CIs.

Percutaneous ultrasonography

5.2.4.2.5 Percutaneous US-guided Core

Table 31: Summary of clinical evidence for percutaneous US-guided core to detect malignancy in people without jaundice but who have a pancreatic abnormality on imaging

Study	N	Risk of bias[1]	Inconsistency[2]	Indirectness[3]	Imprecision[4]	Point estimates of sensitivity (95% CI)	Point estimates of specificity (95% CI)	Positive likelihood ratio (95% CI)[5]	Negative likelihood ratio (95% CI)[5]	Quality
Yang et al. 2015	60	Not serious	Not applicable	Not serious	Serious[6]	0.93 (0.82-0.98)	1.0 (0.54-1.0)	12.85 (0.89-186-03)[7]	0.07 (0.03-0.19)	LOW

[1] risk of bias evaluated using risk of bias items of QUADAS-2 checklist;

[2], Inconsistency was assessed by inspection of the 95% prediction region in a summary ROC plot if a diagnostic meta-analysis was conducted. If between 2 and 3 studies, inconsistency was assessed by visual inspection of the point estimates of sensitivity and specificity. If only one study, then inconsistency is not applicable;

[3], indirectness was evaluated using the applicability items of QUADAS-2;

[4], judgement of imprecision was based on consideration of the 95% CIs of test sensitivity as this was considered to be the primary measure of interest as a false negative - missing malignancy - risks a potentially avoidable death, whilst a false positive - indicating malignancy when there is none - risks potentially avoidable surgery or other treatment such as chemotherapy. Studies were considered to be of high sensitivity (and not imprecise) if the 95% CI was above 0.9 or of low sensitivity if it was below 0.75. Studies were assessed as subject to serious imprecision if the 95% CI crossed either 0.75 or 0.9, or subject to very serious imprecision if it crossed both 0.75 and 0.9;

[5], positive and negative likelihood ratios calculated from raw diagnostic test accuracy data if not already reported; 95% CIs calculated using log method (see Chapter 4.3.3.2.2 for details).

[6], 95% CIs of sensitivity crosses 0.9 threshold

[7], since the specificity was 1, a continuity correction of 0.5 was added to all cells to enable calculation of the positive likelihood ratio and related 95% CIs.

1*5.2.4.2.6 Percutaneous US-guided FNA + Core*

Table 32: Summary of clinical evidence for percutaneous US-guided FNA + core to detect malignancy in people without jaundice but who have a pancreatic abnormality on imaging

Study	N	Risk of bias[1]	Inconsistency[2]	Indirectness[3]	Imprecision[4]	Point estimates of sensitivity (95% CI)	Point estimates of specificity (95% CI)	Positive likelihood ratio (95% CI)[5]	Negative likelihood ratio (95% CI)[5]	Quality
Yang et al. 2015	15	Not serious	Not applicable	Not serious	Very serious[6]	0.92 (0.64-1.0)	1.0 (0.16-1.0)	5.36 (0.42-67.71)[7]	0.08 (0.01-0.51)	LOW

[1], risk of bias evaluated using risk of bias items of QUADAS-2 checklist;

[2], Inconsistency was assessed by inspection of the 95% prediction region in a summary ROC plot if a diagnostic meta-analysis was conducted. If between 2 and 3 studies, inconsistency was assessed by visual inspection of the point estimates of sensitivity and specificity. If only one study, then inconsistency is not applicable;

[3], indirectness was evaluated using the applicability items of QUADAS-2;

[4], judgement of imprecision was based on consideration of the 95% CIs of test sensitivity as this was considered to be the primary measure of interest as a false negative - missing malignancy - risks a potentially avoidable death, whilst a false positive - indicating malignancy when there is none - risks potentially avoidable surgery or other treatment such as chemotherapy. Studies were considered to be of high sensitivity (and not imprecise) if the 95% CI was above 0.9 or of low sensitivity if it was below 0.75. Studies were assessed as subject to serious imprecision if the 95% CI crossed either 0.75 or 0.9, or subject to very serious imprecision if it crossed both 0.75 and 0.9;

[5], positive and negative likelihood ratios calculated from raw diagnostic test accuracy data if not already reported; 95% CIs calculated using log method (see Chapter 4.3.3.2.2 for details).

[6], 95% CIs of sensitivity crosses both 0.75 and 0.9 thresholds

[7], since the specificity was 1, a continuity correction of 0.5 was added to all cells to enable calculation of the positive likelihood ratio and related 95% CIs.

5.2.5 Economic evidence

A literature review of published cost effectiveness analyses did not identify any relevant studies for this topic. Although there were potential implications for resource use associated with making recommendations in this area, other topics in the guideline were agreed as a higher economic priority. Consequently, bespoke economic modelling was not done for this topic.

5.2.6 Evidence statements

5.2.6.1 Computed tomography

Diagnostic accuracy

Moderate quality evidence from 1 single centre retrospective cohort study (n=117) found that multidetector CT had a high sensitivity of 0.97 (95% CI, 0.91-0.99) and a low specificity of 0.72 (95% CI, 0.46-0.89) in detecting malignant incidental solid pancreatic lesions in adults with suspected pancreatic cancer. The positive likelihood ratio of 3.49 (1.66-7.36) suggests that a positive result for malignancy is not particularly useful for ruling it in, though there is uncertainty in the estimate. The negative likelihood ratio of 0.04 (95% CI, 0.01-0.13) suggests that a negative result for malignancy is very useful for ruling it out, though there is uncertainty in the estimate.

Adverse events

No evidence was identified to inform this outcome

5.2.6.2 Endoscopic ultrasonography

5.2.6.2.1 EUS

Diagnostic accuracy

Moderate to high quality evidence from 2 single centre cohort studies - one prospective (n=213) and one retrospective (n=117) - found that EUS had a high sensitivity ranging from 0.99 to 1.0 and low specificity ranging from 0.5 to 0.66 in detecting malignant incidental solid pancreatic lesions in adults with suspected pancreatic cancer. The positive likelihood ratios were 1.98 (95% CI, 1.25-3.14) and 2.94 (95% CI, 2.25-3.85) suggesting that a positive result for malignancy is not useful for ruling it in. The negative likelihood ratios were 0 and 0.02 (95% CI, 0-0.15) suggesting that a negative result for malignancy is very useful for ruling it out, though there is uncertainty in the latter estimate.

Adverse events

No evidence was identified to inform this outcome

5.2.6.2.2 EUS-FNA

Diagnostic accuracy

Moderate quality evidence from a meta-analysis of 22 studies (n=2869) found that endoscopic ultrasound fine needle aspiration had a moderate pooled sensitivity of 0.89 (95% CI, 0.85-0.92) and a high pooled specificity of 0.99 (95% CI, 0.96-1.0) in detecting malignant incidental solid pancreatic lesions in adults with suspected pancreatic cancer. The positive likelihood ratio of 121.03 (95%, 20.64-709.55) suggests that a positive result for malignancy

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is very useful for ruling it in. The negative likelihood ratio of 0.11 (0.08-0.15) suggests that a negative result for malignancy is moderately useful for ruling it out, though there is uncertainty in the estimate.

A subgroup analysis by study type (RCTs and prospective cohort studies vs retrospective cohort studies) showed that there was no significant difference between the two groups in the estimated pooled sensitivity (0.89 [95% CI, 0.84-0.93] vs 0.88 [95% CI, 0.84-0.91], respectively) and pooled specificity (0.99 [95% CI, 0.91-1.0] vs 0.99 [95% CI, 0.97-1.0], respectively), although there was more uncertainty in the pooled estimates from the RCT/prospective cohort study group. The similar positive likelihood ratios of 92.82 (95% CI, 9.29-927.71) and 109.95 (95% CI, 25.14-480.83) in the two subgroups support the conclusion above that a positive result for malignancy is very useful for ruling it in. Similarly, the negative likelihood ratios for the subgroups of 0.11 (95% CI, 0.07-0.17) and 0.12 (95% CI, 0.09-0.16) also support the conclusion above that a negative result for malignancy is moderately useful for ruling it out, though there is uncertainty in the estimates.

Adverse events

Fourteen studies (N=2123) reported data on adverse events with complication rates ranging from 0% to 4%. Nine studies reported that there were no adverse events, whilst the most common adverse event reported in the remaining 8 studies was mild pancreatitis (13 reported cases). Other reported adverse events included post-procedural pain (2 cases), bleeding and fever (one case each).

5.2.6.2.3 EUS-Core (FNB or trucut)

Diagnostic accuracy

Very low quality evidence from a meta-analysis of 4 studies (n=154) found that endoscopic ultrasound core biopsy had a low pooled sensitivity of 0.7 (95% CI, 0.3-0.93) and a high pooled specificity of 0.99 (95% CI, 0.03-1.0) in detecting malignant incidental solid pancreatic lesions in adults with suspected pancreatic cancer. The positive likelihood ratio of 176.61 (95% CI, 0.02-1867693) suggests that a positive result for malignancy is very useful for ruling it in, though there is substantial uncertainty in the estimate. The negative likelihood ratio of 0.3 (95% CI, 0.09-1.02) suggests that a negative result for malignancy is not particularly useful for ruling, though there is substantial uncertainty in the estimate.

Adverse events

The studies reported no serious procedure-related adverse events. The complication rate ranged from 0% to 5.2%. One study reported a case of mild acute pancreatitis that required hospitalisation for 2 days, and one study reported 2 cases of gastric haematoma and one case of mild bleeding.

5.2.6.2.4 EUS-FNA + Core

Diagnostic accuracy

Low quality evidence from one single-centre prospective cohort study (N=36) found that combining EUS-FNA with EUS-Core biopsy had a moderate sensitivity of 0.76 (95% CI, 0.55-0.91) and a high specificity of 1.0 (95% CI, 0.72-1.0) in detecting malignant incidental solid pancreatic lesions in adults with suspected pancreatic cancer. The positive likelihood ratio of 18 (95% CI, 1.18-273.95) suggests that a positive result for malignancy is very useful for ruling it in, though there is substantial uncertainty in the estimate. The negative likelihood ratio of 0.24 (95% CI, 0.12-0.48) suggests that a negative result for malignancy is not particularly useful for ruling it out, though there is uncertainty in the estimate.

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Adverse events

The study did not report any serious adverse events. There was a 3% complication rate with one case of moderate self-limiting abdominal pain (not requiring analgesia) after biopsy of a pancreatic tail lesion.

5.2.6.3 Percutaneous ultrasonography

5.2.6.3.1 Percutaneous US-guided Core

Diagnostic accuracy

Low quality evidence from one multicentre retrospective cohort study (n=60) found that percutaneous US-guided core biopsy had a high sensitivity of 0.93 (95% CI, 0.82-0.98) and a high specificity of 1.0 (95% CI, 0.54-1.0) in detecting malignant incidental solid lesions in adults with suspected pancreatic cancer. The positive likelihood ratio of 12.85 (95% CI, 0.89-186.03) suggests that a positive result for malignancy is very useful for ruling it in, though there is substantial uncertainty in the estimates. The negative likelihood ratio of 0.07 (95% CI, 0.03-0.19) suggests that a negative result for malignancy is very useful for ruling it out, though there is uncertainty in the estimates.

Adverse events

The study did not report any serious adverse events. There was a 3% complication rate with one case of haematoma and one case of pain, both reported immediately after the biopsy was taken.

5.2.6.3.2 Percutaneous US-guided FNA + Core

Diagnostic accuracy

Low quality evidence from one multicentre retrospective cohort study (n=15) found that percutaneous US-guided core biopsy combined with PUS-FNA had high sensitivity of 0.92 (95% CI, 0.64-1.0) and a high specificity of 1.0 (95% CI, 0.16-1.0) in detecting malignant incidental solid lesions in adults with suspected pancreatic cancer. The positive likelihood ratio of 5.36 (95% CI, 0.42-67.71) suggests that a positive result for malignancy is moderately useful for ruling it in, though there is substantial uncertainty in the estimates. The negative likelihood ratio of 0.08 (95% CI, 0.01-0.51) suggests that a negative result for malignancy is very useful for ruling it out, though there is substantial uncertainty in the estimates.

Adverse events

The study did not report any serious adverse events. There was a complication rate of 7% with one case of pain reported immediately after the biopsy was taken.

5.2.7 Recommendations

4. **Offer a pancreatic protocol CT scan to people with pancreatic abnormalities but no jaundice.**

5. **If the diagnosis is still unclear or if cytological or histological samples are needed, offer endoscopic ultrasound and EUS-guided tissue sampling.**

5.2.8 Evidence to recommendations

5.2.8.1 Relative value placed on the outcomes considered

Diagnostic accuracy (sensitivity, specificity, positive predictive value and negative predictive value) and adverse events were considered the critical outcomes for this question. Diagnostic accuracy was reported for all interventions of interest. Adverse events were reported for all interventions except CT and EUS.

5.2.8.2 Quality of evidence

Evidence was identified on the diagnostic accuracy of CT, EUS, EUS-FNA, EUS-core, EUS-FNA + core, percutaneous US-guided core and percutaneous US-guided FNA + core. The quality of the evidence for CT and EUS-FNA was moderate, for EUS was high, for all other investigations was either very low or low.

Given the low quality of the data for EUS-core, EUS-FNA + core, percutaneous US-guided core and percutaneous US-guided FNA + core, the committee were less certain of the balance between diagnostic accuracy and potential adverse events for these investigations. They, therefore, agreed to apply more weight to the investigations with moderate and high quality data. They did not make any recommendations about core biopsy by percutaneous routes.

No evidence was identified on percutaneous liver or pancreatic biopsy or laparoscopy + biopsy. Therefore, no recommendations were made about these investigations. No further research was recommended since these were not considered high priorities for research funding.

5.2.8.3 Consideration of clinical benefits and harms

The committee noted that of the investigations with moderate or high quality evidence, EUS had shown the highest sensitivity but the lowest specificity for diagnosing malignancy in a solid lesion suspected to be pancreatic cancer. Given that other investigations had similar sensitivities but better specificities, they agreed not to make a recommendation about EUS alone.

The committee noted, based on the evidence, that whilst the positive likelihood ratio for CT was not as good as that for EUS-FNA/FNB, CT had a better negative likelihood ratio. They also agreed, based on their knowledge and experience, that CT was more widely available than EUS-FNA and was non-invasive so the risk of adverse events was lower. Therefore, they agreed to recommend a CT scan as the first option in people with a solid lesion suspected to be pancreatic cancer as a ruling out test. Based on their clinical knowledge and experience, the committee noted that if a CT scan is used a pancreatic protocol CT scan would be needed to ensure good visualisation of any pathology in the pancreas.

The committee noted that EUS-guided tissue sampling can provide cytology or histology, which a CT scan is unable to do. Based on their knowledge and experience, the committee agreed that having cytology or histology would help to resolve diagnostic uncertainty, facilitate oncological management and is needed to enrol people in clinical trials. Therefore, based on the evidence and their knowledge, the committee agreed to recommend EUS-guided tissue sampling for those people whose CT scan was inconclusive. They were unable to specify whether FNA or FNB should be used for the tissue sampling as the evidence did not support recommending one method over another.

The committee considered that the potential benefits of the recommendations made would be more accurate diagnosis of pancreatic cancer in people with a solid lesion. The potential harms of the recommendations were the potential for complications associated with EUS-guided tissue sampling. However, the committee agreed that the benefits outweighed the

harms as tissue sampling was only recommended for a sub-set of the people being investigated.

5.2.8.4 Consideration of economic benefits and harms

The committee noted that no relevant published economic evaluations had been identified and no additional economic analysis had been undertaken in this area.

The committee agreed that there was unlikely to be a significant resource impact from the recommendations made as they are in line with the investigations that are currently used.

5.2.9 References

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5.3 Pancreatic Cysts

Review question: In adults with a pancreatic cyst, what is the diagnostic pathway to identify the cyst(s) at high risk of pancreatic malignancy?

5.3.1 Introduction

The diagnosis of pancreatic cysts continues to increase in frequency as more people undergo cross sectional imaging.

The morphological identification of a cyst is straightforward on both MRI and CT but the identification of the exact nature of the cystic lesion continues to present diagnostic difficulty.

Three broad groups of cystic lesions can be identified; definitely malignant, definitely benign and indeterminate. There are features on imaging that suggest a cyst is suspicious in nature, but often these are not definitive.

The presence of mucin within the cyst and the measurement of markers such as CEA and amylase can help determine whether a lesion is benign or pre-malignant, and the role of cytology and histology is important.

Several diagnostic pathways have been suggested within the literature but there remains inconsistency within the UK as to the most effective method for diagnosis.

Guidance is needed on the most effective diagnostic pathway to identify cysts at high risk of malignancy in people with pancreatic cysts.

5.3.1.1 Review protocol summary

The review protocol summary used for this question can be found in Table 33. Full details of the review protocol can be found in Appendix C.

Table 33: Clinical review protocol summary for the review of most effective diagnostic pathway to identify the cyst(s) at high risk of pancreatic malignancy

Population	Adults with pancreatic cysts
Index test	• CA 19–9, CEA – in serum and cyst fluid • Histology • Cytology • Imaging (MRI/MRCP, PET/CT, CT, Ultrasound, needle Confocal Laser Endomicroscopy, EUS+/-FNA)
Reference standard	• Definitive diagnosis (preferably pathological diagnosis) • Each Other
Outcomes	Diagnostic Accuracy including: • Sensitivity • Specificity • Positive Predictive Value • Negative Predictive Value • Adverse events

5.3.2 Description of Clinical Evidence

Thirty-three publications were included in this review: 2 of these were systematic reviews (Cao et al. 2016; Zhu et al. 2017), 5 were prospective cohort studies (Brugge et al. 2004; Cizginer et al. 2011; Frossard et al. 2003; Pitman et al. 2013; Sperti et al. 2005), and 26 of them were retrospective cohort studies (Ardengh et al. 2007; Gaddam et al. 2015; Gerke et al. 2006; Hirono et al. 2012; Jang et al. 2014; Jin et al. 2015; Kamata et al. 2016; Kim et al. 2012; Kim et al. 2014; Lee et al. 2001; Linder et al. 2006; Moris et al. 2016; Nagashio et al. 2014; Oh et al. 2014; Oppong et al. 2015; Othman et al. 2012; Pais et al. 2007; Park et al. 2011; Pitman et al. 2010; Smith et al. 2016; Song et al. 2007; Sperti et al. 2001; Takanami et al. 2011; Talar-Wojnarowska et al. 2013; Wu et al. 2007; Zhang et al. 2010). A summary of the included studies is presented in Table 35.

Fourteen studies examined the diagnostic accuracy of cyst fluid analysis, cytology and imaging for differentiating between mucinous cystic neoplasms (MCNs; including IPMNs) and non-mucinous cystic neoplasms (NMCNs) of the pancreas (Brugge et al. 2004; Cizginer et al. 2011; Frossard et al. 2003; Gaddam et al. 2015; Jin et al. 2015; Linder et al. 2006; Moris et al. 2016; Nagashio et al. 2014; Oh et al. 2014; Oppong et al. 2015; Park et al. 2011; Pitman et al. 2010; Song et al. 2007; Zhang et al. 2010).

Eighteen studies examined the diagnostic accuracy of cyst fluid analysis, cytology and imaging for differentiating between benign and potentially malignant or malignant pancreatic cystic lesions (PCLs) (Ardengh et al. 2007; Cao et al. 2016; Gerke et al. 2006; Hirono et al. 2012; Jang et al. 2014; Kamata et al. 2016; Kim et al. 2012; Kim et al. 2014; Lee et al. 2011; Othman et al. 2012; Pais et al. 2007; Pitman et al. 2013; Smith et al. 2016; Sperti et al. 2001, Sperti et al. 2005; Takanami et al. 2011; Talar-Wojnarowska et al. 2013; Wu et al. 2007).

One study (Park et al. 2011) examined the diagnostic accuracy of cyst fluid analysis, cytology and imaging for differentiating between (i) MCNs and NMCNs and (ii) benign and potentially malignant PCLs.

One of the systematic reviews (Cao et al. 2016) aimed to evaluate the diagnostic value of serum CA 19-9 in identifying malignant PCLs and included 13 studies (n=1437). The other systematic review (Zhu et al. 2017) evaluated the morbidity and mortality associated with EUS-FNA for the diagnosis of PCLs, and included 40 studies (n=5147). Both systematic reviews were assessed as being of high methodological quality, but included very low to moderate quality evidence. See Table 35 for more details of the included studies.

Positive and likelihood ratios were calculated, where appropriate, from the sensitivity and specificity of the studies to enable evaluation of the relevant tests. The QUADAS-2 tool was used for assessing risk of bias and indirectness of included studies.

Further information about the search strategy can be found in Appendix D. See study selection flow chart in Appendix E, single and multiple test ROC curves and forest plots in Appendix H, summary of QUADAS-2 study quality evaluations in Appendix J, study evidence tables in Appendix F and list of excluded studies in Appendix G.

5.3.2.1 CEA

5.3.2.1.1 Cystic fluid CEA

Thirteen studies (n=1542) examined the diagnostic accuracy of cyst fluid CEA: 2 of these were prospective cohort studies (Brugge et al. 2004; Cizginer et al. 2011), whilst the remaining 11 were retrospective cohort studies. The median number of patients was 112 (range 52-226).

Nine studies focused on differentiating between MCNs and NMCNs (Brugge et al. 2004; Cizginer et al. 2011; Gaddam et al. 2015; Jin et al. 2015; Linder et al. 2006; Moris et al. 2016; Nagashio et al. 2014; Oppong et al. 2015; Oh et al. 2014). One study examined the diagnostic accuracy of CEA for differentiating between both types of cystic lesions (Park et al. 2011). The cut-off value of cystic fluid CEA used to differentiate pancreatic MCNs and NMCNs ranged from 5 to 6000 ng/ml, and were categorised as detailed in Table 34:

Table 34: Studies on cystic fluid CEA by cut-off level

Cystic fluid CEA cut-off level	Studies
<10	Gaddam et al. 2015; Oppong et al. 2015
<30-701	Jin et al. 2015; Oh et al. 2014; Oppong et al. 2015; Park et al. 2011; Nagashio et al. 2014
<30	Hirono et al. 2012
<45	Talar-Wojnarowska et al. 2013
<105	Gaddam et al. 2015
<110	Cizginer et al. 2011; Oppong et al. 2015
<129	Moris et al. 2016
<192a	Brugge et al. 2004; Gaddam et al. 2015; Jin et al. 2015; Oppong et al. 2015
<200	Park et al. 2011

Cystic fluid CEA cut-off level	Studies
<300	Jin et al. 2015
<800	Gaddam et al. 2015; Jin et al. 2015; Park et al. 2011
<6000	Linder et al. 2006

[1] *sufficient studies to permit meta-analysis of diagnostic test accuracy data.*

Three studies evaluated the diagnostic accuracy of cyst fluid CEA for differentiating between benign from potentially malignant and malignant PCLs (Hirono et al. 2012; Othman et al. 2012; Talar-Wojnarowska et al. 2013). The cut-off value of cystic fluid CEA used to differentiate benign from malign cysts ranged from 30 to 6000 ng/ml, and were categorised as follow:

- 30-70 ng/ml: Hirono et al. 2012; Talar-Wojnarowska et al. 2013
- 6000 ng/ml: Othman et al. 2012

5.3.2.1.2 Serum CEA

One retrospective study (n= 85) conducted in Taiwan evaluated serum levels of CEA for the differential diagnosis of pancreatic cystadenoma (benign PLC) or cystadenocarcinoma (malign PLC) (Wu et al. 2007).

5.3.2.2 CA 19-9

5.3.2.2.1 Cystic fluid CA 19-9

One meta-analysis (n=1437; Cao et al. 2016) of 13 observational studies (Fritz et al. 2011; Goh et al. 2008; Grobmyer et al. 2009; Hirono et al. 2012; Hwang et al. 2011; Ingkakul et al. 2010; Jones et al. 2009; Kitagawa et al. 2003; Ohtsuka et al. 2012; Sadakari et al. 2010; Shin et al. 2010; Sperti et al. 2007; and Xu et al. 2011) and one additional retrospective study (n=52; Talar-Wojnarowska et al. 2013) examined the diagnostic accuracy of CA 19-9 for differentiating between benign and potentially malignant and malignant PCLs. The cut-off levels ranged from 35 to 45 ng/ml.

5.3.2.2.2 Serum CA 19-9

One study (n=85) conducted in Taiwan evaluated serum levels of CA 19-9 (Wu et al. 2007) for the differential diagnosis of pancreatic cystadenoma (benign PLC) or cystadenocarcinoma (malign PLC) (Wu, Yan et al. 2007).

5.3.2.3 Cytology: EUS-FNA

Ten studies (n=1164), 4 prospective and 6 retrospective cohort, examined the diagnostic accuracy of EUS-FNA cytology (Ardengh et al. 2007; Brugge et al. 2004; Cizginer et al. 2011; Frossard et al. 2003; Oppong et al. 2015; Pais et al. 2007; Pitman et al. 2010; Pitman et al. 2013; Smith et al. 2016; Zhang et al. 2010). Six of the studies evaluated the diagnostic accuracy of EUS-FNA based cytology for differentiating between pancreatic MCNs and NMCNs (Brugge et al. 2004; Cizginer et al. 2011; Frossard et al. 2003; Oppong et al. 2015; Pitman et al. 2010; Zhang et al. 2010), whilst the remaining studies focused on differentiating benign from potentially malignant or malignant PCLs (Ardengh et al. 2007; Pais et al. 2007; Pitman et al. 2013; Smith et al. 2016).

5.3.2.4 Imaging: CT

Five studies (n=263), 1 prospective and 4 retrospective cohort, examined the diagnostic accuracy of CT (Gerke et al. 2006; Lee et al. 2011; Song et al. 2007; Sperti et al. 2001, Sperti et al. 2005). Four of the studies focused on differentiating between benign from

potentially malignant and malignant PCLs (Gerke et al. 2006; Lee et al. 2011; Sperti et al. 2001, Sperti et al. 2005).

5.3.2.5 Imaging: EUS

Seven studies (n=670), 3 prospective and 4 retrospective cohort, examined the diagnostic accuracy of EUS for the morphological evaluation of suspected pancreatic cystic neoplasms (Brugge et al. 2004; Cizginer et al. 2011; Frossard et al. 2003; Gerke et al. 2006; Kamata et al. 2016; Kim et al. 2012; and Oppong et al. 2015). Three of the studies evaluated the accuracy of EUS for differentiating between pancreatic MCNs and NMCNs (Gerke et al. 2006; Kamata et al. 2016 and Kim et al. 2012); 4 studies focused on differentiating between benign from potentially malignant and malignant PCLs (Brugge et al. 2004; Cizginer et al. 2011; Frossard et al. 2003; Oppong et al. 2015); and 3 studies evaluated the accuracy of EUS.

5.3.2.6 Imaging: EUS-FNA

One retrospective cohort study (n=119) examined the diagnostic accuracy of EUS-FNA for differentiating between pancreatic MCNs and NMCNs (Oppong et al. 2015).

5.3.2.7 Imaging: PET/CT

Three studies (n=165), 1 prospective and 2 retrospective, examined the diagnostic accuracy of 18-fluorodeoxyglucose PET in distinguishing benign from malignant cystic lesions of the pancreas (Sperti et al. 2001, Sperti et al.2005; Takanami et al. 2011).

5.3.2.8 Imaging: MRI

Five retrospective cohort studies (n=324) examined the diagnostic accuracy of MRI: 4 of these (n=271) examined the diagnostic accuracy of MRI for differentiating benign from malignant PCLs (Jang et al. 2014; Kim et al. 2012; Kim et al. 2014; and Lee et al. 2011), whilst 1 of these examined the accuracy of MRI in the differentiation of IPMNS from other pancreatic cystic masses (n=53; Song et al. 2007).

5.3.3 Summary of included studies

A summary of the studies that were included in this review is presented in Table 35

Table 35: Summary of included studies

Study	Population	Study design Country	Index test (s)	Reference standard*	Outcomes and results	Overall risk of bias^
Ardengh et al. 2007	Sample size n=197 Characteristics M/F (n): n.r./n.r. Median age (range): n.r.	Retrospective observational study Brazil	Index test 1 (n= 196): EUS-FNA cytology Final diagnosis: Benign (n): 44 Malign (n): 152	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)	Diagnostic accuracy	Serious risk of bias
Brugge et al. 2004	Sample size n=112 Characteristics M/F (n): 41/71 Mean age (yr): 60.1	Prospective observational study (multicentre) USA	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	The final diagnosis was based on surgical histopathology (n=111)	Diagnostic accuracy	Serious risk of bias
Cao et al. 2016 Time frame: The literature search	Sample size 13 studies with 1437 patients	1 MA of 13 studies (1 prospective-12 retrospectives)	Index test 1 (n=1437): Cyst fluid CA 19-9 [35 ng/ml (n=1 studies); 37	The final diagnosis was based on surgical	Diagnostic accuracy	Fritz et al. 2011

Study	Population	Study design Country	Index test (s)	Reference standard*	Outcomes and results	Overall risk of bias^
was up to March 2016. The included paper ranged from 2007 to 2011	Fritz et al. 2011 (n=142) Goh et al. 2008 (n=176) Grobmyer et al. 2009 (n=78) Hirono et al. 2012 (n=134) Hwang et al. 2011 (n=237) Ingkakul et al. 2010 (n=200) Jones et al. 2009 (n=114) Kitagawa et al. 2003 (n=63) Ohtsuka et al. 2012 (n=138) Sadakari et al. 2010 (n=73) Shin et al. 2010 (n=204) Sperti et al. 2007 (n=64) Xu et al. 2011 (n=86)		ng/ml (n=9); 45 ng/ml (n=1); n.r. (n=2)] Final diagnosis: Benign (n): 948 Malign (n): 489	histopathology (n=11 studies – 1227 patients), histopathology results and clinical follow-up (n=2 - 310)		Serious risk of bias Goh et al. 2008 Serious risk of bias Grobmyer et al. 2009 No serious risk of bias Hirono et al. 2012 No serious risk of bias Hwang et al. 2011 No serious risk of bias Ingkakul et al. 2010 Very serious

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Study	Population	Study design Country	Index test (s)	Reference standard*	Outcomes and results	Overall risk of bias^
						risk of bias Jones et al. 2009 Serious risk of bias Kitagawa et al. 2003 No serious risk of bias Ohtsuka et al. 2012 Serious risk of bias Sadakari et al. 2010 No serious risk of bias Shin et al. 2010 No serious risk of bias Sperti et al. 2007

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Study	Population	Study design Country	Index test (s)	Reference standard*	Outcomes and results	Overall risk of bias^
						Very serious risk of bias Xu et al. 2011 No serious risk of bias
Cizginer et al. 2011	Sample size n=198 Characteristics M/F (n): 77/121 Mean age (yr): 60.6	Prospective observational study USA	Index test 1 (n=154): Cyst fluid CEA - 109,9 ng/ml 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	The final diagnosis was based on histology (n=194) or malignant cytology (n=4) -number provided for the total study cohort, n=198	Diagnostic accuracy	Serious risk of bias
Frossard et al. 2003	Sample size n=127 Characteristics M/F (n): 49/78 Median age (range): 59.3 (15)	Prospective observational study France	Index test 1 (n=67): EUS Index test 2 (n=67): EUS -FNA cytology Final diagnosis: Mucinous(n):40 Non-mucinous(n): 27	The final diagnosis was based on surgery (n=59) or post-mortem (n=8)	Diagnostic accuracy	Serious risk of bias

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Study	Population	Study design Country	Index test (s)	Reference standard*	Outcomes and results	Overall risk of bias^
Gaddam et al. 2015	Sample size n=226 Characteristics M/F (n): 88/138 Mean age (SD): 60.9 (13.1)	Retrospective observational study USA	Index test 1 (n=226): Cyst fluid CEA -5, 105,192, 800 ng/ml Final diagnosis: Mucinous(n): 150 Non-mucinous(n): 76	The final diagnosis was based on surgical histopathology (n=226)	Diagnostic accuracy	Serious risk of bias
Gerke et al. 2006	Sample size n=66 Characteristics M/F (n): 28/38 Median age (range): 59 (27-82)	Retrospective observational study USA	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	The final diagnosis was based on surgical pathology (n = 43), diagnostic fine needle aspiration (n = 13) or follow-up imaging (n = 10)	Diagnostic accuracy	Serious risk of bias
Hirono et al. 2012	Sample size n=134 Characteristics M/F (n): 74/60 Mean age (SD): 68.9 (9.7)	Retrospective observational study Japan	Index test 1 (n=134): Cyst fluid CEA 30 ng/ml Final diagnosis: Benign (n): 78 Malign (n): 56	The final diagnosis was based on histopathology (n=134)	Diagnostic accuracy	Serious risk of bias
Jang et al. 2014	Sample size n=65 Characteristics M/F (n): 38/23 Mean age (SD): n.r.	Retrospective observational study Korea	Index test 1 (n=61): MRI Final diagnosis: Benign (n): 42 Malign (n): 19	The final diagnosis was based on surgical histopathology (n=61)	Diagnostic accuracy	Very serious risk of bias
Jin et al. 2015	Sample size n=86 Characteristics M/F (n): 32/54	Retrospective observational study USA	Index test 1 (n=86): Cyst fluid CEA – 30.7, 192, 300, 800 ng/ml Final diagnosis: Mucinous(n): 77	The final diagnosis was based on surgical histology (n=86)	Diagnostic accuracy	Serious risk of bias

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Study	Population	Study design Country	Index test (s)	Reference standard*	Outcomes and results	Overall risk of bias^
	Mean age (SD): 65.0 (13.0)		Non-mucinous(n): 9			
Kamata et al. 2016	Sample size n=70 Characteristics M/F (n): 31/29 Mean age (SD): 62.0 (n.r)	Retrospective observational study Japan	Index test 1 (n=70): EUS Final diagnosis: Benign (n): 40 Malign (n): 30	The final diagnosis was based on surgical histopathology (n=70)	Diagnostic accuracy	Very serious risk of bias
Kim et al. 2012	Sample size n=51 Characteristics M/F (n): 23/28 Mean age (years): 43	Retrospective observational study Korea	Index test 1 (n=51): EUS Index test 2 (n=51): MRI Final diagnosis: Benign (n): 15 Malign (n): 36	The final diagnosis was based on surgical histopathology (n=51)	Diagnostic accuracy	No serious risk of bias
Kim et al. 2014	Sample size N= 123 Characteristics M/F (n): n.r. Mean age (SD): n.r.	Retrospective observational study Korea	Index test 1 (n=96): MRI Final diagnosis: Benign (n): 51 Malign (n): 45	The final diagnosis was based on surgical histopathology (n=96)	Diagnostic accuracy	Very serious risk of bias
Lee et al. 2001	Sample size n=63 Characteristics M/F (n): 25/38 Mean age (range): 55.7 (12-79)	Retrospective observational study Korea	Index test 1 (n=63): CT Index test 2 (n=63): MRI Final diagnosis: Benign (n): 37 Malign (n): 26	The final diagnosis was based on surgical histopathology (n=63)	Diagnostic accuracy	Serious risk of bias
Linder et al. 2006	Sample size n=102 Characteristics M/F (n): 60/42	Retrospective observational study USA	Index test 1 (n=71): Cyst fluid CEA – 6000 ng/ml Final diagnosis: Mucinous(n): 35 Non-mucinous(n): 36	The final diagnosis was based on surgical histopathology (n=71)	Diagnostic accuracy	Serious risk of bias

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Study	Population	Study design Country	Index test (s)	Reference standard*	Outcomes and results	Overall risk of bias^
	Mean age (range): 51 (23-76)					
Moris et al. 2016	Sample size n=180 Characteristics M/F (n): 58/83 Mean age (SD): 68 (9.2)	Retrospective observational study USA	Index test 1 (n=180): Cyst fluid CEA – 129 ng/ml Final diagnosis: Mucinous(n): 145 Non-mucinous(n): 35	The final diagnosis was based on surgical histopathology (n=180)	Diagnostic accuracy	Serious risk of bias
Nagashio et al. 2014	Sample size n=78 Characteristics M/F (n): 26/42 Mean age (range): n.r.	Retrospective observational study Japan	Index test 1 (n=68): Cyst fluid CEA –67.3 ng/ml Final diagnosis: Mucinous(n): 39 Non-mucinous(n): 29	The final diagnosis was based on surgical histopathology (n=58) or cytology, imaging or clinical follow-up (n=20)	Diagnostic accuracy	Serious risk of bias
Oh et al. 2014	Sample size n=69 Characteristics M/F (n): 32/46 Median age (range): 62 (24-84)	Retrospective observational study USA	Index test 1 (n=78): Cyst fluid CEA – 50 ng/ml Final diagnosis: Mucinous(n):62 Non-mucinous [pseudocysts] (n): 16	The final diagnosis was based on surgical histology (n=78)	Diagnostic accuracy	Serious risk of bias
Oppong et al. 2015	Sample size n=119 Characteristics M/F (n): 37/82 Mean age (range): 61.4 (19-84)	Retrospective observational study UK	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	The final diagnosis was based on definitive tissue sampling (n=119 - diagnostic malignant cytology, resection histology or biopsy histology)	Diagnostic accuracy	Serious risk of bias

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Study	Population	Study design Country	Index test (s)	Reference standard*	Outcomes and results	Overall risk of bias^
			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			
Othman et al. 2012	Sample size n=63 Characteristics M/F (n): 19/44 Mean age (SD): 68.9 (0.8)	Retrospective observational study USA	Index test 1 (n=63): Cyst fluid CEA – 6000 ng/ml Final diagnosis: Benign (n): 47 Malign (n): 16	The final diagnosis was based on surgical histopathology (n=63)	Diagnostic accuracy	Serious risk of bias
Pais et al. 2007	Sample size n=74 Characteristics M/F (n): 38/36 Mean age (range): 65 (41-84)	Retrospective observational study USA	Index test 1 (n=65): EUS-FNA cytology Final diagnosis: Benign (n): 45 Malign (n): 20	The final diagnosis was based on histopathology (n=65)	Diagnostic accuracy	Serious risk of bias
Park et al. 2011	Sample size n=124 Characteristics M/F (n): n.r./n.r. Median age (range): n.r.	Retrospective observational study USA	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 – n.r. Final diagnosis: Mucinous(n): 81	The final diagnosis was based on surgical histopathology (n=104), true-cut histology or cytology (22)	Diagnostic accuracy	Serious risk of bias

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Study	Population	Study design Country	Index test (s)	Reference standard*	Outcomes and results	Overall risk of bias^
			Non-mucinous(n): 43			
Pitman et al. 2010	Sample size n=112 Characteristics M/F (n): 39/73 Mean age (years): 68	Retrospective observational study USA	Index test 1 (n=112): EUS-FNA cytology Final diagnosis: Mucinous(n): 39 Non-mucinous(n): 73	The final diagnosis was based on confirmed histology (n=112)	Diagnostic accuracy	Serious risk of bias
Pitman et al. 2013	Sample size n=70 Characteristics M/F (n): 24/46 Mean age (range): 57 (19-60)	Prospective observational study USA	Index test 1 (n=66): EUS-FNA cytology Final diagnosis: Benign (n): 24 Malign (n): 42	The final diagnosis was based on confirmed histology (n=66)	Diagnostic accuracy	Serious risk of bias
Smith et al. 2016	Sample size n=127 Characteristics M/F (n): 38/89 Median age (range):	Retrospective observational study USA	Index test 1 (n=127): EUS-FNA cytology Final diagnosis: Benign (n): 29 Malign (n): 98	The final diagnosis was based on confirmed histology (n=127)	Diagnostic accuracy	Serious risk of bias
Song et al. 2007	Sample size n=53 Characteristics M/F (n): 29/24 Median age (range): 67 (44-87)	Retrospective observational study South Korea	Index test 1 (n=53): CT Index test 2 (n=53): MRI Final diagnosis: Mucinous(n): 31 Non-mucinous(n): 22	The final diagnosis was based on histopathology findings (n=53)	Diagnostic accuracy	No serious risk of bias
Sperti et al. 2001	Sample size n=56 Characteristics M/F (n): 21/35	Retrospective observational study Italy	Index test 1 (n=56): CT Index test 2 (n=56): F-18-PET Final diagnosis: Benign (n): 39	The final diagnosis was based on definitive pathology: resection (n=36)	Diagnostic accuracy	Serious risk of bias

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Study	Population	Study design Country	Index test (s)	Reference standard*	Outcomes and results	Overall risk of bias^
	Mean age (range): 60.1 (31-86)		Malign (n): 17	biopsy (n=19); and follow-up (n=1)		
Sperti et al. 2005	Sample size n=50 Characteristics M/F (n): 17/33 Mean age (range): 58.1 (14-87)	Prospective observational study Italy	Index test 1 (n=50): CT Index test 2 (n=50): F-18-PET Final diagnosis: Benign (n): 33 Malign (n): 17	The final diagnosis was based on pathologic findings of resected specimen, biopsy, or follow-up (numbers are not provided)	Diagnostic accuracy	Serious risk of bias
Takanami et al. 2011	Sample size n=59 Characteristics M/F (n): 56/3 Mean age (SD): 66 (n.r.)	Retrospective observational study Japan	Index test 1 (n=16): F-18-PET Final diagnosis: Benign (n): 7 Malign (n): 9	The final diagnosis was based on surgical histopathology	Diagnostic accuracy	Very serious risk of bias
Talar-Wojnarowska et al. 2013	Sample size n=52 Characteristics M/F (n): 28/24 Mean age (SD): 55 (3.2)	Retrospective observational study Poland	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: Benign (n): 36 Malign (n): 16	The final diagnosis was based on surgical histopathology, cytology results and/or imaging follow-up (>18 months)	Diagnostic accuracy	Serious risk of bias
Wu et al. 2007	Sample size n=85 Characteristics M/F (n): 26/69 Median age (range): n.r.	Retrospective observational study Taiwan	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.	The final diagnosis was based on surgical histopathology (n=85)	Diagnostic accuracy	Serious risk of bias

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Study	Population	Study design Country	Index test (s)	Reference standard*	Outcomes and results	Overall risk of bias^
			Final diagnosis: Benign (n): 37 Malign (n): 48			
Zhang et al. 2010	Sample size n=140 Characteristics M/F (n): n.r./n.r. Median age (range): n.r.	Retrospective observational study USA	Index test 1 (n=54): EUS-FNA cytology Final diagnosis: Mucinous(n): 25 Non-mucinous(n): 29	The final diagnosis was based on surgical histopathology (n=54)	Diagnostic accuracy	Serious risk of bias
Zhu et al. 2017 Time frame: The literature search was up to September 2015. The included paper ranged from 1997 to 2015	Sample size 40 studies with 5124 patients	1 MA of 40 studies (19 prospective-21 retrospectives)	Aims and intervention To systematically evaluate morbidity and mortality associated with EUS-FNA for the diagnosis of PCLs	Exclusion criteria conference abstracts and letters reviews and guidelines case reports insufficient data therapeutic EUS-FNA	Adverse events/complications	No serious risk of bias^^

Notes: *^, QUADAS 2 checklist; ^^ the Assessment of Multiple Systematic Reviews (AMSTAR) appraisal tool to evaluate methodological quality;.* ***Abbreviations:*** *CA, Carbohydrate antigen; CEA, Carcinoembryonic antigen; CT, Computed tomography; EUS, Endoscopic ultrasound; FNA, Fine-needle aspiration; IPMN, intraductal papillary mucinous neoplasm; MCN, Mucinous cystic neoplasm; MRI, Magnetic resonance imaging; NMCN, Non-mucinous cystic neoplasms; NPV, Negative predictive value; PCL, Pancreatic cystic lesion; PET/CT, Positron emission tomography/computed tomography; PPV, Positive predictive value; SCA, Serous cystadenoma.*

5.3.4 Clinical evidence profile

The clinical evidence profiles for this review are presented in Table 39 to Table 54

5.3.4.1 Cystic fluid or serum CEA

5.3.4.1.1 Cystic fluid CEA

Table 36: Summary of clinical evidence for meta-analyses of cystic fluid CEA to differentiate between mucinous cystic and non-mucinous cystic neoplasms of the pancreas

Study	N	CEA level (ng/ml)	Risk of bias[1]	Inconsistency[2]	Indirectness[3]	Imprecision[4]	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	Positive likelihood ratio (95% CI)[5]	Negative likelihood ratio (95% CI)[5]	Quality
5 retrospective cohort studies	434	<30-70	Serious[6]	Not serious	Not serious	Serious[7]	0.88 (0.82-0.92)	0.82 (0.72–0.89)	4.83 (3.08-7.58)	0.15 (0.1-0.23)	LOW
4 studies (1 prospective and 3 retrospective cohort)	401	<192	Serious[8]	Not serious	Not serious	Not serious	0.58 (0.49-0.67)	0.87 (0.74-0.94)	4.33 (2.27-8.26)	0.48 (0.39-0.59)	MODERATE

[1], risk of bias evaluated using risk of bias items of QUADAS-2 checklist;

[2], Inconsistency was assessed by inspection of the 95% prediction region in a summary ROC plot if a diagnostic meta-analysis was conducted. If between 2 and 3 studies, inconsistency was assessed by visual inspection of the point estimates of sensitivity and specificity. If only one study, then inconsistency is not applicable;

[3], indirectness was evaluated using the applicability items of QUADAS-2;

[4], judgement of imprecision was based on consideration of the 95% CIs of test sensitivity as this was considered to be the primary measure of interest as a false negative - missing malignancy - risks a potentially avoidable death, whilst a false positive - indicating malignancy when there is none - risks potentially avoidable surgery or other treatment such as chemotherapy. Studies were considered to be of high sensitivity (and not imprecise) if the 95% CI was above 0.9 or of low sensitivity if it was below 0.75. Studies were assessed as subject to serious imprecision if the 95% CI crossed either 0.75 or 0.9, or subject to very serious imprecision if it crossed both 0.75 and 0.9;

[5], positive and negative likelihood ratios calculated from meta-analysis;

[6], Unclear risk of review bias (lack of blinding in the interpretation both of the index test and reference standard – no details are given in the text) for all studies. Flow and timing of patient unclear for all studies;

[7], 95% CI for sensitivity crosses 0.9;

[8], Unclear risk of review bias (lack of blinding in the interpretation both of the index test and reference standard – no details are given in the text) for 3 studies (Jin et al. 2015, Oppong et al. 2015; Gaddam et al. 2015). High risk of verification bias in Gaddam et al. 2015 (Not all patients received the same reference test).

Table 37: Summary of clinical evidence for other studies on cystic fluid CEA at various cut-offs to differentiate between mucinous cystic and non-mucinous cystic neoplasms of the pancreas

Studies	N	CEA level (ng/ml)	Risk of bias[1]	Inconsistency[2]	Indirectness[3]	Imprecision[4]	Point estimates of sensitivity (95% CI)	Point estimates of specificity (95% CI)	Positive likelihood ratio (95% CI)[5]	Negative likelihood ratio (95% CI)[5]	Quality
Gaddam et al. 2015	226	<5	Very serious[6]	Not applicable	Not serious	Not serious	0.94 (0.89-0.97)	0.42 (0.31-0.54)	1.62 (1.33-1.98)	0.14 (0.07-0.28)	LOW
Oppong et al. 2015	78	<7	Serious[7]	Not applicable	Not serious	Serious[8]	0.94 (0.83-0.99)	0.75 (0.55-0.89)	3.76 (1.97-7.17)	0.08 (0.03-0.24)	LOW
Gaddam et al. 2015	226	<105	Very serious[9]	Not applicable	Not serious	Serious[10]	0.7 (0.62-0.77)	0.63 (0.51-0.74)	1.9 (1.39-2.6)	0.48 (0.35-0.64)	VERY LOW
Cizginer et al. 2011	154	<110	Serious[11]	Not serious	Not serious	Serious[10]	0.81 (0.72-0.88)	0.98 (0.88-1.0)	35.6 (5.12-247.66)	0.2 (0.13-0.29)	LOW
Oppong et al. 2015	78	<110	Serious[7]	Not serious	Not serious	Not serious	0.62 (0.47-0.75)	0.93 (0.77-0.99)	8.68 (2.24-33.58)	0.41 (0.28-0.59)	MODERATE
Overall	232	<110	Serious	Not serious	Serious[12]	Serious[10]					VERY LOW
Moris et al. 2016	180	<129	Serious[7]	Not applicable	Not serious	Serious10	0.77 (0.70-0.84)	0.83 (0.66-0.93)	4.51 (2.16-9.38)	0.27 (0.2-0.38)	LOW
Park et al. 2011	124	<200	Serious[7]	Not applicable	Not serious	Not serious	0.6 (0.49-0.71)	0.93 (0.81-0.99)	8.67 (2.87-26.19)	0.42 (0.32-0.56)	MODERATE
Jin et al. 2015	86	<300	Serious[7]	Not applicable	Not serious	Not serious	0.41 (0.30-0.53)	0.89 (0.52-1.0)	3.86 (0.6-24.92)	0.64 (0.48-0.87)	MODERATE

Studies	N	CEA level (ng/ml)	Risk of bias[1]	Inconsistency[2]	Indirectness[3]	Imprecision[4]	Point estimates of sensitivity (95% CI)	Point estimates of specificity (95% CI)	Positive likelihood ratio (95% CI)[5]	Negative likelihood ratio (95% CI)[5]	Quality
Gaddam et al. 2015	226	<800	Very serious[6]	Not applicable	Not serious	Not serious	0.33 (0.26-0.42)	0.86 (0.76-0.93)	2.3 (1.27-4.16)	0.78 (0.67-0.9)	LOW
Jin et al. 2015	86	<800	Serious[7]	Not applicable	Not serious	Not serious	0.27 (0.18-0.39)	0.89 (0.52-1.0)	2.45 (0.37-16.14)	0.82 (0.63-1.07)	MODERATE
Park et al. 2011	124	<800	Serious[7]	Not applicable	Not serious	Not serious	0.38 (0.28-0.50)	0.95 (0.84-0.99)	8.23 (2.07-32.75)	0.65 (0.54-0.78)	MODERATE
Overall	436	<800	Very serious[13]	Not serious	Not serious	Not serious					LOW
Linder et al. 2006	71	<6000	Serious[14]	Not applicable	Not serious	Very serious[15]	0.86 (0.7-0.95)	1.0 (0.9-1.0)	62.69 (3.98-987.16)[16]	0.14 (0.06-0.32)	VERY LOW

All studies were retrospective cohort except for Cizginer et al., 2011, which was a prospective cohort study;

[1], risk of bias evaluated using risk of bias items of QUADAS-2 checklist;

[2], Inconsistency was assessed by inspection of the 95% prediction region in a summary ROC plot if a diagnostic meta-analysis was conducted. If between 2 and 3 studies, inconsistency was assessed by visual inspection of the point estimates of sensitivity and specificity. If only one study, then inconsistency is not applicable;

[3], indirectness was evaluated using the applicability items of QUADAS-2;

[4], judgement of imprecision was based on consideration of the 95% CIs of test sensitivity as this was considered to be the primary measure of interest as a false negative - missing malignancy - risks a potentially avoidable death, whilst a false positive - indicating malignancy when there is none - risks potentially avoidable surgery or other treatment such as chemotherapy. Studies were considered to be of high sensitivity (and not imprecise) if the 95% CI was above 0.9 or of low sensitivity if it was below 0.75. Studies were assessed as subject to serious imprecision if the 95% CI crossed either 0.75 or 0.9, or subject to very serious imprecision if it crossed both 0.75 and 0.9;

[5], positive and negative likelihood ratios calculated from raw diagnostic test accuracy data if not already reported; 95% CIs calculated using log method (see Chapter 4.3.3.2.2 for details);

[6], Unclear risk of review bias (lack of blinding in the interpretation both of the index test and reference standard – no details are given in the text), high risk of verification bias (not all patients received the same reference test);

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[7], unclear risk of review bias (lack of blinding in the interpretation both of the index test and reference standard – no details are given in the text);

[8], 95%CI of sensitivity crosses 0.9;

[9], Unclear risk of review bias (lack of blinding in the interpretation both of the index test and reference standard – no details are given in the text), high risk of verification bias (not all patients received the same reference test);

[10], 95% CI of sensitivity crosses 0.75;

[11], Unclear risk of review bias for all studies (lack of blinding in the interpretation both of the index test and reference standard – no details are given in the text);

[12], sensitivity estimates range from 0.62 to 0.81;

[13], Gaddam et al. (2015) 226 contributes more than 50% of total sample;

[14], Unclear risk of review bias (lack of blinding in the interpretation both of the index test and reference standard – no details are given in the text). Flow and timing of patient unclear;

[15], 95% CI of sensitivity crosses both 0.75 and 0.9

[16], since the specificity was 1, a continuity correction of 0.5 was added to all cells to enable calculation of the positive likelihood ratio and related 95% CIs.

Table 38: Summary of clinical evidence for studies on cystic fluid CEA to differentiate between (potentially) malignant and benign pancreatic cystic lesions

Studies	N	CEA level (ng/ml)	Risk of bias[1]	Inconsistency[2]	Indirectness[3]	Imprecision[4]	Point estimates of sensitivity (95% CI)	Point estimates of specificity (95% CI)	Positive likelihood ratio (95% CI)[5]	Negative likelihood ratio (95% CI)[5]	Quality
Hirono et al. 2012	134	<30	Very serious[6]	Not applicable	Not serious	Serious[7]	0.95 (0.85-0.99)	0.85 (0.75-0.92)	6.15 (3.64-10.39)	0.06 (0.02-0.19)	VERY LOW
Talar-Wojnarowska et al. 2013	52	<45	Serious[8]	Not applicable	Not serious	Very serious[9]	0.94 (0.7-1.0)	0.64 (0.46-0.79)	2.6 (1.65-4.08)	0.1 (0.01-0.66)	VERY LOW
Othman et al. 2012	63	<6000	Serious[10]	Not applicable	Not serious	Not serious	0.31 (0.11-0.59)	0.85 (0.72-0.94)	2.1 (0.77-5.69)	0.81 (0.57-1.15)	MODERATE

All studies were retrospective cohort;

[1], risk of bias evaluated using risk of bias items of QUADAS-2 checklist;

[2], Inconsistency was assessed by inspection of the 95% prediction region in a summary ROC plot if a diagnostic meta-analysis was conducted. If between 2 and 3 studies, inconsistency was assessed by visual inspection of the point estimates of sensitivity and specificity. If only one study, then inconsistency is not applicable;

[3], indirectness was evaluated using the applicability items of QUADAS-2;

[4], judgement of imprecision was based on consideration of the 95% CIs of test sensitivity as this was considered to be the primary measure of interest as a false negative - missing malignancy - risks a potentially avoidable death, whilst a false positive - indicating malignancy when there is none - risks potentially avoidable surgery or other treatment such as chemotherapy. Studies were considered to be of high sensitivity (and not imprecise) if the 95% CI was above 0.9 or of low sensitivity if it was below 0.75. Studies were assessed as subject to serious imprecision if the 95% CI crossed either 0.75 or 0.9, or subject to very serious imprecision if it crossed both 0.75 and 0.9;

[5], positive and negative likelihood ratios calculated from raw diagnostic test accuracy data if not already reported; 95% CIs calculated using log method (see Chapter 4.3.3.2.2 for details);

[6], Unclear risk of review bias (lack of blinding in the interpretation both of the index test and reference standard – no details are given in the text), high risk of verification bias (not all patients received the same reference test);

[7], 95% CI for sensitivity crosses 0.9;

[8], Unclear risk of review bias (lack of blinding in the interpretation both of the index test and reference standard – no details are given in the text);

[9], 95% CI of sensitivity crosses both 0.75 and 0.9;

[10], Unclear risk of review bias (lack of blinding in the interpretation both of the index test and reference standard – no details are given in the text). Flow and timing of patient unclear.

5.3.4.1.2 Serum CEA

Table 39: Summary of clinical evidence for studies on serum CEA to differentiate between benign and (potentially) malignant pancreatic cystic lesions

Studies	N	CEA level (ng/ml)	Risk of bias[1]	Inconsistency[2]	Indirectness[3]	Imprecision[4]	Point estimates of sensitivity (95% CI)	Point estimates of specificity (95% CI)	Positive likelihood ratio (95% CI)[5]	Negative likelihood ratio (95% CI)[5]	Quality
Wu et al. 2007	85	Not specified	Very serious[6]	Not applicable	Not serious	Not serious	0.35 (0.22-0.51)	0.84 (0.68-0.94)	2.18 (0.96-4.99)	0.77 (0.6-0.99)	LOW

[1], risk of bias evaluated using risk of bias items of QUADAS-2 checklist;

[2], Inconsistency was assessed by inspection of the 95% prediction region in a summary ROC plot if a diagnostic meta-analysis was conducted. If between 2 and 3 studies, inconsistency was assessed by visual inspection of the point estimates of sensitivity and specificity. If only one study, then inconsistency is not applicable;

[3], indirectness was evaluated using the applicability items of QUADAS-2;

[4], judgement of imprecision was based on consideration of the 95% CIs of test sensitivity as this was considered to be the primary measure of interest as a false negative - missing malignancy - risks a potentially avoidable death, whilst a false positive - indicating malignancy when there is none - risks potentially avoidable surgery or other treatment such as chemotherapy. Studies were considered to be of high sensitivity (and not imprecise) if the 95% CI was above 0.9 or of low sensitivity if it was below 0.75. Studies were assessed as subject to serious imprecision if the 95% CI crossed either 0.75 or 0.9, or subject to very serious imprecision if it crossed both 0.75 and 0.9;

[5], positive and negative likelihood ratios calculated from raw diagnostic test accuracy data if not already reported; 95% CIs calculated using log method (see Chapter 4.3.3.2.2 for details);

[6], potential risk of review bias (lack of blinding in the interpretation both of the index test and reference standard – no details are given in the text); flow and timing of patient unclear; and cut-off value not reported.

5.3.4.2 Cystic fluid or serum CA 19-9

5.3.4.2.1 Cystic fluid CA 19-9

Table 40: Summary of clinical evidence for meta-analysis of cystic fluid CA 19-9 to differentiate between mucinous cystic and non-mucinous cystic neoplasms of the pancreas

Studies	N	CA 19-9 level (ng/ml)	Risk of bias[1]	Inconsistency[2]	Indirectness[3]	Imprecision[4]	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	Positive likelihood ratio (95% CI)[5]	Negative likelihood ratio (95% CI)[5]	Quality
14 studies (Cao et al. 2016 + Talar-Wojnarowska et al. 2013)	1489	<35-45	Serious[6]	Not serious	Not serious	Not serious	0.5 (0.37-0.63)	0.87 (0.84-0.9)	3.92 (3.16-4.87)	0.58 (0.46-0.73)	MODERATE

[1], risk of bias evaluated using risk of bias items of QUADAS-2 checklist;

[2], Inconsistency was assessed by inspection of the 95% prediction region in a summary ROC plot if a diagnostic meta-analysis was conducted. If between 2 and 3 studies, inconsistency was assessed by visual inspection of the point estimates of sensitivity and specificity. If only one study, then inconsistency is not applicable;

[3], indirectness was evaluated using the applicability items of QUADAS-2;

[4], judgement of imprecision was based on consideration of the 95% CIs of test sensitivity as this was considered to be the primary measure of interest as a false negative - missing malignancy - risks a potentially avoidable death, whilst a false positive - indicating malignancy when there is none - risks potentially avoidable surgery or other treatment such as chemotherapy. Studies were considered to be of high sensitivity (and not imprecise) if the 95% CI was above 0.9 or of low sensitivity if it was below 0.75. Studies were assessed as subject to serious imprecision if the 95% CI crossed either 0.75 or 0.9, or subject to very serious imprecision if it crossed both 0.75 and 0.9;

[5], positive and negative likelihood ratios calculated from meta-analysis;

[6], *Unclear risk of review bias (lack of blinding in the interpretation both of the index test and reference standard – no details are given in the text) for most part of studies.*

25.3.4.2.2 *Serum CA 19-9*

Table 41: Summary of clinical evidence for studies on serum CA 19-9 to differentiate between malignant and benign pancreatic cystic lesions

Studies	N	CA 19-9 level (ng/ml)	Risk of bias[1]	Inconsistency[2]	Indirectness[3]	Imprecision[4]	Point estimates of sensitivity (95% CI)	Point estimates of specificity (95% CI)	Positive likelihood ratio (95% CI)[5]	Negative likelihood ratio (95% CI)[5]	Quality
Wu et al. 2007	85	Not specified	Very serious[6]	Not applicable	Not serious	Not serious	0.58 (0.43-0.72)	0.86 (0.71-0.95)	4.32 (1.85-10.09)	0.48 (0.34-0.69)	LOW

[1], *risk of bias evaluated using risk of bias items of QUADAS-2 checklist;*

[2], *Inconsistency was assessed by inspection of the 95% prediction region in a summary ROC plot if a diagnostic meta-analysis was conducted. If between 2 and 3 studies, inconsistency was assessed by visual inspection of the point estimates of sensitivity and specificity. If only one study, then inconsistency is not applicable;*

[3], *indirectness was evaluated using the applicability items of QUADAS-2;*

[4], *judgement of imprecision was based on consideration of the 95% CIs of test sensitivity as this was considered to be the primary measure of interest as a false negative - missing malignancy - risks a potentially avoidable death, whilst a false positive - indicating malignancy when there is none - risks potentially avoidable surgery or other treatment such as chemotherapy. Studies were considered to be of high sensitivity (and not imprecise) if the 95% CI was above 0.9 or of low sensitivity if it was below 0.75. Studies were assessed as subject to serious imprecision if the 95% CI crossed either 0.75 or 0.9, or subject to very serious imprecision if it crossed both 0.75 and 0.9;*

[5], *positive and negative likelihood ratios calculated from raw diagnostic test accuracy data if not already reported; 95% CIs calculated using log method (see Chapter 4.3.3.2.2 for details);*

[6], *Potential risk of review bias (lack of blinding in the interpretation both of the index test and reference standard – no details are given in the text). Flow and timing of patient unclear. Cut-off value not reported.*

5.3.4.3 Cytology: EUS-FNA

Table 42: Summary of clinical evidence for meta-analysis of EUS-FNA cytology to differentiate between mucinous cystic and non-mucinous cystic neoplasms of the pancreas

Studies	N	Risk of bias[1]	Inconsistency[2]	Indirectness[3]	Imprecision[4]	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	Positive likelihood ratio (95% CI)[5]	Negative likelihood ratio (95% CI)[5]	Quality
6 studies (3 prospective and 3 retrospective cohort)	639	Serious[6]	Very serious[7]	Not serious	Serious[8]	0.55 (0.27-0.8)	0.94 (0.86-0.97)	8.52 (3.41-21.31)	0.48 (0.25-0.91)	VERY LOW

[1], risk of bias evaluated using risk of bias items of QUADAS-2 checklist;

[2], Inconsistency was assessed by inspection of the 95% prediction region in a summary ROC plot if a diagnostic meta-analysis was conducted. If between 2 and 3 studies, inconsistency was assessed by visual inspection of the point estimates of sensitivity and specificity. If only one study, then inconsistency is not applicable;

[3], indirectness was evaluated using the applicability items of QUADAS-2;

[4], judgement of imprecision was based on consideration of the 95% CIs of test sensitivity as this was considered to be the primary measure of interest as a false negative - missing malignancy - risks a potentially avoidable death, whilst a false positive - indicating malignancy when there is none - risks potentially avoidable surgery or other treatment such as chemotherapy. Studies were considered to be of high sensitivity (and not imprecise) if the 95% CI was above 0.9 or of low sensitivity if it was below 0.75. Studies were assessed as subject to serious imprecision if the 95% CI crossed either 0.75 or 0.9, or subject to very serious imprecision if it crossed both 0.75 and 0.9;

[5], positive and negative likelihood ratios calculated from meta-analysis;

[6], Reference test varied depending on index test in Frossard et al. 2003. Four patients were excluded from the analysis for unclear reasons (Cizginer et al. 2011). One study was likely to be subject to unclear risk of review bias (Frossard et al. 2003);

[7], 95% prediction region was very wide, with sensitivity ranging from approximately 0 to 1.0, and specificity ranging from approximately 0.3 to 1.0;

[8], 95% CI of sensitivity crosses 0.75.

Table 43: Summary of clinical evidence for meta-analysis of EUS-FNA cytology to differentiate between malignant and benign pancreatic cystic lesions

Studies	N	Risk of bias[1]	Inconsistency[2]	Indirectness[3]	Imprecision[4]	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	Positive likelihood ratio (95% CI)[5]	Negative likelihood ratio (95% CI)[5]	Quality
4 studies (1 prospective and	454	Not serious	Very serious[6]	Not serious	Serious[7]	0.7 (0.54-0.81)	0.93 (0.88-0.96)	9.67	0.33 (0.21-0.5)	VERY LOW

Studies	N	Risk of bias[1]	Inconsistency[2]	Indirectness[3]	Imprecision[4]	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	Positive likelihood ratio (95% CI)[5]	Negative likelihood ratio (95% CI)[5]	Quality
3 retrospective cohort)								(6.14-15.24)		

[1], risk of bias evaluated using risk of bias items of QUADAS-2 checklist;

[2], Inconsistency was assessed by inspection of the 95% prediction region in a summary ROC plot if a diagnostic meta-analysis was conducted. If between 2 and 3 studies, inconsistency was assessed by visual inspection of the point estimates of sensitivity and specificity. If only one study, then inconsistency is not applicable;

[3], indirectness was evaluated using the applicability items of QUADAS-2;

4, judgement of imprecision was based on consideration of the 95% CIs of test sensitivity as this was considered to be the primary measure of interest as a false negative - missing malignancy - risks a potentially avoidable death, whilst a false positive - indicating malignancy when there is none - risks potentially avoidable surgery or other treatment such as chemotherapy. Studies were considered to be of high sensitivity (and not imprecise) if the 95% CI was above 0.9 or of low sensitivity if it was below 0.75. Studies were assessed as subject to serious imprecision if the 95% CI crossed either 0.75 or 0.9, or subject to very serious imprecision if it crossed both 0.75 and 0.9;

[5], positive and negative likelihood ratios calculated from meta-analysis;

[6], 95% prediction region was very wide, with sensitivity ranging from approximately 0 to 1.0, and specificity ranging from approximately 0.4 to 1.0;

[7], 95% CI of sensitivity crosses 0.75.

5.3.4.4 Imaging: CT

Table 44: Summary of clinical evidence for studies on computed tomography to differentiate between mucinous cystic and non-mucinous cystic neoplasms of the pancreas

Studies	N	Risk of bias[1]	Inconsistency[2]	Indirectness[3]	Imprecision[4]	Point estimates of sensitivity (95% CI)	Point estimates of specificity (95% CI)	Positive likelihood ratio (95% CI)[5]	Negative likelihood ratio (95% CI)[5]	Quality
Song et al. 2007	53	Not serious	Not applicable	Not serious	Very serious[6]	0.81 (0.63-0.93)	0.86 (0.78-0.93)	5.96 (3.49-10.16)	0.22 (0.11-0.46)	LOW

Study was retrospective cohort;

[1], risk of bias evaluated using risk of bias items of QUADAS-2 checklist;

[2], Inconsistency was assessed by inspection of the 95% prediction region in a summary ROC plot if a diagnostic meta-analysis was conducted. If between 2 and 3 studies, inconsistency was assessed by visual inspection of the point estimates of sensitivity and specificity. If only one study, then inconsistency is not applicable;

[3], indirectness was evaluated using the applicability items of QUADAS-2;

[4], judgement of imprecision was based on consideration of the 95% CIs of test sensitivity as this was considered to be the primary measure of interest as a false negative - missing malignancy - risks a potentially avoidable death, whilst a false positive - indicating malignancy when there is none - risks potentially avoidable surgery or other treatment such as chemotherapy. Studies were considered to be of high sensitivity (and not imprecise) if the 95% CI was above 0.9 or of low sensitivity if it was below 0.75. Studies were assessed as subject to serious imprecision if the 95% CI crossed either 0.75 or 0.9, or subject to very serious imprecision if it crossed both 0.75 and 0.9;

[5], positive and negative likelihood ratios calculated from raw diagnostic test accuracy data if not already reported; 95% CIs calculated using log method (see Chapter 4.3.3.2.2 for details);

[6], 95% Ci of sensitivity crosses both 0.75 and 0.9.

Table 45: Summary of clinical evidence for meta-analysis of computed tomography to differentiate between malignant and benign pancreatic cystic lesions

Studies	N	Risk of bias[1]	Inconsistency[2]	Indirectness[3]	Imprecision[4]	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	Positive likelihood ratio (95% CI)[5]	Negative likelihood ratio (95% CI)[5]	Quality
4 studies (1 prospective and 3 retrospective cohort)	210	Serious[6]	Very serious[7]	Not serious	Not serious	0.64 (0.53-0.74)	0.82 (0.74-0.88)	3.6 (2.39-5.44)	0.44 (0.32-0.59)	VERY LOW

[1], risk of bias evaluated using risk of bias items of QUADAS-2 checklist;

[2], Inconsistency was assessed by inspection of the 95% prediction region in a summary ROC plot if a diagnostic meta-analysis was conducted. If between 2 and 3 studies, inconsistency was assessed by visual inspection of the point estimates of sensitivity and specificity. If only one study, then inconsistency is not applicable;

[3], indirectness was evaluated using the applicability items of QUADAS-2;

[4], judgement of imprecision was based on consideration of the 95% CIs of test sensitivity as this was considered to be the primary measure of interest as a false negative - missing malignancy - risks a potentially avoidable death, whilst a false positive - indicating malignancy when there is none - risks potentially avoidable surgery or other treatment such as chemotherapy. Studies were considered to be of high sensitivity (and not imprecise) if the 95% CI was above 0.9 or of low sensitivity if it was below 0.75. Studies were assessed as subject to serious imprecision if the 95% CI crossed either 0.75 or 0.9, or subject to very serious imprecision if it crossed both 0.75 and 0.9;

[5], positive and negative likelihood ratios calculated from meta-analysis;

[6], Unclear flow and timing of patient for all studies;

[7], 95% prediction region was very wide with sensitivity ranging from approximately 0.3 to 0.9 and specificity ranging from approximately 0 to 1.0.

5.3.4.5 Imaging: EUS

Table 46: Summary of clinical evidence for meta-analysis of EUS to differentiate between mucinous cystic and non-mucinous cystic neoplasms of the pancreas

Studies	N	Risk of bias[1]	Inconsistency[2]	Indirectness[3]	Imprecision[4]	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	Positive likelihood ratio (95% CI)[5]	Negative likelihood ratio (95% CI)[5]	Quality
4 studies (1 prospective and 3 retrospective cohort)	210	Not serious	Very serious[6]	Not serious	Serious[7]	0.67 (0.43-0.84)	0.65 (0.48-0.78)	1.88 (1.18-3.0)	0.52 (0.28-0.96)	VERY LOW

[1], *risk of bias evaluated using risk of bias items of QUADAS-2 checklist;*

[2], *Inconsistency was assessed by inspection of the 95% prediction region in a summary ROC plot if a diagnostic meta-analysis was conducted. If between 2 and 3 studies, inconsistency was assessed by visual inspection of the point estimates of sensitivity and specificity. If only one study, then inconsistency is not applicable;*

[3], *indirectness was evaluated using the applicability items of QUADAS-2;*

[4], *judgement of imprecision was based on consideration of the 95% CIs of test sensitivity as this was considered to be the primary measure of interest as a false negative - missing malignancy - risks a potentially avoidable death, whilst a false positive - indicating malignancy when there is none - risks potentially avoidable surgery or other treatment such as chemotherapy. Studies were considered to be of high sensitivity (and not imprecise) if the 95% CI was above 0.9 or of low sensitivity if it was below 0.75. Studies were assessed as subject to serious imprecision if the 95% CI crossed either 0.75 or 0.9, or subject to very serious imprecision if it crossed both 0.75 and 0.9;*

[5], *positive and negative likelihood ratios calculated from meta-analysis;*

[6], *95% prediction region was very wide with both sensitivity and specificity ranging from approximately 0 to 1.0;*

[7], *95% CI of sensitivity crosses 0.75.*

Table 47: Summary of clinical evidence for studies on EUS to differentiate between malignant and benign pancreatic cystic lesions

Studies	N	Risk of bias[1]	Inconsistency[2]	Indirectness[3]	Imprecision[4]	Point estimates of sensitivity (95% CI)	Point estimates of specificity (95% CI)	Positive likelihood ratio (95% CI)[5]	Negative likelihood ratio (95% CI)[5]	Quality
Gerke et al. 2006	66	Serious[6]	Not applicable	Not serious	Serious[7]	0.71 (0.52-0.86)	0.63 (0.45-0.79)	1.91 (1.17-3.11)	0.46 (0.25-0.85)	LOW

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Studies	N	Risk of bias[1]	Inconsistency[2]	Indirectness[3]	Imprecision[4]	Point estimates of sensitivity (95% CI)	Point estimates of specificity (95% CI)	Positive likelihood ratio (95% CI)[5]	Negative likelihood ratio (95% CI)[5]	Quality
Kamata et al. 2016	70	Very Serious[8]	Not applicable	Not serious	Serious[7]	0.97 (0.83-1.0)	0.4 (0.25-0.57)	1.61 (1.24-2.09)	0.08 (0.01-0.59)	VERY LOW
Kim et al. 2012	51	Serious6	Not applicable	Not serious	Serious[7]	0.97 (0.85-1.0)	0.73 (0.45-0.92)	3.65 (1.57-8.45)	0.04 (0.01-0.27)	LOW
Overall	187	Serious9	Serious[10]	Not serious	Very serious[11]					VERY LOW

All studies were retrospective cohort;

[1], risk of bias evaluated using risk of bias items of QUADAS-2 checklist;

[2], Inconsistency was assessed by inspection of the 95% prediction region in a summary ROC plot if a diagnostic meta-analysis was conducted. If between 2 and 3 studies, inconsistency was assessed by visual inspection of the point estimates of sensitivity and specificity. If only one study, then inconsistency is not applicable;

[3], indirectness was evaluated using the applicability items of QUADAS-2;

[4], judgement of imprecision was based on consideration of the 95% CIs of test sensitivity as this was considered to be the primary measure of interest as a false negative - missing malignancy - risks a potentially avoidable death, whilst a false positive - indicating malignancy when there is none - risks potentially avoidable surgery or other treatment such as chemotherapy. Studies were considered to be of high sensitivity (and not imprecise) if the 95% CI was above 0.9 or of low sensitivity if it was below 0.75. Studies were assessed as subject to serious imprecision if the 95% CI crossed either 0.75 or 0.9, or subject to very serious imprecision if it crossed both 0.75 and 0.9;

[5], positive and negative likelihood ratios calculated from raw diagnostic test accuracy data if not already reported; 95% CIs calculated using log method (see Chapter 4.3.3.2.2 for details);

[6], High risk of verification bias: all patients did not receive the same reference test;

[7], 95% CI of sensitivity crosses 0.75 or 0.9;

[8], 419 (85.7%) patients were excluded from the analysis for unclear reasons, and the study was likely to be subject to risk of review bias;

[9], Gerke et al. 2006 and Kim et al. 2012 comprise over 50% of the total sample;

[10], sensitivity estimates range from 0.71 to 0.97. Specificity estimates range from 0.4 to 0.73;

[11], 95% CIs of sensitivity point estimates cross both 0.75 and 0.9.

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5.3.4.6 Imaging: EUS-FNA

Table 48: Summary of clinical evidence for studies on EUS-FNA to differentiate between mucinous cystic and non-mucinous cystic neoplasms of the pancreas

Studies	N	Risk of bias[1]	Inconsistency[2]	Indirectness[3]	Imprecision[4]	Point estimates of sensitivity (95% CI)	Point estimates of specificity (95% CI)	Positive likelihood ratio (95% CI)[5]	Negative likelihood ratio (95% CI)[5]	Quality
Oppong et al. 2015	119	Serious[6]	Not applicable	Not serious	Serious[7]	0.76 (0.65-0.85)	0.73 (0.56--0.85)	2.76 (1.64-4.64)	0.33 (0.21-0.51)	LOW

Study was retrospective cohort;

[1], risk of bias evaluated using risk of bias items of QUADAS-2 checklist;

[2], Inconsistency was assessed by inspection of the 95% prediction region in a summary ROC plot if a diagnostic meta-analysis was conducted. If between 2 and 3 studies, inconsistency was assessed by visual inspection of the point estimates of sensitivity and specificity. If only one study, then inconsistency is not applicable;

[3], indirectness was evaluated using the applicability items of QUADAS-2;

[4], judgement of imprecision was based on consideration of the 95% CIs of test sensitivity as this was considered to be the primary measure of interest as a false negative - missing malignancy - risks a potentially avoidable death, whilst a false positive - indicating malignancy when there is none - risks potentially avoidable surgery or other treatment such as chemotherapy. Studies were considered to be of high sensitivity (and not imprecise) if the 95% CI was above 0.9 or of low sensitivity if it was below 0.75. Studies were assessed as subject to serious imprecision if the 95% CI crossed either 0.75 or 0.9, or subject to very serious imprecision if it crossed both 0.75 and 0.9;

[5], positive and negative likelihood ratios calculated from raw diagnostic test accuracy data if not already reported; 95% CIs calculated using log method (see Chapter 4.3.3.2.2 for details);

[6], Unclear risk of review bias (lack of blinding in the interpretation both of the index test and reference standard – no details are given in the text);

[7], 95% CI of sensitivity crosses 0.75.

5.3.4.7 Imaging: PET/CT

Table 49: Summary of clinical evidence for studies on PET/CT to differentiate between (potentially) malignant and benign pancreatic cystic lesions

Studies	N	Risk of bias[1]	Inconsistency[2]	Indirectness[3]	Imprecision[4]	Point estimates of sensitivity (95% CI)	Point estimates of specificity (95% CI)	Positive likelihood ratio (95% CI)[5]	Negative likelihood ratio (95% CI)[5]	Quality
Sperti et al. 2005	50	Serious[6]	Not applicable	Not serious	Very serious[7]	0.94 (0.71-1.0)	0.94 (0.8-0.99)	15.53 (4.03-59.82)	0.06 (0.01-0.42)	VERY LOW
Sperti et al. 2001	56	Serious[6]	Not applicable	Not serious	Very serious[7]	0.94 (0.71-1.0)	0.97 (0.87-1.0)	36.71 (5.28-255.01)	0.06 (0.01-0.4)	VERY LOW
Takanami et al. 2011	59	Very serious[8]	Not applicable	Not serious	Very serious[7]	0.78 (0.4-0.97)	1.0 (0.59-1.0)	12.0 (0.8-179.92)[9]	0.22 (0.07-0.75)	VERY LOW
Overall	164	Serious[10]	Not serious	Not serious	Very serious[11]					VERY LOW

All studies retrospective cohort except for Sperti et al. 2005, which was a prospective cohort study;

[1], risk of bias evaluated using risk of bias items of QUADAS-2 checklist;

[2], Inconsistency was assessed by inspection of the 95% prediction region in a summary ROC plot if a diagnostic meta-analysis was conducted. If between 2 and 3 studies, inconsistency was assessed by visual inspection of the point estimates of sensitivity and specificity. If only one study, then inconsistency is not applicable;

[3], indirectness was evaluated using the applicability items of QUADAS-2;

[4], judgement of imprecision was based on consideration of the 95% CIs of test sensitivity as this was considered to be the primary measure of interest as a false negative - missing malignancy - risks a potentially avoidable death, whilst a false positive - indicating malignancy when there is none - risks potentially avoidable surgery or other treatment such as chemotherapy. Studies were considered to be of high sensitivity (and not imprecise) if the 95% CI was above 0.9 or of low sensitivity if it was below 0.75. Studies were assessed as subject to serious imprecision if the 95% CI crossed either 0.75 or 0.9, or subject to very serious imprecision if it crossed both 0.75 and 0.9;

[5], positive and negative likelihood ratios calculated from raw diagnostic test accuracy data if not already reported; 95% CIs calculated using log method (see Chapter 4.3.3.2.2 for details);

[6], Unclear risk of review bias (lack of blinding in the interpretation both of the index test and reference standard – no details are given in the text);

[7], 95% CI of sensitivity crosses both 0.75 and 0.9;

[8], 43 (72.9%) patients were excluded from the analysis for unclear reasons, and the study was likely to be subject to risk of review bias;

[9], since the specificity was 1, a continuity correction of 0.5 was added to all cells to enable calculation of the positive likelihood ratio and related 95% CIs.

[10], Sperti et al 2001 and 2005 comprise greater than 50% of total sample;

[11], 95% CIs of sensitivity estimates cross both 0.75 and 0.9.

5.3.4.8 Imaging: MRI

Table 50: Summary of clinical evidence for meta-analysis of MRI to differentiate between mucinous cystic and non-mucinous cystic neoplasms of the pancreas

Studies	N	Risk of bias[1]	Inconsistency[2]	Indirectness[3]	Imprecision[4]	Point estimates of sensitivity (95% CI)	Point estimates of specificity (95% CI)	Positive likelihood ratio (95% CI)[5]	Negative likelihood ratio (95% CI)[5]	Quality
Song et al. 2007	53	Not serious	Not applicable	Not serious	Serious[6]	0.97 (0.83-1.0)	0.91 (0.71--0.99)	10.65 (2.84-39.97)	0.04 (0.01-0.25)	MODERATE

[1], risk of bias evaluated using QUADAS-2 checklist;

[2], Inconsistency was assessed by inspection of the 95% prediction region in a summary ROC plot if a diagnostic meta-analysis was conducted. If between 2 and 3 studies, inconsistency was assessed by visual inspection of the point estimates of sensitivity and specificity. If only one study, then inconsistency is not applicable;

[3], indirectness was evaluated using the applicability items of QUADAS-2;

[4], judgement of imprecision was based on consideration of the 95% CIs of test sensitivity as this was considered to be the primary measure of interest as a false negative - missing malignancy - risks a potentially avoidable death, whilst a false positive - indicating malignancy when there is none - risks potentially avoidable surgery or other treatment such as chemotherapy. Studies were considered to be of high sensitivity (and not imprecise) if the 95% CI was above 0.9 or of low sensitivity if it was below 0.75. Studies were assessed as subject to serious imprecision if the 95% CI crossed either 0.75 or 0.9, or subject to very serious imprecision if it crossed both 0.75 and 0.9;

[5], positive and negative likelihood ratios calculated from raw diagnostic test accuracy data if not already reported; 95% CIs calculated using log method (see Chapter 4.3.3.2.2 for details);

[6], 95% CI of sensitivity crosses 0.9.

Table 51: Summary of clinical evidence for studies on MRI to differentiate between (potentially) malignant and benign pancreatic cystic lesions

Studies	N	Risk of bias[1]	Inconsistency[2]	Indirectness[3]	Imprecision[4]	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	Positive likelihood ratio (95% CI)[5]	Negative likelihood ratio (95% CI)[5]	Quality
4 retrospective cohort studies	271	Serious6	Not serious	Not serious	Serious7	0.79 (0.64-0.89)	0.84 (0.69-0.92)	4.81 (2.54-9.08)	0.25 (0.15-0.43)	LOW

[1], risk of bias evaluated using QUADAS-2 checklist;

[2], Inconsistency was assessed by inspection of the 95% prediction region in a summary ROC plot if a diagnostic meta-analysis was conducted. If between 2 and 3 studies, inconsistency was assessed by visual inspection of the point estimates of sensitivity and specificity. If only one study, then inconsistency is not applicable;

[3], indirectness was evaluated using the applicability items of QUADAS-2;

[4], judgement of imprecision was based on consideration of the 95% CIs of test sensitivity as this was considered to be the primary measure of interest as a false negative - missing malignancy - risks a potentially avoidable death, whilst a false positive - indicating malignancy when there is none - risks potentially avoidable surgery or other treatment such as chemotherapy. Studies were considered to be of high sensitivity (and not imprecise) if the 95% CI was above 0.9 or of low sensitivity if it was below 0.75. Studies were assessed as subject to serious imprecision if the 95% CI crossed either 0.75 or 0.9, or subject to very serious imprecision if it crossed both 0.75 and 0.9;

[5], positive and negative likelihood ratios calculated from meta-analysis;

[6], Risk of inappropriate exclusions and flow and timing of patient unclear in two studies (Jang et al. 2014, and Kim et al. 2014). Unclear risk of review bias in all included studies;

[7], 95% CI of sensitivity crosses 0.75.

5.3.5 Economic evidence

A literature review of published cost effectiveness analyses did not identify any relevant studies for this topic. Although there were potential implications for resource use associated with making recommendations in this area, other topics in the guideline were agreed as a higher economic priority. Consequently, bespoke economic modelling was not done for this topic.

5.3.6 Evidence statements

5.3.6.1 Cystic fluid and serum CEA

5.3.6.1.1 Cystic fluid CEA

Mucinous cystic neoplasms versus non-mucinous cystic neoplasms of the pancreas

Diagnostic accuracy

Moderate quality evidence from a meta-analysis of 4 cohort studies (1 prospective and 3 retrospective) (n=401) found that cystic fluid CEA with a cut-off level of 192 ng/ml had a low sensitivity of 0.58 (95% CI, 0.49-0.67) and a moderate specificity of 0.87 (95% CI, 0.74-0.94) for differentiating between mucinous and non-mucinous cystic neoplasms of the pancreas in adults with pancreatic cysts. The positive likelihood ratio of 4.33 (95% CI, 2.27-8.26) suggests that a positive result for a mucinous cystic neoplasm is not particularly useful for ruling it in, though there is uncertainty in the estimate. The negative likelihood ratio of 0.48 (95% CI, 0.39-0.59) suggests that a negative result for a mucinous cystic neoplasm is not particularly useful for ruling it in or ruling it out.

Low quality evidence from a meta-analysis of 5 retrospective cohort studies (n=434) found that cystic fluid CEA with a cut-off level of between 30 and 70 ng/ml had a moderate sensitivity of 0.88 (95% CI, 0.82-0.92) and moderate specificity of 0.82 (95% CI, 0.72–0.89) for differentiating between mucinous and non-mucinous cystic neoplasms of the pancreas in adults with pancreatic cysts. The positive likelihood ratio of 4.83 (95% CI, 3.08-7.58) suggests that a positive result for a mucinous cystic neoplasm is not particularly useful in ruling it in, though there is uncertainty in the estimates. The negative likelihood ratio of 0.15 (0.1-0.23) suggests that a negative result for a mucinous cystic neoplasm is moderately useful for ruling it out, though there is uncertainty in the estimates.

Low quality evidence from 1 retrospective cohort study (n=226) found that cystic fluid CEA with a cut-off level of 5 ng/ml had a high sensitivity of 0.94 (95% CI, 0.89-0.97) and a low specificity of 0.42 (95% CI, 0.31-0.54) for differentiating between mucinous and non-mucinous cystic neoplasms of the pancreas in adults with pancreatic cysts. The positive likelihood ratio of 1.62 (95% CI, 1.33-1.98) suggests that a positive result for a mucinous cystic neoplasm is not particularly useful for ruling it in. The negative likelihood ratio of 0.4 (95% CI, 0.07-0.28) suggests that neither a negative result for a mucinous cystic neoplasm is not particularly useful for ruling it out, though there is substantial uncertainty in the estimate.

Very low quality evidence from 1 retrospective cohort study (n=78) found that cystic fluid CEA with a cut-off level of 7 ng/ml had a high sensitivity of 0.94 (95% CI, 0.83-0.99) and a moderate specificity of 0.75 (95% CI, 0.55-0.89) for differentiating between mucinous and non-mucinous cystic neoplasms of the pancreas in adults with pancreatic cysts. The positive likelihood ratio of 3.76 (95% CI, 1.97-7.17) suggests that a positive result for a mucinous cystic neoplasm is not particularly useful in ruling it in, though there is uncertainty in the estimate. The negative likelihood ratio of 0.08 (95% CI, 0.03-0.24) suggests that a negative result for a mucinous cystic neoplasm is very useful for ruling it out, though there is substantial uncertainty in the estimate.

Very low quality evidence from 1 retrospective cohort study (n=226) found that cystic fluid CEA with a cut-off level of 105 ng/ml had a moderate sensitivity of 0.7 (95% CI, 0.62-0.77) and a low specificity of 0.63 (95% CI, 0.51-0.74) for differentiating between mucinous and non-mucinous cystic neoplasms of the pancreas in adults with pancreatic cysts. The positive likelihood ratio of 1.9 (95% CI, 1.39-2.6) and negative likelihood ratio of 0.48 (95% CI, 0.35-0.64) suggests that neither a positive or negative result for a mucinous cystic neoplasm is particularly useful for ruling it in or ruling it out.

Very low quality evidence from 2 cohort studies (1 prospective and 1 retrospective) (n=436) found that cystic fluid CEA with a cut-off level of 110 ng/ml had a low to moderate sensitivity ranging from 0.62 to 0.81 and a high specificity ranging from 0.93 to 0.98 for differentiating between mucinous and non-mucinous cystic neoplasms of the pancreas in adults with pancreatic cysts. The positive likelihood ratios were 8.68 (95% CI, 2.24-33.58) to 35.6 (5.12-247.66) suggesting that a positive result for a mucinous cystic neoplasm is either moderately useful or very useful for ruling it in, though there is substantial uncertainty in the estimates. The negative likelihood ratios were 0.2 (95% CI, 0.13-0.29) and 0.41 (95% CI, 0.28-0.59) suggesting that a negative result for a mucinous cystic neoplasm is not particularly useful for ruling it out, though there is uncertainty in the estimates.

Low quality evidence from 1 retrospective cohort study (n=180) found that cystic fluid CEA with a cut-off level of 129 ng/ml had a moderate sensitivity of 0.77 (95% CI, 0.7-0.84) and a moderate specificity of 0.83 (95% CI, 0.66-0.93) for differentiating between mucinous and non-mucinous cystic neoplasms of the pancreas in adults with pancreatic cysts. The positive likelihood ratio of 4.51 (95% CI, 2.16-9.38) suggests that a positive result for a mucinous cystic neoplasm is not particularly useful for ruling it out, though there is uncertainty in the estimate. The negative likelihood ratio of 0.27 (95% CI, 0.2-0.38) suggests that a negative result for a mucinous cystic neoplasm is not particularly useful for ruling it out.

Moderate quality evidence from 1 retrospective cohort study (n=124) found that cystic fluid CEA with a cut-off level of 200 ng/ml had a low sensitivity of 0.6 (95% CI, 0.49-0.71) and a high specificity of 0.93 (95% CI, 0.81-0.99) for differentiating between mucinous and non-mucinous cystic neoplasms of the pancreas in adults with pancreatic cysts. The positive likelihood ratio of 8.67 (95% CI, 2.87-26.19) suggests that a positive result for a mucinous cystic neoplasm is moderately useful for ruling it in, though there is substantial uncertainty in the estimate. The negative likelihood ratio of 0.42 (95% CI, 0.32-0.56) suggests that a negative result for a mucinous cystic neoplasm is not particularly useful for ruling it out.

Very low quality evidence from 1 retrospective cohort study (n=71) found that cystic fluid CEA with a cut-off level of 300 ng/ml had a low sensitivity of 0.41 (95% CI, 0.3-0.53) and a moderate specificity of 0.89 (95% CI, 0.52-1.0) for differentiating between mucinous and non-mucinous cystic neoplasms of the pancreas in adults with pancreatic cysts. The positive likelihood ratio of 3.86 (95% CI, 0.6-24.92) suggests that a positive result for a mucinous cystic neoplasm is not particularly useful for ruling it in, though there is substantial uncertainty in the estimate. The negative likelihood ratio of 0.64 (95% CI, 0.48-0.87) suggests that a negative result for a mucinous cystic neoplasm is not particularly useful for ruling it out.

Low quality evidence from 3 retrospective cohort studies (n=436) found that cystic fluid CEA with a cut-off level of 800 ng/ml had a low sensitivity ranging from 0.27 to 0.38 and a moderate to high specificity ranging from 0.86 to 0.95 for differentiating between mucinous and non-mucinous cystic neoplasms of the pancreas in adults with pancreatic cysts. The positive likelihood ratios were 2.3 (95% CI, 1.27-4.16), 2.45 (95% CI, 0.37-16.14) to 8.23 (95% CI, 2.07-32.75) suggesting that a positive result for a mucinous cystic neoplasm is either not particularly useful or moderately useful, though there is uncertainty in the estimates the negative likelihood ratios were 0.65 (95% CI, 0.57-0.78), 0.78 (95% CI, 0.67-0.9) to 0.82 (95% CI, 0.63-1.07) suggesting that a negative result for a mucinous cystic neoplasm is not particularly useful for ruling it out.

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Moderate quality evidence from 1 retrospective cohort study (n=71) found that cystic fluid CEA with a cut-off level of 6000 ng/ml had a moderate sensitivity of 0.86 (95% CI, 0.7-0.95) and a high specificity of 1.0 (0.9-1.0) for differentiating between mucinous and non-mucinous cystic neoplasms of the pancreas in adults with pancreatic cysts. The positive likelihood ratio of 62.69 (95% CI, 3.98-987.16) suggests that a positive result for a mucinous cystic neoplasm is very useful for ruling it in, though there is substantial uncertainty in the estimate. The negative likelihood ratio of 0.14 (95% CI, 0.06-0.32) suggests that a negative result for a mucinous cystic neoplasm is moderately useful for ruling it out, though there is substantial uncertainty in the estimate.

Adverse events

No evidence was identified to inform this outcome

Malignant versus benign pancreatic cystic lesions

Diagnostic accuracy

Very low quality evidence from 1 retrospective cohort study (n=134) found that cystic fluid CEA with a cut-off level of 30 ng/ml had a high sensitivity of 0.95 (95% CI, 0.85-0.99) and a moderate specificity of 0.85 (95% CI, 0.75-0.92) for detecting malignancy or potential malignancy of pancreatic cystic lesions in adults. The positive likelihood ratio of 6.15 (95% CI, 3.64-10.39) suggests that a positive result for malignancy is moderately useful for ruling it in, though there is substantial uncertainty in the estimate. The negative likelihood ratio of 0.06 (95% CI, 0.02-0.19) suggests that a negative result for malignancy is very useful for ruling it out, though there is uncertainty in the estimate.

Low quality evidence from 1 retrospective cohort study (n=52) found that cystic fluid CEA with a cut-off level of 45 ng/ml had a high sensitivity of 0.94 (95% CI, 0.7-1.0) and a low specificity of 0.64 (95% CI, 0.46-0.79) for detecting malignancy or potential malignancy of pancreatic cystic lesions in adults. The positive likelihood ratio of 2.6 (95% CI, 1.65-4.08) suggests that positive result for malignancy is not particularly useful for ruling it in, whilst the negative likelihood ratio of 0.1 (95% CI, 0.01-0.66) suggests that a negative result for malignancy is moderately useful in ruling it out, though there is substantial uncertainty in the estimate.

Low quality evidence from 1 retrospective cohort study (n=63) found that cystic fluid CEA with a cut-off level of 6000 ng/ml had a low sensitivity of 0.31 (95% CI, 0.11-0.59) and moderate specificity of 0.85 (95% CI, 0.72-0.94) for detecting malignancy or potential malignancy of pancreatic cystic lesions in adults. The positive likelihood ratio of 2.1 (95% CI, 0.77-5.69) suggests that a positive result for malignancy is not particularly useful for ruling it in, though threre is uncertainty in the estimate. The negative likelihood ratio of 0.81 (95% CI, 0.57-1.15) suggests that a negative result for malignancy is not particularly useful for ruling it out.

Adverse events

No evidence was identified to inform this outcome

5.3.6.1.2 Serum CEA

Low quality evidence from 1 retrospective study (n= 85), which did not specify the cut-off level, found that serum CEA had a low sensitivity of 0.35 (95% CI, 0.22-0.51) and moderate specificity of 0.84 (95% CI, 0.68-0.94) for detecting malignancy or potential malignancy of pancreatic cystic lesions in adults. The positive likelihood ratio of 2.18 (95% CI, 0.96-4.99) and negative likelihood ratio of 0.77 (95% CI, 0.6-0.99) suggest that neither a positive or negative result for malignancy is particularly useful for ruling it and ruling it out.

Adverse events

No evidence was identified to inform this outcome

5.3.6.2 Cystic fluid and serum CA 19-9

5.3.6.2.1 Cystic fluid CA 19-9

Diagnostic accuracy

Moderate quality evidence from a meta-analysis of 14 studies (n=1489) found that cystic fluid CA 19-9 at a cut-off of between 35 and 45 ng/ml had a low sensitivity of 0.5 (95% CI, 0.37-0.63) and moderate specificity of 0.87 (95% CI, 0.84-0.9) for differentiating between mucinous and non-mucinous cystic neoplasms of the pancreas in adults with pancreatic cysts. The positive likelihood ratio of 3.92 (95% CI, 3.16-4.87) and negative likelihood ratio of 0.58 (95% CI, 0.46-0.73) suggest that neither a positive or negative result for a mucinous cystic neoplasm is particularly useful for ruling it in and ruling it out.

Adverse events

No evidence was identified to inform this outcome

5.3.6.2.2 Serum CA 19-9

Low quality evidence from 1 retrospective study (n= 85), which did not specify the cut-off level, found that serum CA 19-9 had a low sensitivity of 0.58 (95% CI, 0.43-0.72) and moderate specificity of 0.86 (95% CI, 0.71-0.95) for detecting malignancy or potential malignancy of pancreatic cystic lesions in adults. The positive likelihood ratio of 4.32 (95% CI, 1.85-10.09) suggest that a positive result for malignancy is not particularly useful for ruling it in, though there is substantial uncertainty in the estimate. The negative likelihood ratio of 0.48 (95% CI, 0.34-0.69) suggest that a negative result for malignancy is not particularly useful for ruling it out.

Adverse events

No evidence was identified to inform this outcome

5.3.6.3 Cytology: EUS-FNA

5.3.6.3.1 Mucinous cystic neoplasms versus non-mucinous cystic neoplasms of the pancreas

Diagnostic accuracy

Very low quality evidence from a meta-analysis of 6 cohort studies (3 prospective and 3 retrospective) (n=639) found EUS-FNA-based cytology had a low sensitivity of 0.55 (95% CI, 0.27-0.8) and high specificity of 0.94 (95% CI, 0.86-0.97) for differentiating between mucinous and non-mucinous cystic neoplasms of the pancreas in adults with pancreatic cysts. The positive likelihood ratio of 8.52 (95% CI, 3.41-21.31) suggests that a positive result for a mucinous cystic neoplasm is moderately useful for ruling it in, though there is substantial uncertainty in the estimate, the negative likelihood ratio of 0.48 (95% CI, 0.25-0.91) suggests that a negative result for a mucinous cystic neoplasm is not particularly useful for ruling it out.

Adverse events
No evidence was identified to inform this outcome.

5.3.6.3.2 Malignant versus benign pancreatic cystic lesions

Diagnostic accuracy

Low quality evidence from a meta-analysis of 4 cohort studies (1 prospective and 3 retrospective) (n=454) found that EUS-FNA-based cytology had a low sensitivity of 0.7 (95% CI, 0.54-0.81) and a high specificity of 0.93 (95% CI, 0.88-0.96) for detecting malignancy or potential malignancy of pancreatic cystic lesions in adults. The positive likelihood ratio of 9.67 (95% CI, 6.14-15.24) suggests that a positive result for a mucinous cystic neoplasm is moderately useful for ruling it in, though there is uncertainty in the estimate. The negative likelihood ratio of 0.33 (95% CI, 0.21-0.5) suggests that a negative result for malignancy is not particularly useful for ruling it out.

Adverse effects

High quality evidence from a meta-analysis of 40 studies (n=5124) found that EUS-FNA cytology is a safe procedure for diagnosis of pancreatic cystic lesions and is associated with a relatively low incidence of adverse events.

5.3.6.4 Imaging: CT

5.3.6.4.1 Mucinous cystic neoplasms versus non-mucinous cystic neoplasms of the pancreas

Diagnostic accuracy

Low quality evidence from 1 retrospective cohort study (n=53) found that CT had a moderate sensitivity of 0.81 (95% CI, 0.63-0.93) and a moderate specificity of 0.86 (95% CI, 0.78-0.93) for differentiating between mucinous and non-mucinous cystic neoplasms of the pancreas in adults with pancreatic cysts. The positive likelihood ratio of 5.96 (95% CI, 3.49-10.16) suggests that a positive result for a mucinous cystic neoplasm is moderately useful for ruling it in, though there is substantial uncertainty in the estimate. The negative likelihood ratio of 0.22 (95% CI, 0.11-0.46) suggests that a negative result for a mucinous cystic neoplasm is not particularly useful for ruling it out, though there is uncertainty in the estimate.

Adverse events
No evidence was identified to inform this outcome.

5.3.6.4.2 Malignant versus benign pancreatic cystic lesions

Diagnostic accuracy

Low quality evidence from a meta-analysis of 4 cohort studies (1 prospective and 3 retrospective) (n=210) found that CT had a low sensitivity of 0.64 (95% CI, 0.53-0.74) and a moderate specificity of 0.82 (95% CI, 0.74-0.88) for detecting malignancy or potential malignancy of pancreatic cystic lesions in adults. The positive likelihood ratio of 3.6 (95% CI, 2.39-5.44) suggests that a positive result for malignancy is not particularly useful for ruling it in, though there is uncertainty in the estimate. The negative likelihood ratio of 0.44 (95% CI, 0.32-0.59) suggests that a negative result for malignancy is not particularly useful for ruling it and ruling it out.

Adverse events
No evidence was identified to inform this outcome.

5.3.6.5 Imaging: EUS

Mucinous cystic neoplasms versus non-mucinous cystic neoplasms of the pancreas

Diagnostic accuracy

Very low quality evidence from a meta-analysis of 4 cohort studies (1 prospective and 3 retrospective) (n=210) found that EUS had a low sensitivity of 0.67 (95% CI, 0.43-0.84) and low specificity of 0.65 (95% CI, 0.48-0.78) for differentiating between mucinous and non-mucinous cystic neoplasms of the pancreas in adults with pancreatic cysts. The positive

likelihood ratio of 1.88 (95% CI, 1.18-3.0) and negative likelihood ratio of 0.52 (95% CI, 0.28-0.96) suggests that neither a positive or negative result for a mucinous cystic neoplasm is particularly useful for ruling it in or ruling it out.

Adverse events
No evidence was identified to inform this outcome.

5.3.6.5.1 Malignant versus benign pancreatic cystic lesions

Diagnostic accuracy

Very low quality evidence from 3 retrospective cohort studies (n=187) found that EUS had a low to high sensitivity ranging from 0.71 to 0.97 and a low specificity ranging from 0.4 to 0.73 for detecting malignancy or potential malignancy of pancreatic cystic lesions in adults. The positive likelihood ratios were 1.61 (95% CI, 1.24-2.09), 1.91 (95% CI, 1.17-3.11) and 3.65 (95% CI, 1.57-8.45) suggesting that a positive result for malignancy is not particularly useful for ruling it in. The negative likelihood ratios were 0.04 (95% CI, 0.01-0.27), 0.08 (95% CI, 0.01-0.59) and 0.46 (95% CI, 0.25-0.85) suggesting that a negative result for malignancy is either very useful or not particularly useful in ruling it out, though there is substantial uncertainty in the estimates.

Adverse events
No evidence was identified to inform this outcome.

5.3.6.6 Imaging: EUS-FNA

Diagnostic accuracy

Low quality evidence from 1 retrospective study (n=119) found that EUS-FNA had a moderate sensitivity of 0.76 (95% CI, 0.65-0.85) and a low specificity of 0.73 (95% CI, 0.56--0.85) for differentiating between mucinous and non-mucinous cystic neoplasms of the pancreas in adults with pancreatic cysts. The positive likelihood ratio of 2.76 (95% CI, 1.64-4.64) and negative likelihood ratio of 0.33 (95% CI, 0.21-0.51) suggests that neither a positive or negative result for a mucinous cystic neoplasm is particularly useful for ruling it in or ruling it out.

Adverse events
No evidence was identified to inform this outcome.

5.3.6.7 Imaging: PET/CT

Diagnostic accuracy

Very low quality evidence from 3 cohort studies (1 prospective and 2 retrospective) (n=164) found that 18-FDG PET/CT had a moderate to high sensitivity ranging from 0.78 to 0.94 and a high specificity ranging from 0.94 to 1.0 for detecting malignancy or potential malignancy of pancreatic cystic lesions in adults. The positive likelihood ratios were 12.0 (95% CI, 0.8-179.92), 15.53 (95% CI, 4.03-59.82) and36.71 (95% CI, 5.28-255.01) suggesting that a positive result for malignancy is very useful for ruling it in, though there is substantial uncertainty in the estimates. The negative likelihood ratios were 0.06 (95% CI, 0.01-0.4), 0.06 (95% CI, 0.01-0.4) and 0.22 (95% CI, 0.07-0.75) suggesting that a negative result for malignancy is either very or moderately useful for ruling it out, though there is substantial uncertainty in the estimates.

Adverse events

No evidence was identified to inform this outcome.

5.3.6.8 Imaging: MRI

5.3.6.8.1 Mucinous cystic neoplasms versus non-mucinous cystic neoplasms of the pancreas

Diagnostic accuracy

Moderate quality evidence from 1 retrospective study (n=53) found that MRI had a high sensitivity of 0.97 (95% CI, 0.83-1.0) and a high specificity of 0.91 (95% CI, 0.71-0.99) for differentiating between non-mucinous and mucinous neoplasms. The positive likelihood ratio of 10.65 (95% CI, 2.84-39.97) and negative likelihood ratio of 0.04 (95% CI 0.01-0.25, suggest that both a positive and negative result for a mucinous cystic neoplasm are very useful for ruling it in and ruling it out, though there is substantial uncertainty in the estimates.

Adverse events
No evidence was identified to inform this outcome.

5.3.6.8.2 Malignant versus benign pancreatic cystic lesions

Low quality evidence from a meta-analysis of 4 retrospective cohort studies (n=271) found that MRI had a moderate sensitivity of 0.79 (95% CI, 0.64-0.89) and a moderate sensitivity of 0.84 (95% CI, 0.69-0.92) for detecting malignancy or potential malignancy of pancreatic cystic lesions in adults. The positive likelihood ratio of 4.81 (95% CI, 2.54-9.08) and negative likelihood ratio of 0.25 (95% CI, 0.15-0.43) suggest that neither a positive or negative result for malignancy is particularly useful for ruling it and ruling it out, though there is uncertainty in the estimates.

Adverse events
No evidence was identified to inform this outcome.

5.3.7 Recommendations

6. **Offer a pancreatic protocol CT scan or magnetic resonance cholangiopancreatography (MRI-MRCP) to people with pancreatic cysts. If more information is needed after one of these tests, offer the other one.**

7. **Refer people with any of these high-risk features for resection:**
    - obstructive jaundice with cystic lesions in the head of the pancreas
    - enhancing solid component in the cyst
    - a main pancreatic duct that is 10 mm diameter or larger.

8. **Offer EUS after CT and MRI-MRCP if more information on the likelihood of malignancy is needed, or if it is not clear whether surgery is needed.**

9. **Consider fine-needle aspiration during EUS if more information on the likelihood of malignancy is needed.**

10. **When using fine-needle aspiration, perform carcinoembryonic antigen (CEA) assay in addition to cytology if there is sufficient sample.**

5.3.8 Evidence to recommendations

5.3.8.1 Relative value placed on the outcomes considered

Diagnostic accuracy (sensitivity, specificity, positive predictive value and negative predictive value) and adverse events were considered the critical outcomes for this question.

Diagnostic accuracy was reported for all comparisons of interest. Adverse events were only reported for EUS-FNA.

5.3.8.2 Quality of evidence

Evidence was identified on the diagnostic accuracy of CEA, CA 19-9, EUS-FNA, CT, EUS, PET and MRI. The evidence for CEA ranged from very low to moderate quality, for CA 19-9 was very low, for EUS-FNA ranged from very low to low, for CT was low quality, for EUS ranged from low to moderate quality, for PET was very low and for MRI was moderate quality.

The committee noted several limitations with the evidence base. First, a good proportion of the included studies are old and imaging quality is known to have improved since. Second, many of these older studies do not differentiate between IPMN and mucinous cystic neoplasms. Information which is now considered important in identifying which cysts are at higher risk of becoming cancer. Third, there is no validated assay for CEA that is consistently used across all laboratories. This makes it difficult to assess the true diagnostic accuracy of the test. Fourth, the evidence was very fragmented due to different descriptions for malignancy, gold standard of diagnosis, study design and type of cysts.

The committee noted, whilst there was a good amount of data on the diagnostic accuracy of investigations to differentiate mucinous cysts from non-mucinous cysts, there was very little data about what investigations can accurately identify those mucinous cysts which are at high risk of becoming pancreatic cancer. The committee focused on making recommendations about the most effective diagnostic pathway to identify cysts at high risk of becoming malignant as this was the focus of the question.

The committee noted that the data on PET appeared to be promising but, being mindful of the low quality of the currently available evidence and the forthcoming HTA in this area, declined to make any recommendations on its use.

5.3.8.3 Consideration of clinical benefits and harms

Based on the evidence, the committee noted that MRI had moderate sensitivity and specificity for differentiating benign from malignant pancreatic cysts. They also noted that whilst CT had low sensitivity, it had moderate specificity for differentiating benign from malignant pancreatic cysts. The committee agreed, based on their knowledge, that both of these investigations are widely available, non-invasive and can provide information on high-risk features of cysts. However they also noted that MRI is more expensive than CT, waiting lists are longer for this investigation and the use of MRI can be contraindicated for some people. Therefore, despite the evidence showing that the sensitivity of CT was not equivalent to that of MRI, the committee recommended either CT or MRI as the initial diagnostic investigation for people with pancreatic cysts in light of the practical constraints around the use of MRI.

Based on their clinical knowledge and experience, the committee noted that if a CT scan is used a pancreatic protocol CT scan would be needed to ensure good visualisation of any pathology in the pancreas. They agreed that if MRI is used MRI-MRCP should be used as this will enable the pancreatic duct anatomy to be visualised.

The committee agreed, based on their knowledge, that if the initial CT/MRI identified any high-risk features then the cyst was likely to become malignant so resection would be indicated. They noted that the evidence did not help to identify what the ‘high-risk’ features are. However, they agreed that their recommendation would need to specify them in order to be implementable. The committee agreed the high-risk features that should prompt resection based on their experience and informed by their knowledge of currently accepted definitions.

The committee considered that after an initial CT/MRI there may be some instances where there is uncertainty over whether or not to operate. In these equivocal cases the committee agreed, based on the evidence, that EUS and FNA could help to provide additional information. However, because both EUS and FNA are more invasive, and carry the risk of potential complications, the committee recommended these investigations be reserved for when more information must be obtained in order to determine whether to operate or not.

The committee also agreed, based on the evidence and their experience, whilst CEA was not helpful in differentiating between benign and malignant pancreatic cysts, it can provide additional useful diagnostic information. They, therefore, recommended that if an FNA was being done, CEA should be requested at the same time to avoid unnecessary repeat procedures.

The committee agreed that the potential benefits of the recommendations made would be improved and streamlined diagnosis of pancreatic cancer in people with cysts. They considered that EUS/FNA are more invasive investigations and, therefore, are associated with potential complications. They balanced these harms by only recommending the more invasive investigations for a sub-set of people where additional diagnostic information is necessary.

5.3.8.4 Consideration of economic benefits and harms

The committee noted that no relevant published economic evaluations had been identified and no additional economic analysis had been undertaken in this area.

The committee agreed that current practice is to use EUS to investigate most cysts. There should, therefore, be some decrease in costs associated with the recommendations as EUS will now only be used in a sub-set of the population. However, there may also be a corresponding increase in costs associated with the use of the other investigations recommended. The committee agreed that overall the recommendations were likely to be cost neutral.

5.3.9 References

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5.4 People with inherited high risk of pancreatic cancer

Review question: What is the most effective monitoring protocol for adults with an inherited high risk of pancreatic cancer in secondary care to ensure early diagnosis?

5.4.1 Introduction

There are three main groups of people who are at a high risk of developing pancreatic cancer:

1. those with familial pancreatic cancer
2. those with hereditary pancreatitis

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3. those with hereditary tumour predisposition syndromes

People with hereditary pancreatitis have a 70 fold increased risk of pancreatic cancer. The life time risk is 35-40% and rises with age. People with familial pancreatic cancer have a life time risk of 30-50% which rises with age.

Guidance is needed on the most effective monitoring protocol to ensure early diagnosis in people with an inherited high risk of pancreatic cancer.

5.4.1.1 Review protocol summary

The review protocol summary used for this question can be found in Table 57. Full details of the review protocol can be found in Appendix C.

Table 52: Clinical review protocol summary for the review of most effective monitoring protocol for adults with an inherited high risk of pancreatic cancer

Population	Adults who have a history of:
	• familial pancreatic cancer (FPC)
	• associated with chronic inflammation of the pancreas, namely cystic fibrosis and hereditary chronic pancreatitis
	• hereditary tumour predisposition syndromes, namely
	  ○ ataxia-telangiectasia
	  ○ familial atypical multiple mole melanoma (FAMMM)
	  ○ familial adenomatous polyposis (FAP)
	  ○ hereditary breast and ovarian cancer syndrome (HBOC)
	  ○ Li-Fraumeni syndrome
	  ○ Lynch syndrome (HNPCC)
	  ○ Peutz-Jeghers syndrome

Index test	• Biomarkers in blood, serum or pancreatic juice
	• CA19-9
	• CEA
	• Kras
	• GNAS
	• p53
	• p16)
	• Imaging
	• Ultrasound
	• CT
	• MRI/MRCP
	• PET-CT
	• Biopsy (cytology or histology)
	  ○ endoscopic ultrasound +/- FNA
	  ○ EUS +/- core biopsy
	  ○ ERCP
	  ○ laparoscopy + biopsy
	  ○ percutaneous pancreatic biopsy

Reference standard	• Definitive diagnosis • Preferably pathological diagnosis • Each Other

	• Alone and in combination
Outcomes	• Early diagnosis • Survival • Diagnostic Accuracy including: • Sensitivity • Specificity • Positive Predictive Value • Negative Predictive Value • Adverse events of interventions • HRQoL

5.4.2 Description of clinical evidence

Eighteen articles were identified: 17 of these concerned screening/surveillance programs, whilst one was a secondary study that reported on the psychological burden/quality of life of participating in one of these screening programs. All 17 of the primary studies reported diagnostic yield (early diagnosis). A summary of the included studies is presented in Table 53.

Seventeen studies (n=2661) were identified that evaluated the diagnostic performance of screening and/or surveillance programs for adults with an inherited 'high' risk of pancreatic cancer: 5 prospective cohort studies (Canto et al. 2006; Chang et al. 2017; Potjer et al. 2013; Vasen et al. 2016; Verna et al. 2010), one retrospective review of a prospective cohort study (Nocholson et al. 2015), and 11 case series (Al-Sukhni et al. 2012; Bartsch et al. 2016; Canto et al. 2004; Canto et al. 2012; Del Chiaro et al. 2015; Harinck et al. 2016; Kimmey et al. 2002; Ludwig et al. 2011; Poley et al. 2009; Sud et al. 2014; Zubarik et al. 2011). The majority of the studies included familial pancreatic cancer (FPC), which was typically defined as an individual that has two or more relatives with pancreatic cancer. In addition, all of the studies (with the exception of Canto et al. 2012 and Harinck et al. 2016) consisted of an initial test(s) and, given an abnormal result, subsequent imaging or other tests. The most common initial test (11 studies) was MRI/MRCP, or MRI combined with EUS±FNA, whilst the most common subsequent test was EUS±FNA. Only two studies (Canto et al. 2006; Canto et al. 2012) used CT as part of the initial screening test and in both cases this was in combination with other tests (EUS and/or MRI). One multicentre prospective study (n=546; Zubarik et al. 2011) used serum CA 19-9 as the initial test and EUS-FNA given an abnormal result (values >37 U/ml). Data on the diagnostic yield and adverse events of screening/surveillance programs is not amenable to a meta-analysis or depiction using forest plots (however see Nicholson et al. 2015 below). Therefore a narrative summary and table listing the relevant results have been presented.

One retrospective review of a prospective cohort study (n=60; Nicholson et al. 2015) examined the incidence of post-ERCP pancreatitis with and without prophylaxis in people with familial pancreatic cancer or hereditary pancreatitis.

One interrupted time series study (n=152; Konings et al. 2016) examined participants enrolled in the annual surveillance program reported in Harinck et al. 2016 (see above). Although this secondary study did not report health-related quality of life, it reported change on the Cancer Worry scale and the HADS-Anxiety and HADS–Depression scales and so was included.

The QUADAS-2 checklist was used to evaluate the risk of bias and applicability (indirectness) of the screening/surveillance studies. Due to the type of data (diagnostic yield) reported, the criteria of inconsistency and imprecision were not evaluated for these studies, and the quality of each study was therefore rated individually. A narrative summary of the evidence is presented. The GRADE risk of bias tool was used to evaluate one study that reported post-ERCP pancreatitis with and without prophylaxis.

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Further information about the search strategy can be found in Appendix D. See study selection flow chart in Appendix E, forest plots in Appendix H, summary of QUADAS-2 study quality evaluations in Appendix J, study evidence tables in Appendix F and list of excluded studies in Appendix G.

5.4.3 Summary of included studies

A summary of the studies that were included in this review is presented in Table 53.

Table 53: Summary of included studies

Study	Country	N	Groups at risk of pancreatic cancer	Initial baseline test(s)	Test(s) conducted if abnormal initial baseline test(s) result	Frequency of follow up if normal result	Frequency of follow up if abnormal result	Outcomes
Al-Sukhni et al. 2012	Canada	262	BRCA1, BRCA2, FDR with multiple primary cancers, FPC, HP, p16, PJS,	MRI	MRI-CT +/or ERCP +/or EUS	Annually	-	Diagnostic yield
Bartsch et al. 2016	Germany (FaPaCa[b])	253	BRCA1, BRCA2, FPC, PALB2	MRI/MRCP + EUS	MRI/MRCP + EUS±FNA	Annually	Every 3 months if no surgery	Diagnostic yield Adverse events
	Spain (PanGen-Fam)			MRI + EUS	MRI + EUS			
	Netherlands (Leiden[b])			MRI/MRCP, EUS*	EUS + CT			
Canto et al. 2006	USA	78	FPC, PJS	EUS + CT	EUS-FNA + CT; ERCP*	Annually	Within 3-6 months of initial test	Diagnostic yield Adverse events
Canto et al. 2004	USA	38	FPC, PJS	EUS	EUS-FNA If high-risk: CT; ERCP*	Annually	Within 3-6 months of initial test	Diagnostic yield Adverse events
Canto et al. 2012	USA	216	BRCA2, FPC, PJS	MRI + CT + linear/radial EUS±FNA	-	Within 1-3 years	<3 months if no surgery; 6-12 months if small cyst or	Diagnostic yield Adverse events

Study	Country	N	Groups at risk of pancreatic cancer	Initial baseline test(s)	Test(s) conducted if abnormal initial baseline test(s) result	Frequency of follow up if normal result	Frequency of follow up if abnormal result	Outcomes
							worrisome lesion	
Chang et al. 2017c	Taiwan	303	FPC, BRCA2, HP	MRI/MRCP	EUS±FNA*	Every 2-3 years	Annually	Diagnostic yield Adverse events
Del Chiaro et al. 2015	Sweden	40	BRCA1, BRCA2, FPC, p16	MRI/MRCP	CT, EUS±FNA	Annually	6 months if unspecific or IPMN without indication for surgery	Diagnostic yield
Harinck et al. 2016/ Konings et al. 2016	Netherlands	166/140	CDKN2A, BRCA1, BRCA2, FPC, p53, PJS	EUS + MRI	-	Annually if normal or cystic lesion>10mm	3 months if unclear; 6 months if cyst or side-branch IPMN >10 mm and <30 mm without malignant features	Diagnostic yield Adverse events/ Quality of life
Kimmey et al. 2002	USA	46	FPC	EUS	ERCP	Not reported	-	Diagnostic yield Adverse events
Ludwig et al. 2011	USA	109	FPC, PJS	MRI/MRCP	EUS±FNA	Annually	-	Diagnostic yield Adverse events
Nicholson et al. 2015	UK	60	FPC, HP	ERCP with and without prophylaxisd	-	Not reported	-	Diagnostic yield Adverse events

Study	Country	N	Groups at risk of pancreatic cancer	Initial baseline test(s)	Test(s) conducted if abnormal initial baseline test(s) result	Frequency of follow up if normal result	Frequency of follow up if abnormal result	Outcomes
Poley et al. 2009	Netherlands	44	BRCA1, BRCA2, FPC, HP, p16, p53	EUS	CT, MRI	Not reported	EUS+MRI every 6 months for cystic lesions	Diagnostic yield Adverse events
Potjer et al. 2013	Germany (FaPaCa[b])	125	FPC	MRI/MRCP + EUS	MRI/MRCP, EUS	Annually	After 3 months	Diagnostic yield
	Netherlands (Leiden[b])	116	p16	MRI/MRCP, EUS*				
Sud et al. 2014	USA	30	FPC, HP, Lynch Syndrome, p16, PJS	EUS	EUS-FNA	Annually	-	Diagnostic yield Adverse events
Vasen et al. 2016	Netherlands (Leiden[b,e])	178	CDKNA2, p16	MRI/MRCP	EUS, CT	Annually	MRI/MRCP within 3-6 months if small lesion	Diagnostic yield Overall survival Adverse events
Verna et al. 2010c	USA	51	BRCA1, BRCA2, FPC, HP, p16, PJS, Other	Moderate risk: EUS±FNA or MRI; ERCP* High-risk: EUS±FNA + MRI; ERCP*	EUS±FNA and/or ERCP**	Annually if low or moderate risk; every 6 months if high risk	-	Diagnostic yield Adverse events
Zubarik et al. 2011	USA	546	BRCA2, FPC, PJS	CA 19-9	EUS-FNA	Annually if normal CA 19-9; After 3 months if normal EUS-FNA	-	Diagnostic yield

*Notes: *, test was optional for participant; **, EUS±FNA and/or ERCP if it was not performed at baseline; $, includes detection at baseline and follow up; ^, Results include only pancreatic neoplasms that were pathologically proven via histology or cytology; a, 'Diagnostic yield' defined as detection of any pathologically-proven malignant or premalignant lesion (PanIN≥2, IPMN and pancreatic adenocarcinoma), or lesions that are morphologically suspicious for BD-IPMNs; b, Multisite study. In FaPaCa*

program, from 2002-2010, participants received annual screening with MRI/MRCP and EUS; from 2011 onwards, participants received annual MRI/MRCP with EUS every 3 years. In Leiden program, participants from 2011 onwards were given option of having EUS. See evidence table (Appendix 4) for further details; c, study included individuals at low risk (i.e. <5% compared to normal population/1 relative of any degree with PC more than 55 years-old). Data presented only for high- and moderate-risk individuals; diagnostic yield including low-risk groups was 15/303 in Chang et al. 2017 and 6/46 in Verna et al 2010; d, participants in this study were part of EUROPAC registry and received CT or MRI (and EUS for FPC group. ERCP was optional; e, Data presented only for Leiden CDKNA2/p16 cohort. Updated results for FPC and BRCA cohorts reported in Bartsch et al. 2017.

Abbreviations: BRCA, breast cancer susceptibility gene; CDKN2A, cyclin dependent kinase inhibitor 2A; CT, computed tomography; EUS-endoscopic ultrasonography; EUS-FNA, endoscopic ultrasound-guided fine-needle aspiration; ERCP, endoscopic retrograde cholangiopancreatography; FPC, familial pancreatic cancer; HP, hereditary pancreatitis; p16, hereditary multiple mole melanoma syndrome; p53, Li-Fraumeni Syndrome; PALB2, partner and localiser of BRCA2; PC, pancreatic cancer; MRI, magnetic resonance imaging; MRI-CT, MRI with contrast, multiphase contrast-enhanced CT; MRCP, magnetic resonance cholangiopancreatography; PET-CT, positron emission tomography-computed tomography; PJS, Peutz-Jeghers Syndrome (LKB1).

5.4.4 Clinical evidence profile

5.4.4.1 Screening/surveillance studies

5.4.4.1.1 Narrative summary of evidence

The majority of the 17 studies were in adults with familial pancreatic cancer, the majority of which also included relatively small numbers of individuals with identified germline mutations such as BRCA, p16 or p53. The majority of the participants were female, ranging from 55% to 75% of the samples (approximately 60% female across 15 studies). One study did not report patient characteristics, and in one study this information was unclear. Nine studies were conducted in the USA/Canada, 6 in Europe (2 of which were international multicentre studies), and 1 in Taiwan. Only one study was conducted in the UK (Nicholson et al. 2015).

The most common initial screening test in the 17 published studies was MRI/MRCP with or without additional EUS (8 studies), whilst the most common test given an abnormal initial result was EUS±FNA (10 studies). Three screening programs did not use a subsequent test given an abnormal result. Fifteen of the articles included only individuals with at least a 5% or more increased risk of pancreatic cancer compared to those in the normal population, whilst two of the studies included individuals at 'average' risk of pancreatic cancer.

The diagnostic yield reported in the identified screening/surveillance studies varied widely, ranging from 0.9% to 39%, depending on the type of malignant or premalignant lesion identified, the population and reference test (e.g. surgical pathology only) employed, whether additional tests were conducted given initial abnormal results, and whether results included baseline results only or included follow up.

Of the 2661 individuals at risk, 2418 were screened: 41 (1.7%) of these were diagnosed with pancreatic cancer, resulting in an overall screening efficiency of 59 screened individuals to detect one case of pancreatic cancer. If individuals with premalignant lesions are included (i.e. those with IPMN and/or PanIN≥2), 145 individuals (including those with pancreatic cancer) were identified, resulting in a screening efficiency of 6.0% (1 malignant or premalignant lesions for every 17 individuals at risk screened). This suggests that screening high- and moderate- individuals at risk for malignant lesions only will be both costly and time consuming and that screening programs should include premalignant lesions.

Only one study (Vasen et al. 2016), which evaluated the diagnostic yield of MRI/MRCP, reported overall survival (a 5-year overall survival of 24% for the CDKN2A/p16 cohort with pancreatic ductal adenocarcinoma). Very few adverse events as a result of participating in the screening/surveillance programs were reported in the 13 studies that reported procedure-related complications. The majority of these were reported in one study (Canto et al. 2006) or were related to post-ERCP pancreatitis. Although no studies were found that reported health-related quality of life, there was one secondary study (Konings et al. 2016) related to participation in the screening/surveillance program reported in Harinck et al. 2016 (comprising EUS and MRI), that reported significant decreases in worry associated with having cancer (approximately 0.5 point decrease on the Cancer Worry Scale) for every year enrolled in the program. However, participants in this study reported no significant change in depression and anxiety.

The risk of bias and indirectness for each study was generally low for both quality measures with the exception of 2 studies (Canto et al. 2012; Ludwig et al. 2011) both of which had an unclear risk of bias. Overall, the majority of the studies were of 'high' quality (rated as ++), with the aforementioned 2 studies rated as 'low' (+) quality. Generally it was not clear whether the reference test(s) was interpreted without knowledge of the index test(s) results.

A summary of the evidence for this review question is presented in Table 54.

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Table 54: Summary of evidence and quality evaluation

Study	Risk of bias	Indirectness	Overall study quality[a]	Diagnostic yield[b]	Other outcomes
Al-Sukhni et al. 2012	LOW	LOW	++	19/262 (1.1%)$	Not reported
Bartsch et al. 2016	LOW	LOW	++	15/253 (5.9%)^, $	No MRI- nor EUS-related complications
Canto et al. 2006	LOW	LOW	++	8/78 (10.3%)^, $	No severe EUS/EUS-FNA complications Mild post-EUS/EUS-FNA abdominal pain=22/78 Other mild adverse events=2 Post-ERCP pancreatitis=5/67 No significant post-operative complications
Canto et al. 2004	LOW	LOW	++	2/38 (5.3%)^	No post-EUS-FNA complications. Mild post-ERCP pancreatitis=2/24
Canto et al. 2012	UNCLEAR	LOW	+c	5/216 (2.3%)^ 85/216 (39.4%)$	No surgery-related complications
Chang et al. 2017	LOW	LOW	++	6/131c (4.6%)^, $	No procedure-related complications
Del Chiaro et al. 2015	LOW	LOW	++	5/40 (12.5%)^, $	Not reported
Harinck et al. 2016/ Konings et al. 2016	LOW	LOW	++	9/139 (6.4%)	No procedure-related complications Significant improvement on Cancer Worry Scale (decrease of 0.5 point every year); mean score=13 (sd 3.6) No significant change on depression scores (HADS-D) over time; mean score=2.8 (sd 3.2); 5% of participants had clinically significant scores (HADS-D>10)

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Study	Risk of bias	Indirectness	Overall study quality[a]	Diagnostic yield[b]	Other outcomes
					No significant change on anxiety scores (HADS-A) over time; mean score=4.5 (sd 3.7); 7% of participants had clinically significant scores (HADS-A>10)
Kimmey et al. 2002	LOW	LOW	++	12/46 (26.0%)^, $	No post-ERCP complications (0/28)
Ludwig et al. 2011	UNCLEAR	LOW	+d	9/109 (8.3%)$	No procedure-related complications
Nicholson et al. 2015	LOW	LOW	++	2/60 (3.3%)^	Post-ERCP pancreatitis=13 cases in 56 procedures (No prophylaxis group=7 cases in 16 procedures; Prophylaxis group=6 in 40 procedures) Post-ERCP duodenal perforation=1
Poley et al. 2009	LOW	LOW	++	10/44 (23.0%)	No EUS-related complications
Potjer et al. 2013	LOW	LOW	++	FPC: 7/125 (5.6%)^, $	Not reported
			++	p16: 7/116 (6.0%)^, $	
Sud et al. 2014	LOW	LOW	++	3/16 (18.8%)^, $	No EUS-related complications
Vasen et al. 2016	LOW	LOW	++	15/178[e] (8.4%)^, $	No procedure-related complications Resection rate of 75% and 5-year survival rate of 24% for p16 cohort with PDAC
Verna et al. 2010	LOW	LOW	++	6/46c (13.0%)^	No procedure-related complications
Zubarik et al. 2011	LOW	LOW	++	5/546 (0.9%)^, $	Not reported

Notes: Data on diagnostic yield is not amenable to evaluation of imprecision and inconsistency and so are not applicable. $, includes detection at baseline and follow up; ^, Results include only pancreatic neoplasms that were pathologically proven via histology or cytology; a, Since a meta-analysis was not possible, overall study quality

was assessed using the following method: '++' indicates that all or most of the QUADAS-2 checklist criteria were fulfilled, and where they were not fulfilled the conclusions are unlikely to alter; '+' indicates that some of the QUADAS-2 checklist criteria were fulfilled, and whether they were not fulfilled or not adequately described, the conclusions are unlikely to alter; '-' indicates that few or none of the checklist criteria were fulfilled and the conclusions are likely to alter; b, 'Diagnostic yield', in line with the definition suggested by the CAPS Consortium summit (Canto, M. I., Harinck, F., Hruban, R. H., Offerhaus, G. J., Poley, J. W., Kamel, I., ... & Levy, M. J. (2013). International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. Gut, 62(3), 339-347.), is defined as detection of any pathologically-proven malignant or premalignant lesion (PanIN≥2, IPMN and pancreatic adenocarcinoma), or lesion that is morphologically suspicious for BD-IPMNs; c, study included individuals at low risk (i.e. <5% compared to normal population/1 relative of any degree with PC more than 55 years-old). Data presented only for high- and moderate-risk individuals; diagnostic yield including low-risk groups was 15/303 (5.0%) in Chang et al. 2017 and 6/51 (11.8%) in Verna et al 2010; d, there was 4% dropout rate. Participants were included in the data for diagnostic yield if they had an abnormal result on any one of the index texts (MRI, CT or EUS±FNA). Ten percent of the sample received initial CT rather than MRI/MRCP; e, Data presented only for Leiden CDKNA2/p16 cohort. Updated results for FPC and BRCA cohorts reported in Bartsch et al. 2017.

5.4.4.2 ERCP with prophylaxis versus ERCP only

Table 55: Summary clinical evidence profile for ERCP with prophylaxis versus ERCP only on reducing post-ERCP pancreatitis in people at high risk of pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	ERCP only	ERCP with prophylaxis				
# ERCP procedures resulting in pancreatitis - Familial Pancreatic Cancer group	438 per 1000[1]	149 per 1000 (61 to 376)[1]	RR 0.34 (0.14 to 0.86)	48 (1 study)	⨁⊖⊖⊖ very low[2,3]	There were no cases of pancreatitis in hereditary pancreatitis subgroup in either prophylaxis or no prophylaxis group.

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes.*

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

1 Data/relative effect is given in terms of number of cases of post-ERCP pancreatitis relative to number of ERCP procedures (n=56) (rather than number of patients [n=48]).
2 Nicholson et al. (2015): Unclear risk of selection bias (study period of 13 years, groups not matched, confounders not controlled for); unclear selective reporting (adverse events reported by number of ERCP procedures rather than number of events per patient). [Risk of bias assessed using Newcastle-Ottawa Scale for assessing quality of nonrandomised studies].
3 95% CI crosses 1 default MID (0.8 or 1.25).

5.4.5 Economic evidence

A literature review of published cost effectiveness analyses did not identify any relevant studies for this topic. Although there were potential implications for resource use associated with making recommendations in this area, other topics in the guideline were agreed as a higher economic priority. Consequently, bespoke economic modelling was not done for this topic.

5.4.6 Evidence Statements

5.4.6.1 Screening/surveillance studies

Diagnostic yield

There was inconsistent evidence from 17 prospective cohort studies (n=2661) on the diagnostic yield – i.e. early diagnosis or identification of malignant and premalignant pancreatic lesions - of pancreatic cancer screening/surveillance programs in high- and moderate- risk adults. Although the majority of the studies reporting the results of these programs were of high (++) quality and used pathological diagnosis, the diagnostic yield was highly variable, ranging from 0.9% to 39%. This variability is likely dependent on the initial index tests on the subgroups (e.g. breast cancer susceptibility gene, p16, p53) and types of

lesion included in the samples recruited by the programs. The overall screening efficiency of the programs, which were mainly conducted in the USA, in detecting pancreatic cancer was 1.7% (1 detected case of pancreatic cancer for every 59 individuals at risk screened or monitored) and 6.0% if premalignant lesions (IPMN and PanIN≥2) are included (1 detected case for every 16 individuals at risk screened or monitored).

Overall survival

No evidence was identified to inform this outcome.

Adverse events

Eleven high (++) quality and 2 low (+) quality prospective cohort studies (n=1329) indicated that the incidence of adverse events related to the tests used in the screening/surveillance programs of high- and moderate-risk individuals was very low (<1% excluding post-ERCP pancreatitis). The majority of the reported adverse events – 22 cases of post-test abdominal pain (of 78 participants), and 5 cases of post-ERCP pancreatitis (of 65 participants) - were from one 'high' (++) quality study (Canto 2006) that combined EUS with CT as either the initial index test or subsequent test given an initial abnormal finding. In the 3 studies (excluding Nicholson 2015; see below) that utilised ERCP, there were 7 cases of post-ERCP pancreatitis (5.9%) out of the 119 participants that received it.

5.4.6.2 ERCP with prophylaxis vs ERCP only

Adverse events

Very low quality evidence from 1 single centre prospective cohort study (n=48, 56 ERCP procedures) showed that there is a clinically important difference favouring ERCP with prophylaxis on reducing post-ERCP pancreatitis in people with familial pancreatic cancer compared to ERCP without prophylaxis: RR 0.34 (95%CI, 0.14-0.86).

Very low quality evidence from 1 single centre prospective cohort study (n=12, 24 ERCP procedures) showed no clinically important difference between ERCP with prophylaxis and ERCP without prophylaxis in people with hereditary pancreatitis (there were no cases in either group).

5.4.7 Recommendations

11. Ask people with pancreatic cancer if any of their first-degree relatives has had it. Address any concerns the person has about inherited risk.

12. Offer surveillance for pancreatic cancer to people with:

- hereditary pancreatitis and a PRSS1 mutation
- BRCA1, BRCA2, PALB2, or CDKN2A (p16) mutations, and one or more first-degree relatives with pancreatic cancer
- Peutz–Jeghers syndrome.

13. Consider surveillance for pancreatic cancer for people with:

- 3 or more first-degree relatives with pancreatic cancer, across 2 or more generations
- Lynch syndrome (mismatch repair gene [MLH1, MSH2, MSH6, or PMS2] mutations) and any first-degree relatives with pancreatic cancer.

14. **Consider a pancreatic protocol CT scan, MRI-MRCP or EUS for pancreatic cancer surveillance.**

15. **Do not offer EUS to detect pancreatic cancer in people with hereditary pancreatitis.**

5.4.8 Evidence to recommendations

5.4.8.1 Relative value placed on the outcomes considered

Early diagnosis, survival, diagnostic accuracy (including sensitivity, specificity, positive predictive value and negative predictive value), adverse events of interventions and health related quality of life were considered to be the critical outcomes for this question.

Diagnostic yield was reported for all studies and adverse events were reported for the majority of studies. Overall survival was only reported by one study and early diagnosis and health-related quality of life were not reported.

5.4.8.2 Quality of evidence

The QUADAS-2 checklist was used to evaluate the risk of bias and applicability of the screening or surveillance studies. Due to the type of data reported (diagnostic yield), the criteria of inconsistency and imprecision were not evaluated for the screening or surveillance studies. The GRADE risk of bias tool was used to evaluate the study that reported post-ERCP pancreatitis with and without prophylaxis.

For screening or surveillance, there were high quality studies for diagnostic yield and overall survival. The studies reporting adverse events were mostly high quality but with two low quality studies. For ERCP with prophylaxis versus ERCP only, there was only low quality evidence on adverse events.

5.4.8.3 Consideration of clinical benefits and harms

Based on their clinical knowledge, the committee noted that 5-10% of cases of pancreatic cancer are caused by hereditary factors. Consequently they agreed that it was very important to discuss family history with everyone who has pancreatic cancer so that people who have any hereditary factors can be identified earlier.

The committee noted, based on the evidence, that there are certain groups of hereditary factors that carry a higher risk of developing pancreatic cancer (an affected individual with hereditary pancreatitis with a PRSS1 mutation; people who are BRCA1, BRCA2, PALB2 or CDKN2A (p16) mutation carriers with one or more affected first-degree relatives with pancreatic cancer; people with Peutz–Jeghers syndrome, regardless of family history). The committee acknowledged that the data on survival were too limited to prove there is a survival benefit to surveilling these people. However, they noted the data from Vasen et al (2016), who had surveilled individuals at high risk of pancreatic cancer, reported an overall resection rate of 75% and overall survival at 5 years of 24% compared to a resection rate of 15% and 5-year survival rate of 4-7% for patients with sporadic symptomatic pancreatic ductal adenocarcinoma. Since these figures are higher than what would normally be expected for people with pancreatic cancer, the committee agreed these data were suggestive that surveillance could confer benefits to survival outcomes.

The committee also noted that these hereditary factors are usually associated with very poor prognosis which can cause a lot of anxiety to the people who have them. The committee considered that offering surveillance to those people with hereditary factors that carry a higher risk of developing pancreatic cancer, would help to resolve this anxiety. They also agreed, based on their experience, that surveillance of these people should lead to earlier

diagnosis of pancreatic cancer and earlier treatment, which will help to improve the experience of patients. They therefore agreed to recommend that people with these hereditary factors should be offered surveillance for pancreatic cancer.

The committee also noted there are other groups of hereditary factors that carry an increased risk of developing pancreatic cancer, but which are not as 'high risk'. The committee agreed that there were likely to be benefits to surveilling these people for pancreatic cancer but the balance was less clear. They therefore agreed a weaker recommendation for surveillance in people with first-degree relatives (FDRs) with pancreatic cancer from a familial pancreatic cancer kindred with at least three FDRs in two or more generations; people with mismatch repair gene (MLH1, MSH2, MSH6, PMS2) mutations (Lynch syndrome) and one affected FDR with pancreatic cancer.

The committee agreed that the evidence on the diagnostic yield of CT, MRI and EUS in surveillance had shown they were all accurate at identifying early tumours. However, from the available evidence the committee could not identify which of these investigations was the most effective. They therefore recommended all of them could be considered as options for surveillance. The committee also noted that, based on the available data, it was not possible to specify a frequency for surveillance. Given this uncertainty, the committee recommended further research to evaluate the surveillance tests and frequency of surveillance that produce the greatest diagnostic yield and overall surveillance efficiency.

Based on their clinical knowledge and experience, the committee noted that if a CT scan is used a pancreatic protocol CT scan would be needed to ensure good visualisation of any pathology in the pancreas. They also agreed that if MRI is used MRI-MRCP should be used as this will enable the pancreatic duct anatomy to be visualised.

The committee noted, based on their knowledge and experience, that the fibrosis, distortion and calcium deposits caused by hereditary pancreatitis prevent the detection of small pancreatic tumours by EUS. They therefore agreed that EUS should not be used to detect pancreatic cancer if the person has hereditary pancreatitis.

The committee noted that the data had shown ERCP with prophylaxis was better at reducing post-ERCP pancreatitis in people with familial pancreatic cancer, compared to ERCP without prophylaxis. However, given that the evidence was from a single, very low quality study the committee agreed not to make a recommendation about this intervention.

The committee agreed that the potential benefits of the recommendations made would be more directed and integrated management of people with hereditary factors, improved detection of pre-malignant lesions and potential improvements in survival. They noted that the recommendations for surveillance had the potential to both increase and decrease anxiety of the person; knowing you are at high risk of developing pancreatic cancer may increase anxiety which would hopefully be offset by being offered surveillance. However, anxiety may also increase around the time that the surveillance occurs as you wait to find out if you have developed pancreatic cancer or not. On balance, the committee agreed that the potential benefits outweighed the harms.

5.4.8.4 Consideration of economic benefits and harms

The committee noted that no relevant published economic evaluations had been identified and no additional economic analysis had been undertaken in this area.

The committee agreed that the recommendations made were unlikely to have a significant resource impact due to the small number of people who have an inherited risk of developing pancreatic cancer.

5.4.9 Research recommendations

1. Research should be undertaken to evaluate the most clinically effective and cost effective initial surveillance tests, additional tests and frequency of surveillance that produce the greatest diagnostic yield and overall surveillance efficiency.

At the present time we do not know what the best initial surveillance and subsequent tests are, nor the frequency of the surveillance that will produce the best diagnostic yield for people with an inherited high risk of pancreatic cancer, whilst maintaining quality of life. These will depend upon the accuracy of the tests available, the level of risk and the rate at which the risk materialises.

Individuals with an inherited risk of pancreatic cancer have a highly variable risk dependent on their particular genotype, each with a widely differing levels of risk, or the particular phenotype each also with a variable level of risk. In each case there is a threshold of risk and frequency of testing that would need to be determined to make surveillance effective.

5.4.10 References

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Del Chiaro M, Verbeke CS, Kartalis N et al. (2015) Short-term Results of a Magnetic Resonance Imaging–Based Swedish Screening Program for Individuals at Risk for Pancreatic Cancer. JAMA Surgery 150(6): 512-518

Harinck F, Konings IC, Kluijt I 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

Kimmey MB, Bronner MP, Byrd DR et al. (2002) Screening and surveillance for hereditary pancreatic cancer. Gastrointestinal Endoscopy 56(4): S82-S86

Konings IC, Sidharta GN, Harinck, F et al. (2015) Repeated participation in pancreatic cancer surveillance by high-risk individuals imposes low psychological burden. Psycho-Oncology 25(8): 971-978

Ludwig E, Olson SH, Bayuga S et al. (2011) Feasibility and yield of screening in relatives from familial pancreatic cancer families. The American Journal of Gastroenterology 106(5): 946-954

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Poley JW, Kluijt I, Gouma DJ 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

Potjer TP, Schot I, Langer P et al. (2013) Variation in precursor lesions of pancreatic cancer among high-risk groups. Clinical Cancer Research, 19(2): 442-449.

Sud A, Wham D, Catalano M et al. (2014) Promising outcomes of screening for pancreatic cancer by genetic testing and endoscopic ultrasound. Pancreas 43(3): 458-461

Vasen H, Ibrahim I, Ponce CG 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

Verna EC, Hwang C, Stevens PD 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

Zubarik R, Gordon SR, Lidofsky, SD 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

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6 Referral to specialist multidisciplinary teams

Review question: Does referral of all adults with suspected pancreatic cancer to a specialist MDT for review improve patient management and outcomes?

6.1 Introduction

Central to the UK's cancer services are multidisciplinary teams (MDTs). Before the introduction of multidisciplinary team working, a cancer patient's care was often determined solely by one clinician. Care at this time was characterised by unequal access to specialist care, disjointed referrals, and missed opportunities for adjuvant treatment. Variation in treatment uptake, caseload for each clinician and ultimately in outcomes for patients was widespread.

An MDT approach was enshrined in England's Cancer Plan in 2000 and was rapidly adopted across the UK. MDT working was officially included in national guidance in 2004. This stated that all patients newly diagnosed with cancer in England should be discussed at an MDT meeting. The 2015 cancer strategy for England described MDTs as the 'gold standard' for cancer patient management. However, recognising the significant challenges faced by MDTs today, the strategy also made several recommendations to streamline MDT working.

Given the widespread use of MDTs and the complex nature of healthcare systems, it is extremely difficult to robustly assess the impact of introducing MDT working. There is some limited evidence to link decision-making through MDT working to improved survival for some cancer types.

Guidance is needed on whether review by a specialist MDT, for people with suspected pancreatic cancer, improves patient management and outcomes.

6.1.1 Review protocol summary

The review protocol summary used for this question can be found in Table 56. Full details of the review protocol can be found in Appendix C.

Table 56: Clinical review protocol summary for the review of specialist versus local MDTs

Population	Adults with suspected pancreatic cancer Stage • I • II • III • IV
Intervention	Referral by region to • Specialist pancreatic MDT • Local MDT
Comparison	Each Other
Outcomes	• Survival Outcomes • Proportion receiving chemotherapy • Entry into clinical trials • Resection rates • Post-operative mortality

	• Patient Satisfaction • Quality of Life

6.2 Description of the clinical evidence

No relevant studies were identified for this review question.

Further information about the search strategy can be found in Appendix D. See study selection flow chart in Appendix E, and list of excluded studies in Appendix G.

6.3 Summary of included studies

No relevant studies were identified for this review question.

6.4 Clinical evidence profile

No relevant studies were identified for this review question.

6.5 Economic evidence

A literature review of published cost effectiveness analyses did not identify any relevant studies for this topic. Although there were potential implications for resource use associated with making recommendations in this area, other topics in the guideline were agreed as a higher economic priority. Consequently, bespoke economic modelling was not done for this topic.

6.6 Evidence statements

No relevant studies were identified for this review question.

6.7 Recommendations

16. A specialist pancreatic cancer multidisciplinary team should decide what care is needed, and involve the person with suspected or confirmed pancreatic cancer in the decision. Care should be delivered in partnership with local cancer units.

6.8 Evidence to recommendations

6.8.1 Relative value placed on the outcomes considered

Survival outcomes, proportion of people receiving chemotherapy, entry into clinical trials, resection rates, post-operative mortality, patient satisfaction and quality of life were the critical outcomes for this question. None of these outcomes were reported.

6.8.2 Quality of evidence

No evidence was identified that met the inclusion criteria for this question. Therefore the committee made recommendations based on their knowledge and experience.

6.8.3 Consideration of clinical benefits and harms

Based on their knowledge and experience, the committee agreed that people with pancreatic cancer have multiple, complex needs which would be optimally managed by a specialist

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multidisciplinary approach that ensures a range of opinions by specialists are considered and that surgery is centralised. The pancreatic-cancer specific expertise available at a specialist MDT, compared with a local MDT, means that there would be more access to novel treatments and a greater knowledge of relevant ongoing clinical trials that patients can be recruited to. It would also provide an opportunity for people to access specialist pancreatic cancer nutritional assessment and intervention. In addition, people often report that they would prefer their case to be discussed by a specialist MDT as this provides reassurance that they are receiving specialist input on potential relevant treatments, this is something that is particularly important given the poor prognosis of this cancer.

The committee were also aware that there are likely to be some people for whom it would be advantageous for their management to be undertaken by a local MDT, for example those who have very advanced disease and are very poorly. They discussed whether it would be possible for the specialist MDT to issue a protocol for the management of these people. However, it was noted that doing so could lead to the local MDT simply following the protocol and not involving the specialist MDT at all which would not be appropriate. They agreed that for these people, the specialist MDT should determine the management protocol, but that this management could be delivered locally.

Given these factors and that referral to, and management by, specialist MDTs has already been recommended by the Improving Outcomes in Upper Gastro-intestinal Cancers guidance, and is part of peer review measures, the committee agreed to make a strong recommendation that all people with a suspected or confirmed diagnosis of pancreatic cancer should have their management determined by a specialist pancreatic cancer MDT.

The committee agreed that making this recommendation would help to standardise the quality of care and the involvement of specialists should help to improve patient outcomes. No potential harms of these recommendations were identified.

6.8.4 Consideration of economic benefits and harms

Specialist pancreatic cancer MDTs already exist so there should not be any additional costs to set them up. The recommendations will increase the number of people who are discussed by the specialist MDT. These specialist MDTs can develop pathways to make the discussion in the MDT more efficient so the time needed to discuss patients is unlikely to significantly increase. However, should there be an increase in discussion time, the committee agreed that the discussion by specialists within the MDTs would lead to better management decisions resulting in downstream cost savings that would offset any additional costs from increased discussion time.

6.9 References

No relevant studies were identified for this review question.

7 Staging

Review question: What is the most effective investigative pathway for staging adults with newly diagnosed pancreatic cancer or a non-definitive diagnostic result as resectable, borderline resectable, locally advanced or metastatic disease?

7.1 Introduction

Pancreatic cancer is one of the most difficult cancers to stage accurately but given that surgical resection is the only potential cure it is vital that an accurate staging of the disease at the time of diagnosis can be obtained. Accurate staging is very important to avoid unsuccessful surgical intervention and a failure to resect the pancreatic tumour. Staging of pancreatic cancer can be undertaken by multiple imaging modalities including pancreatic CT, MRI, CT-PET and endoscopic ultrasound, both in isolation and using various combinations.

Guidance is needed the best investigative pathway to accurately stage people with pancreatic cancer.

7.1.1 Review protocol summary

The review protocol summary used for this question can be found in Table 57. Full details of the review protocol can be found in Appendix C.

Table 57: Clinical review protocol summary for the review of most effective investigative pathway for staging adults with pancreatic cancer

Population	Adults with newly diagnosed pancreatic cancer or a non-definitive diagnostic result
Index Test	Investigative pathways including combinations of: • Imaging (MRI/MRCP, PET/CT, CT, Ultrasound, EUS) • Laparoscopy (with or without ultrasound) • CA 19–9 • Histology • cytology
Reference Standard	• Each Other • Histological TNM classification • Surgery
Outcomes	Diagnostic test accuracy data (diagnostic accuracy, sensitivity, specificity, positive predictive value, negative predictive value) for the following outcomes: • Precise Staging • N Staging • M Staging • Resectability • Vascular invasion • Adverse events
Study design	• Prospective diagnostic test accuracy studies (including retrospective reviews of prospective studies)

	• Systematic reviews of diagnostic test accuracy studies • Sample size ≥50 patients

7.2 Description of clinical evidence

Thirty datasets in 29 observational studies (including 22 prospective cohort studies and 7 retrospective reviews of prospective databases) were identified. The majority of studies reported data on the ability of the relevant imaging test (mainly CT) to determine resectability and were in adults with suspected pancreatic cancer who had had prior imaging tests (also predominantly CT). The majority of studies used a histopathological reference standard but did not report TNM classification. A summary of the included studies is presented in Table 58.

Two studies (n=110) were identified that reported diagnostic accuracy data of imaging tests on overall TNM staging of pancreatic tumours (Shami et al. 2011; Soriano et al. 2004). One study (Shami et al. 2011) compared EUS-FNA and MRI, whilst one study (Soriano et al. 2004) compared CT, EUS and MRI.

Sixteen studies were identified that reported diagnostic accuracy data on imaging tests on resectability (DeWitt et al. 2004; Doucas et al. 2007; Fang et al. 2012; Fristrup et al. 2006; Furukawa et al. 2008; Imbriaco et al. 2005; Klauss et al. 2008; Koelblinger et al. (2011); Kwon et al. 2002; Mansfield et al. 2008; Minniti et al. 2003; Phoa et al. 2005; Schacter et al. 2000; Shah et al. 2008; Soriano et al. 2004; Taylor et al. 2001). Twelve studies (n=768) evaluated CT (DeWitt et al. 2004; Doucas et al. 2007; Fang et al. 2012; Furukawa et al. 2008; Imbriaco et al. 2005; Klauss et al. 2008; Koelblinger et al. (2011); Mansfield et al. 2008; Minniti et al. 2003; Phoa et al. 2005; Soriano et al. 2004; Taylor et al. 2001). There were a sufficient number of studies on the ability of CT to determine resectability to enable a meta-analysis, as well as a subgroup analysis comparing the studies whose participants had prior imaging with those who did not. One study (n=64) evaluated abdominal ultrasound (Minniti et al. 2003), 1 study (n=57) evaluated CT-3D (Fang et al. 2012), 3 studies (n=191) evaluated EUS (DeWitt et al. 2004; Mansfield et al. 2008; Soriano et al. 2004), and 3 studies (n=) evaluated MRI (Fischer et al. 2002; Koelblinger et al. 2011; Soriano et al. 2004). One study (n=52 to 59; Soriano et al. 2004) also evaluated three combinations of CT and EUS: CT and EUS, CT and EUS only if deemed resectable on CT, and EUS and CT only if deemed resectable on EUS. Six studies (n=278) evaluated the accuracy of laparoscopy with laparoscopic ultrasound (Doucas et al. 2007; Fristrup et al. 2006; Kwon et al. 2002; Schacter et al. 2000; Shah et al. 2008; Taylor et al. 2001). A meta-analysis was also conducted on laparoscopy with laparoscopic ultrasound.

Three studies (n=138) were identified that reported diagnostic accuracy data of imaging tests on tumour or T staging (DeWitt et al. 2004; Maluf-Filho et al. 2004; Soriano et al. 2004). Two studies compared CT and EUS (DeWitt et al. 2004; Maluf-Filho et al. 2004), whilst 1 study compared CT, EUS and MRI (Soriano et al. 2004).

Eight studies were identified that reported diagnostic accuracy data of imaging tests on lymph node or N staging (DeWitt et al. 2004; Furukawa et al. 2008; Klek et al. 2004; Lemke, et al. 2004; Mansfield et al. 2008; Roche et al. 2003; Soriano et al. 2004; Yoneyama et al. 2014). Seven studies (n=329) evaluated the accuracy of CT (DeWitt et al. 2004; Furukawa et al. 2008; Klek et al. 2004; Lemke et al. 2004; Mansfield et al. 2008; Roche et al. 2003; Soriano et al. 2004). There was a sufficient number of studies to conduct a meta-analysis of the ability of CT to detect nodal involvement. One study (n=126) evaluated abdominal ultrasound (Klek et al. 2004), 3 studies (n=187) evaluated EUS (DeWitt et al. 2004; Mansfield et al. 2008; Soriano et al. 2004), 1 study (n=53) evaluated MRI (Soriano et al. 2004), and 2 studies (n=195) evaluated PET/CT (Lemke et al. 2004; Yoneyama et al. 2014). One study calculated the diagnostic test accuracy of CT using the number of lymph nodes deemed to

have nodal involvement (Roche et al. 2003), with the remaining 7 studies using the number of participants deemed to have such involvement

Five studies were identified that reported diagnostic accuracy data on imaging tests on metastatic or M staging. Two studies (n=141) evaluated the accuracy of CT (Farma et al. 2008; Soriano et al. 2004), 1 study (n=52) evaluated EUS (Soriano et al. 2004), 1 study (n=53) evaluated MRI (Soriano et al. 2004), 2 studies (n=177) evaluated PET/CT (Farma et al. 2008; Yoneyama et al. 2014), and 1 study (n=82) evaluated CT combined with PET/CT (Farma et al. 2008). Two studies (n=164) evaluated staging information provided by diagnostic laparoscopy conducted on participants with no evidence of metastasis on CT (Liu & Traverso 2005; White et al. 2001).

Five studies were identified that reported diagnostic accuracy data on imaging tests on the extent of vascular invasion (Klauss et al. 2007; Klek et al. 2004; Lemke, et al. 2004; Soriano et al. 2004; Tellez-Avila et al. 2012). All five of these studies (n=409) evaluated the accuracy of CT, thus enabling a meta-analysis of these studies. Two studies (n=102) also evaluated EUS (Soriano et al. 2004; Tellez-Avila et al. 2012), 1 study (n=126) evaluated abdominal US (Klek et al. 2004), 1 study (n=53) evaluated MRI (Soriano et al. 2004) and 1 study (n=47) evaluated PET/CT (Lemke et al. 2004).

Two studies were identified that reported diagnostic accuracy data on the tumour marker CA 19-9 with a threshold of 130 kU/ml as an indication for laparoscopic resectability in participants who had prior imaging (Connor et al. 2005; Maithel et al. 2008). One of these studies also examined the accuracy of CA 19-9 in those with and without jaundice (Connor et al. 2005).

Positive and likelihood ratios were calculated, where appropriate, from the sensitivity and specificity of the studies to enable evaluation of the relevant tests. The QUADAS-2 checklist was used to evaluate the risk of bias and indirectness (applicability) of the studies.

Further information about the search strategy can be found in Appendix D. See study selection flow chart in Appendix E, single and multiple test ROC curves and forest plots in Appendix H, summary of QUADAS-2 study quality evaluations in Appendix J, study evidence tables in Appendix F and list of excluded studies in Appendix G.

7.3 Summary of included studies

A summary of the studies that were included in this review is presented in Table 58.

Table 58: Summary of included studies

Study	Sample N	Prior imaging test(s)	Index test N	Index test(s)	Reference standard	Outcome
Connor et al. 2005a	159 potentially resectable PC	CE CT	159	CA 19-9	Laparoscopy + LUS	Resectability
DeWitt et al. 2004	120 suspected or recently diagnosed PC	-	104	MDCT EUS	Surgical histopathology or EUS-FNA/previous cytology and clinical FU	T Staging N Staging Resectability
Doucas et al. 2006	100 suspected PC	-	94	CT	Laparoscopy + LUS, surgical histopathology + clinical FU	Resectability
		CT	65 potentially resectable	Laparoscopy + LUS	Surgical histopathology + clinical FU	
Fang et al. 2012	80 confirmed pancreatic or periampullary tumours	-	57 confirmed PAC	MDCT MDCT-3D	Surgical histopathology	Resectability
Farma et al. 2008a	83 suspected PC	-	82	CT PET/CT CT + PET/CT	Histopathology (Percutaneous or EUS-Core, or EUS-FNA)	M Staging
Fischer et al. 2002	99 suspected PC	CT and/or US	29 pancreatic head tumours	MRI	Surgical histopathology	Resectability
			36 solid tumours	MRI		
Fristrup et al. 2006	146 potentially resectable PC	CT or US	52 (after EUS screening)	Laparoscopy with LUS	Surgery	Resectability

Study	Sample N	Prior imaging test(s)	Index test N	Index test(s)	Reference standard	Outcome
Furukawa et al. 2008	213 confirmed PDAC	-	213	MDCT	Surgical histopathology	N Staging Resectability
Imbriaco et al. 2005	71 suspected PC	ERCP or US	71	MDCT	Surgical histopathology or percutaneous FNA and clinical FU	Resectability
Klauss et al. 2007	80 suspected PC	CT or US	80	CE-MDCT + invasion score	Surgery, surgical histopathology or biopsy	Resectability Vascular invasion
Kłęk et al. 2004	140 suspected PC	-	126 confirmed PC	CT US (Routine, Power, Colour, 3D)	Post-operative histopathology	N Staging Vascular invasion
Koelblinger et al. 2011	89 suspected PC	CT or US	23 potentially resectable	MDCT MRI	Surgery, surgical histopathology, CT-/US-guided biopsy, imaging or clinical FU	Resectability
Kwon et al. 2002	118 suspected PC	Angiography, CT, ERCP, MRI, and/or US	52 potentially resectable	Laparoscopy with LUS	Surgery, surgical histopathology or LUS	Resectability
Lemke et al. 2004	104 suspected PC	-	100	MSCT PET/CT	Histopathology or clinical FU	N Staging Vascular invasion
Liu & Traverso 2005a	74 locally advanced, unresectable PAC	-	74	CT	Laparoscopy	M Staging
Maithel et al. 2008a	491 potentially resectable PC	CT or MRI	262	CA 19-9	Laparoscopy/surgery	Resectability
Maluf-Filho et al. 2004	61 suspected pancreatic or ampullary tumours	US or CT	27 confirmed PC	Spiral CT EUS	Surgical histopathology or biopsy from laparotomy or EUS-FNA	T Staging
Mansfield et al. 2008	84 suspected pancreatic tumours[b]	-	35 potentially resectable	EUS	Surgical histopathology	Resectability

Study	Sample N	Prior imaging test(s)	Index test N	Index test(s)	Reference standard	Outcome
				MSCT	Histology	N Staging
Minniti et al. 2003	108 suspected PC	CT or MRI	64	Abdominal US Helical CT	Surgical or post-operative histopathology	Resectability Vascular + arterial invasion
Phoa et al. 2005	72 suspected PC	-	71	MSCT	Surgical histopathology	Resectability
Roche et al. 2003	62 suspected PC	-	9 PDAC	CT	Histopathology	N Staging
Schacter et al. 2000	67 suspected PC	TUS, CE-CT and/or ERCP	67	Laparoscopy with LUS	Laparotomy	Resectability
Shah et al. 2008a,c	88 confirmed PAC	-	88	MDCT	Laparotomy or surgical histopathology	Resectability
		MDCT	19	Laparoscopy with LUS	Surgical histopathology	
Shami et al. 2011	127 confirmed PC	-	127	EUS-FNA MRI	Surgical histopathology or cytology	Overall TNM Stage
Soriano et al. 2004	127 suspected PC	US	59	Helical CT	Surgical histopathology	Overall TNM Stage T-Staging N Staging M Staging Resectability Vascular Invasion
			52	EUS EUS + Helical CT if EUS-resectable Helical CT + EUS Helical CT + EUS if CT-resectable		
			53	MRI		
Taylor et al. 2001	51 potentially resectable pancreatic tumours[b]	US, ERCP	51	CE-CT	Surgery or histopathology	Resectability
		CE-CT	26	Laparoscopy with LUS	Surgery or histopathology	

Study	Sample N	Prior imaging test(s)	Index test N	Index test(s)	Reference standard	Outcome
Tellez-Avila et al. 2012	50 suspected PC	CT or US	50 potentially resectable	EUS±FNA MDCT	Surgical histopathology	Vascular Invasion
White 2001a	98 confirmed PDAC	-	98	CE-CT	Laparoscopy	M Staging
Yoneyama et al. 2014a,d	95 pathologically confirmed PC	MRI and PET/CT	43	CE PET/CT	Surgical histopathology, post-operative histopathology (EUS-FNA) or dynamic CT	N Staging M Staging
			52	Non-CE PET/CT		

Notes: a, retrospective review of prospective database. All other studies were prospective cohort studies; b, sample includes some participants with suspected periampullary cancer; c, criteria for staging laparoscopy were: (i) increased CA 19-9>1000 U/mL, (ii) tumour>4cm, (iii) weight loss>20% body weight, (iv) ascites or (v) liver lesions too small for either CT imaging or percutaneous biopsy; d, inclusion criteria were undetected lesions on MRI and PET/CT. Patients were assigned to undergo CE PET/CT or non-CE PET/CT. Abbreviations: CE CT, contrast enhanced computed tomography; CE MDTC, contrast-enhanced multidetector computed tomography; CE PET/CT; contrast-enhanced positron emission tomography-computed tomography; EUS-endoscopic ultrasonography; EUS-FNA- Endoscopic ultrasound-guided fine-needle aspiration; ERCP-Endoscopic retrograde cholangiopancreatography; PC-pancreatic cancer; MDCT, multidetector computed tomography; MRI-magnetic resonance imaging; PET/CT-positron emission tomography- computed tomography; PAC, pancreatic adenocarcinoma; PDAC, pancreatic ductal adenocarcinoma; TUS, transabdominal ultrasonography.

7.4 Clinical evidence profile

The clinical evidence profiles for this review question are presented in Table 59 to Table 73.

7.4.1 Tests for overall TNM Staging

Table 59: Summary of imaging studies on overall TNM staging in patients with suspected pancreatic cancer

Study	N	Index Test	Reference test	Accuracy (%)	Overstaged (%)	Understaged (%)	Risk of bias[1]	Indirectness[2]	Overall quality
Shami et al. 2011	48	EUS-FNA	Surgical histopathology or cytology	71	2	27	Very serious[3]	Not serious	LOW
		MRI		75	0	25			
Soriano et al. 2004	62	CT	Surgical histopathology	46	8	46	Not serious	Not serious	HIGH
		EUS		40	5	56			
		MRI		36	7	57			

Due to the type of data, inconsistency and imprecision are not applicable here;

[1], *risk of bias evaluated using risk of bias items of QUADAS-2 checklist;*

[2], *indirectness was evaluated using the applicability items of QUADAS-2;*

[3], *unclear reference and index test conduct (blinding), concerns about reference test (not all patients received same reference standard nor included in analysis).*

7.4.2 Tests for resectability

Table 60: Summary of diagnostic accuracy of computed tomography on resectability[1]

Study	N	Risk of bias[2]	Inconsistency [3]	Indirectness 4	Imprecision[5]	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	Summary positive likelihood ratio (95% CI)[6]	Summary negative likelihood ratio (95% CI)[6]	Overall quality
CT for resectability (12 studies)	766	Not serious	Very serious[7]	Not serious	Serious[8]	0.89 (0.76-0.95)	0.74 (0.44-0.91)	3.4 (1.29-8.96)	0.15 (0.06-0.36)	VERY LOW

[1], *positive test result corresponds to CT-resectability;*

[2], *risk of bias evaluated using risk of bias items of QUADAS-2 checklist;*

[3], *Inconsistency was assessed by inspection of the 95% prediction region in a summary ROC plot if a diagnostic meta-analysis was conducted. If between 2 and 3 studies, inconsistency was assessed by visual inspection of the point estimates of sensitivity and specificity. If only one study, then inconsistency is not applicable;*

[4], *indirectness was evaluated using the applicability items of QUADAS-2;*

[5], *judgement of imprecision was based on consideration of the 95% confidence intervals of test sensitivity as this was considered to be the primary measure of interest because a false negative – missing a resectable tumour – risks understaging (and hence a potentially avoidable death), whilst a false positive – indicating a tumour is resectable when it is not - leads to overstaging (and hence potentially avoidable surgery or other treatment such as chemotherapy). Studies were considered to be of high specificity (and not imprecise) if the 95% CI was above 0.9 or of low specificity if it was below 0.75. Studies were assessed as subject to serious imprecision if the 95% CI crossed either 0.75 or 0.9, or subject to very serious imprecision if the 95%CI crossed both 0.75 and 0.9;*

[6], *summary positive and likelihood ratio calculated from the meta-analysis;*

[7], *95% prediction range very wide with sensitivity ranging from approximately 0.1 to 1.0 and specificity ranging from 0 to 1.0;*

[8], *95% CI of sensitivity crosses 0.9.*

Table 61: Subgroup analysis of computed tomography on resectability according to prior imaging

Parameter	Prior tests (7 studies, n=349)	No prior tests (5 studies, n=417)	Significant difference between subgroups (t-value, p-value)[1]
Pooled sensitivity (95% CI)	0.86 (0.71-0.94)	0.91 (0.64-0.98)	t=0.44, p=0.66
Pooled specificity (95% CI)	0.76 (0.30-0.96)	0.65 (0.29-0.89)	t=0.49, p=0.63
Positive likelihood ratio (95% CI)[2]	3.61 (0.86-15.14)	2.58 (0.89-7.5)	
Negative likelihood ratio (95% CI)[2]	0.18 (0.1-0.35)	0.13 (0.02-1.0)	

[1], Unpaired t-test to compare pooled estimates of subgroup that had prior imaging compared to subgroup that did not have prior imaging. Standard errors for each subgroup used to conduct t-test calculated from 95% confidence intervals;

[2], Likelihood ratios calculated from meta-analysis.

Table 62: Summary of other imaging studies on resectability

Study[1]	N	Risk of bias[2]	Inconsistency[3]	Indirectness[4]	Imprecision[5]	Point estimates of sensitivity (95% CI)	Point estimates of specificity (95% CI)	Positive likelihood ratio (95% CI)[6]	Negative likelihood ratio (95% CI)[6]	Overall quality
Abdominal US										
Minniti et al. 2003	64	Not serious	n/a	Not serious	Very serious[7]	0.89 (0.65-0.99)	0.76 (0.55-0.91)	3.7 (1.81-7.58)	0.15 (0.04-0.55)	LOW
CT-3D										
Fang et al. 2012	57	Not serious	n/a	Not serious	Not serious	1.0 (0.91-1.0)	1.0 (0.82-1.0)	39.49 (2.56-609.84)[8]	0	HIGH
CT + EUS										
Soriano et al. 2004	52	Not serious	n/a	Not serious	Serious[9]	0.73 (0.5-0.89)	0.97 (0.83-1.0)	21.82 (3.12-152.43)	0.28 (0.14-0.56)	MODERATE
CT + EUS only if CT-resectable										
Soriano et al. 2004	59	Not serious	n/a	Not serious	Serious[9]	0.98 (0.89-1.0)	0.8 (0.28-0.99)	4.89 (0.85-28.26)	0.03 (0.0-0.19)	MODERATE

Study[1]	N	Risk of bias[2]	Inconsistency[3]	Indirectness[4]	Imprecision[5]	Point estimates of sensitivity (95% CI)	Point estimates of specificity (95% CI)	Positive likelihood ratio (95% CI)[6]	Negative likelihood ratio (95% CI)[6]	Overall quality
EUS										
DeWitt et al. 2004	104	Serious[10]	n/a	Not serious	Very serious[7]	0.88 (0.69-0.97)	0.68 (0.48-0.84)	2.74 (1.57-4.78)	0.18 (0.06-0.53)	VERY LOW
Mansfield et al. 2008	35	Serious[11]	n/a	Not serious	Very serious[7]	0.82 (0.63-0.94)	0.43 (0.1-0.82)	1.44 (0.74-2.79)	0.42 (0.13-1.34)	VERY LOW
Soriano et al. 2004	52	Not serious	n/a	Not serious	Not serious	0.23 (0.08-0.45)	1.0 (0.88-1.0)	14.83 (0.86-254.88)[8]	0.77 (0.62-0.97)	HIGH
Overall	191	Serious[12]	Very serious[13]	Not serious	Very serious[10]					VERY LOW
EUS + CT only if EUS-resectable										
Soriano et al. 2004	52	Not serious	n/a	Not serious	Serious[9]	0.63 (0.38-0.84)	0.97 (0.84-1.0)	20.84 (2.93-148.02)	0.38 (0.21-0.69)	MODERATE
MRI										
Fischer et al. 2002	26	Serious[10]	n/a	Not serious	Serious[9]	0.71 (0.44-0.90)	0.78 (0.40-0.97)	3.18 (0.9-11.2)	0.38 (0.17-0.85)	LOW
Koelblinger et al. 2011	23	Serious[10]	n/a	Not serious	Very serious[7]	0.83 (0.36-1.00)	0.82 (0.57-0.96)	4.72 (1.59-14.01)	0.20 (0.03-1.23)	LOW
Soriano et al. 2004	53	Not serious	n/a	Not serious	Serious[9]	0.57 (0.34- 0.77)	0.90 (0.73-0.98)	5.65 (1.82-17.53)	0.48 (0.3-0.78)	MODERATE
Overall	102	Not serious	Not serious	Not serious	Very serious[7]					LOW

[1], *positive test result corresponds to resectability according to the relevant index test;*

[2], risk of bias evaluated using risk of bias items of QUADAS-2 checklist;

[3], Inconsistency was assessed by inspection of the 95% prediction region in a summary ROC plot if a diagnostic meta-analysis was conducted. If between 2 and 3 studies, inconsistency was assessed by visual inspection of the point estimates of sensitivity and specificity. If only one study, then inconsistency is not applicable;

[4], indirectness was evaluated using the applicability items of QUADAS-2;

[5], judgement of imprecision was based on consideration of the 95% confidence intervals of test sensitivity as this was considered to be the primary measure of interest because a false negative – missing a resectable tumour – risks understaging (and hence a potentially avoidable death), whilst a false positive – indicating a tumour is resectable when it is not - leads to overstaging (and hence potentially avoidable surgery or other treatment such as chemotherapy). Studies were considered to be of high sensitivity (and not imprecise) if the 95% CI was above 0.9 or of low specificity if it was below 0.75. Studies were assessed as subject to serious imprecision if the 95% CI crossed either 0.75 or 0.9, or subject to very serious imprecision if the 95%CI crossed both 0.75 and 0.9;

[6], positive and negative likelihood ratios calculated from raw diagnostic test accuracy data if not already reported; 95% CIs calculated using log method (see Chapter 4.3.3.2.2 for details);

[7], 95% CI of sensitivity crosses both 0.75 and 0.9;

[8], since the specificity was 1, a continuity correction of 0.5 was added to all cells to enable calculation of the positive likelihood ratio and related 95% CIs.[9], 95% CI of sensitivity crosses either 0.75 or 0.9;

[10],concerns over conduct of reference standard and flow and timing of tests;

[11],concerns over conduct of reference standard

[12], Soriano 2004 comprises more than 50% of sample;[13], 95% CI of sensitivity has wide range

Table 63: Summary of laparoscopy with laparoscopic ultrasonography in patients with potentially resectable pancreatic cancer

Study	N	Risk of bias[2]	Inconsistency[3]	Indirectness[4]	Imprecision[5]	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	Summary positive likelihood ratio (95% CI)[6]	Summary negative likelihood ratio (95% CI)[6]	Overall quality
Laparoscopy with LUS for resectability[1] (6 studies)	278	Not serious	Serious[7]	Not serious	Not serious	0.98 (0.93-0.99)	0.67 (0.44-0.83)	3.1 (1.74-5.59)	0.04 (0.01-0.11)	MODERATE

[1], positive test result corresponds to resectability according to the relevant index test;

[2], risk of bias evaluated using risk of bias items of QUADAS-2 checklist;

[3], Inconsistency was assessed by inspection of the 95% prediction region in a summary ROC plot if a diagnostic meta-analysis was conducted. If between 2 and 3 studies, inconsistency was assessed by visual inspection of the point estimates of sensitivity and specificity. If only one study, then inconsistency is not applicable;

[4], indirectness was evaluated using the applicability items of QUADAS-2;

.

[5], judgement of imprecision was based on consideration of the 95% confidence intervals of test sensitivity as this was considered to be the primary measure of interest because a false negative – missing a resectable tumour – risks understaging (and hence a potentially avoidable death), whilst a false positive – indicating a tumour is resectable when it is not - leads to overstaging (and hence potentially avoidable surgery or other treatment such as chemotherapy). Studies were considered to be of high sensitivity (and not imprecise) if the 95% CI was above 0.9 or of low specificity if it was below 0.75. Studies were assessed as subject to serious imprecision if the 95% CI crossed either 0.75 or 0.9, or subject to very serious imprecision if the 95%CI crossed both 0.75 and 0.9;

[6], summary positive and negative likelihood ratios calculated from meta-analysis;

[7], 95% prediction region very wide with specificity ranging from approximately 0 to 1.0.

7.4.3 Tests for T Staging

Table 64: Summary of imaging studies on T Staging in patients with suspected pancreatic cancer

Study	N	Index Test	Reference test	Accuracy (%)	Overstaged (%)	Understaged (%)	Risk of bias[1]	Indirectness[2]	Overall quality
Dewitt et al. 2004	49	CT	Surgical histopathology or EUS-FNA/previous cytology and clinical FU	41	14	45	Serious[4]	Not serious	MODERATE
		EUS		67	18	14			
Maluf-Filho et al. 2004[3]	27	CT	Surgical histopathology or intraoperative biopsy from laparotomy or EUS-FNA	59	7	33	Not serious	Not serious	HIGH
		EUS		89	7	4			
Soriano et al. 2004	62	CT (n=59)	Surgical histopathology	73	2	25	Not serious	Not serious	HIGH
		EUS (n=52)		63	0	37			
		MRI (n=53)		62	6	32			

Due to the type of data, inconsistency and imprecision are not applicable here;

[1], *risk of bias evaluated using risk of bias items of QUADAS-2 checklist;*

[2], *indirectness was evaluated using the applicability items of QUADAS-2;*

[3], *study enrolled 61 people with suspected pancreatic or ampullary tumours. Data shown only for people with confirmed pancreatic cancer;*

[4], *concerns with conduct of reference standard (reference standard not blinded, not all patients received same reference standard nor included in analysis).*

7.4.4 Tests for N Staging

Table 65: Summary of computed tomography studies on N Staging in patients with suspected or confirmed pancreatic cancer (by number of participants)

Study	N	Risk of bias[2]	Inconsistency[3]	Indirectness[4]	Imprecision[5]	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	Summary positive likelihood ratio (95% CI)[6]	Summary negative likelihood ratio (95% CI)[6]	Overall quality
CT for N Staging[1] (6 studies)	329	Serious[7]	Very serious[8]	Not serious	Not serious	0.38 (0.26-0.52)	0.87 (0.7-0.95)	2.86 (0.91-8.97)	0.71 (0.52-0.98)	VERY LOW

[1], *positive test result corresponds to detection of regional lymph node metastasis;*

[2], *risk of bias evaluated using risk of bias items of QUADAS-2 checklist;*

[3], *Inconsistency was assessed by inspection of the 95% prediction region in a summary ROC plot if a diagnostic meta-analysis was conducted. If between 2 and 3 studies, inconsistency was assessed by visual inspection of the point estimates of sensitivity and specificity. If only one study, then inconsistency is not applicable;*

[4], *indirectness was evaluated using the applicability items of QUADAS-2;*

[5], *judgement of imprecision was based on consideration of the 95% confidence intervals of test sensitivity as this was considered to be the primary measure of interest because a false negative - missing cancer that has spread to the regional lymph nodes - risks understaging (and hence potentially avoidable death), whilst a false positive - indicating cancer has spread to the regional lymph nodes when it has not - risks overstaging (and hence potentially avoidable surgery or other treatment such as chemotherapy). Studies were considered to be of high sensitivity (and not imprecise) if the 95% CI was above 0.9 or of low sensitivity if it was below 0.75. Studies were assessed as subject to serious imprecision if the 95% CI crossed either 0.75 or 0.9, or subject to very serious imprecision if the 95%CI crossed both 0.75 and 0.9;*

[6], *summary positive and likelihood ratio calculated from meta-analysis;*

[7], *there were concerns in 3 of the studies about the conduct of the index test, the reference standard used, and/or the patient flow and timing of the tests;*

[8], 95% prediction region was very wide ranging approximately from 0 to 0.9 for sensitivity and from 0 to 1.0 for specificity.

Table 66: Subgroup analysis of computed tomography studies on N Staging according to prior imaging (by number of participants)

Parameter	Prior tests (1 study, n=58)	No prior tests (5 studies, n=271)	Significant difference between subgroups (t-value, p-value)[1]
Pooled sensitivity (95% CI)	0.38 (0.19-0.59)	0.39 (0.25-0.56)	t=0.05, p=0.96
Pooled specificity (95% CI)	0.79 (0.62-0.91)	0.88 (0.67-0.96)	t=0.55, p=0.58
Positive likelihood ratio (95% CI)[2]	1.82 (0.79-4.21)	3.3 (0.78-13.93)	
Negative likelihood ratio (95% CI)[2]	0.79 (0.55-1.12)	0.69 (0.47-1.01)	

[1], Unpaired t-test to compare pooled estimates of subgroup that had prior imaging compared to subgroup that did not have prior imaging. Standard errors for each subgroup used to conduct t-test calculated from 95% confidence intervals;

[2], Likelihood ratios calculated from meta-analysis.

Table 67: Summary of computed tomography studies on N Staging in patients with suspected pancreatic cancer (by number of lymph nodes)[1]

Study	# of participants (# of nodes)	Risk of bias[2]	Inconsistency[3]	Indirectness[4]	Imprecision[5]	Point estimates of sensitivity (95% CI)	Point estimates of specificity (95% CI)	Positive likelihood ratio (95% CI)[6]	Negative likelihood ratio (95% CI)[6]	Overall quality
CT										
Roche et al. 2003	9 (40)	Not serious	n/a	Not serious	Not serious	0.14 (0-0.58)	0.85 (0.68-0.95)	0.94 (0.13-6.87)	1.01 (0.72-1.41)	HIGH

[1], positive test result corresponds to detection of regional lymph node metastasis. Sensitivity and specificity for this study calculated from number of lymph nodes correctly and incorrectly identified as involved (where short-axis diameter > 10 mm indicates nodal involvement);

[2], risk of bias evaluated using relevant items of QUADAS-2 checklist;

[3], Inconsistency was assessed by inspection of the 95% prediction region in a summary ROC plot if a diagnostic meta-analysis was conducted. If between 2 and 3 studies, inconsistency was assessed by visual inspection of the point estimates of sensitivity and specificity. If only one study, then inconsistency is not applicable;

[4], indirectness was evaluated using the applicability items of QUADAS-2;

[5], judgement of imprecision was based on consideration of the 95% confidence intervals of test sensitivity as this was considered to be the primary measure of interest because a false negative - missing cancer that has spread to the regional lymph nodes - risks understaging (and hence potentially avoidable death), whilst a false positive -

indicating cancer has spread to the regional lymph nodes when it has not - risks overstaging (and hence potentially avoidable surgery or other treatment such as chemotherapy). Studies were considered to be of high sensitivity (and not imprecise) if the 95% CI was above 0.9 or of low sensitivity if it was below 0.75. Studies were assessed as subject to serious imprecision if the 95% CI crossed either 0.75 or 0.9, or subject to very serious imprecision if the 95%CI crossed both 0.75 and 0.9;

[6], positive and negative likelihood ratios calculated from raw diagnostic test accuracy data if not already reported; 95% CIs calculated using log method (see Chapter 4.3.3.2.2 for details)..

Table 68: Summary of other imaging studies on N Staging with suspected or confirmed pancreatic cancer (by number of participants)[1]

Study	N	Risk of bias[2]	Inconsistency[3]	Indirectness[4]	Imprecision[5]	Point estimates of sensitivity (95% CI)	Point estimates of specificity (95% CI)	Positive likelihood ratio (95% CI)[6]	Negative likelihood ratio (95% CI)[6]	Overall quality
Abdominal US										
Klek et al. 2004	126	Not serious	n/a	Not serious	Very serious[7]	0.75 (0.53-0.9)	0.91 (0.79-0.98)	8.62 (3.29-22.63)	0.27 (0.14-0.55)	LOW
EUS										
DeWitt et al. 2004	100	Serious8	n/a	Not serious	Not serious	0.25 (0.11-0.43)	0.92 (0.64-1.0)	3.25 (0.45-23.45)	0.81 (0.63-1.05)	MODERATE
Mansfield et al. 2008	35	Not serious	n/a	Not serious	Not serious	0.31 (0.11-0.59)	0.93 (0.68-1.0)	4.69 (0.62-35.63)	0.74 (0.52-1.05)	HIGH
Soriano et al. 2004	52	Not serious	n/a	Not serious	Not serious	0.36 (0.17-0.59)	0.87 (0.69-0.96)	2.73 (0.94-7.93)	0.73 (0.52-1.04)	HIGH
Overall	187	Serious9	Not serious	Not serious	Not serious					MODERATE
MRI										
Soriano et al. 2004	53	Not serious	n/a	Not serious	Not serious	0.15 (0.03-0.38)	0.93 (0.78-0.99)	2.25 (0.41-12.28)	0.91 (0.74-1.12)	HIGH
PET/CT										

Study	N	Risk of bias[2]	Inconsistency[3]	Indirectness[4]	Imprecision[5]	Point estimates of sensitivity (95% CI)	Point estimates of specificity (95% CI)	Positive likelihood ratio (95% CI)[6]	Negative likelihood ratio (95% CI)[6]	Overall quality
Lemke et al. 2004	100	Serious	n/a	Not serious	Not serious	0.32 (0.17-0.51)	0.75 (0.48-0.93)	1.29 (0.48-3.47)	0.9 (0.62-1.31)	MODERATE
Yoneyama et al. 2014 non-CE group	52	Not serious	n/a	Not serious	Very serious[7]	0.73 (0.39-0.94)	0.9 (0.77-0.97)	7.45 (2.75-20.24)	0.3 (0.11-0.8)	LOW
Yoneyama et al. 2014 CE group	43	Not serious	n/a	Not serious	Very serious[7]	0.83 (0.52-0.98)	0.9 (0.74-0.98)	8.61 (2.85-25.99)	0.18 (0.05-0.66)	LOW
Overall	195	Serious[10]	Serious	Not serious	Very serious[11]					VERY LOW

[1], positive test result corresponds to detection of regional lymph node metastasis;

[2], risk of bias evaluated using relevant items of QUADAS-2 checklist;

[3], Inconsistency was assessed by inspection of the 95% prediction region in a summary ROC plot if a diagnostic meta-analysis was conducted. If between 2 and 3 studies, inconsistency was assessed by visual inspection of the point estimates of sensitivity and specificity. If only one study, then inconsistency is not applicable;

[4], indirectness was evaluated using the applicability items of QUADAS-2;

[5], judgement of imprecision was based on consideration of the 95% confidence intervals of test sensitivity as this was considered to be the primary measure of interest because a false negative - missing cancer that has spread to the regional lymph nodes - risks understaging (and hence potentially avoidable death), whilst a false positive - indicating cancer has spread to the regional lymph nodes when it has not - risks overstaging (and hence potentially avoidable surgery or other treatment such as chemotherapy). Studies were considered to be of high sensitivity (and not imprecise) if the 95% CI was above 0.9 or of low sensitivity if it was below 0.75. Studies were assessed as subject to serious imprecision if the 95% CI crossed either 0.75 or 0.9, or subject to very serious imprecision if the 95%CI crossed both 0.75 and 0.9;

[6], positive and negative likelihood ratios calculated from raw diagnostic test accuracy data if not already reported; 95% CIs calculated using log method (see Chapter 4.3.3.2.2 for details);

[7], 95% CI crosses both 0.75 and 0.9;

[8], there were concerns over the reference standard, and the patient flow and timing of tests;

[9], Overall serious risk of bias since DeWitt et al. (2005) contributed over 50% of the overall sample;

[10], overall serious risk of bias since Lemke et al., (2004) contributed over 50% of the overall sample;

[11], *95% CI of sensitivity ranges from 0.17 to 0.98.*

7.4.5 Tests for M Staging

Table 69: Summary of imaging studies on M Staging in patients with suspected pancreatic cancer

Study[1]	N	Risk of bias[2]	Inconsistency[3]	Indirectness[4]	Imprecision[5]	Point estimates of sensitivity (95% CI)	Point estimates of specificity (95% CI)	Positive likelihood ratio (95% CI)[6]	Negative likelihood ratio (95% CI)[6]	Overall quality
CT										
Farma et al. 2008	82	Serious[7]	n/a	Not serious	Serious[8]	0.57 (0.34-0.77)	0.92 (0.81-0.97)	6.67 (2.68-16.6)	0.48 (0.3-0.76)	LOW
Soriano et al. 2004	59	Not serious	n/a	Not serious	Serious[8]	0.55 (0.23-0.83)	0.96 (0.86-0.99)	13.09 (3.04-56.37)	0.47 (0.25-0.91)	MODERATE
Overall	141	Serious[9]	Not serious	Not serious	Serious[8]					LOW
EUS										
Soriano et al. 2004	52	Not serious	n/a	Not serious	Not serious	0	1.0 (0.92-1.0)	5.0 (0.11-235.93)[10]	1.0	HIGH
MRI										
Soriano et al. 2004	53	Not serious	n/a	Not serious	Not serious	0.3 (0.07-0.65)	0.95 (0.84-0.99)	6.45 (1.24-33.64)	0.73 (0.49-1.11)	HIGH
PET/CT										
Farma et al. 2008	82	Serious[7]	n/a	Not serious	Serious[8]	0.61 (0.39-0.8)	1.0 (0.94-1.0)	72.5 (4.5-1167.71)[10]	0.39 (0.24-0.65)	LOW
Yoneyama et al. 2014 non-CE group	52	Not serious	n/a	Not serious	Very serious[11]	0.76 (0.53-0.92)	0.84 (0.66-0.95)	4.72 (2.04-10.92)	0.28 (0.13-0.62)	LOW

Study[1]	N	Risk of bias[2]	Inconsistency[3]	Indirectness[4]	Imprecision[5]	Point estimates of sensitivity (95% CI)	Point estimates of specificity (95% CI)	Positive likelihood ratio (95% CI)[6]	Negative likelihood ratio (95% CI)[6]	Overall quality
Yoneyama et al. 2014 CE group	43	Not serious	n/a	Not serious	Very serious[11]	0.9 (0.7-0.98)	0.91 (0.71-0.99)	9.95 (2.64-37.58)	0.1 (0.03-0.39)	LOW
Overall	134	Not serious	Not serious	Not serious	Very serious[11]					LOW
CT + PET/CT										
Farma et al. 2008	82	Serious[7]	n/a	Not serious	Very serious[12]	0.87 (0.66-0.97)	0.92 (0.81-0.97)	10.26 (4.37-24.09)	0.14 (0.05-0.41)	VERY LOW

[1], *positive test result corresponds to detection of distant metastasis;*

[2], *risk of bias evaluated using risk of bias items of QUADAS-2 checklist;*

[3], *Inconsistency was assessed by inspection of the 95% prediction region in a summary ROC plot if a diagnostic meta-analysis was conducted. If between 2 and 3 studies, inconsistency was assessed by visual inspection of the point estimates of sensitivity and specificity. If only one study, then inconsistency is not applicable;*

[4], *indirectness was evaluated using the applicability items of QUADAS-2;*

[5], *judgement of imprecision was based on consideration of the 95% confidence intervals of test sensitivity as this was considered to be the primary measure of interest because a false negative - missing cancer that has spread to the distant regions of the body such as the liver and lungs - risks understaging (and hence potentially avoidable death), whilst a false positive - indicating cancer has spread to the distant regions of the body when it has not - risks overstaging (and hence potentially avoidable surgery or other treatment such as chemotherapy). Studies were considered to be of high sensitivity (and not imprecise) if the 95% CI was above 0.9 or of low sensitivity if it was below 0.75. Studies were assessed as subject to serious imprecision if the 95% CI crossed either 0.75 or 0.9, or subject to very serious imprecision if the 95%CI crossed both 0.75 and 0.9;*

[6], *positive and negative likelihood ratios calculated from raw diagnostic test accuracy data if not already reported; 95% CIs calculated using log method (see Chapter 4.3.3.2.2 for details);*

[7], *insufficient information regarding index test, reference standard and patient flow and timing of test;*

[8], *95% CI crosses 0.75 or range of 95% CI crosses 0.75;*

[9], *sensitivity is undefined since there are no true positives nor false positives;*

[10], *since the specificity was 1, a continuity correction of 0.5 was added to all cells to enable calculation of the positive likelihood ratio and related 95% CIs;*

[11], *95% CI crosses both 0.75 and 0.9.*

Table 70: Summary of diagnostic laparoscopy studies on M Staging in patients with pancreatic cancer and prior computed tomography

Study[1]	N	Risk of bias[2]	Indirectness[3]	Groups	# patients detected with metastatic disease[4]	Diagnostic yield[4]	NPV	Overall quality
Liu & Traverso 2005	74 CT-unresectable and locally advanced	Not serious	Not serious	n/a	25	34%	0.66	HIGH
White et al. 2001	90 CT-potentially resectable or CT-locally advanced tumours	Not serious	Not serious	Overall	21	23%	0.77	HIGH
				45 CT-potentially resectable	8	18%	0.82	
				55 CT- locally advanced	13	24%	0.76	

[1], CT is the index test and diagnostic laparoscopy is the reference test. Due to the type of data, inconsistency and imprecision are not applicable here;

[2], risk of bias evaluated using risk of bias items of QUADAS-2 checklist;

[3], indirectness was evaluated using the applicability items of QUADAS-2;

[4], the number/percentage of patients (as appropriate) who had CT for whom diagnostic laparoscopy identified distant metastasis and changed management plan.

7.4.6 Tests for vascular invasion

Table 71: Summary of computed tomography studies on vascular invasion

Study	N	Risk of bias[2]	Inconsistency[3]	Indirectness[4]	Imprecision[5]	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	Summary positive likelihood ratio (95% CI)[6]	Summary negative likelihood ratio (95% CI)[6]	Overall quality
CT for vascular invasion (5 studies)[1]	419	Not serious	Serious[7]	Not serious	Serious[7]	0.7 (0.49-0.85)8	0.92 (0.86-0.96)	9.5 (4.47-17.8)	0.33 (0.17-0.55)	LOW

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[1], *positive test result corresponds to detection of vascular invasion by CT;*

[2], *risk of bias evaluated using risk of bias items of QUADAS-2 checklist;*

[3], *Inconsistency was assessed by inspection of the 95% prediction region in a summary ROC plot if a diagnostic meta-analysis was conducted. If between 2 and 3 studies, inconsistency was assessed by visual inspection of the point estimates of sensitivity and specificity. If only one study, then inconsistency is not applicable;*

[4], *indirectness was evaluated using the applicability items of QUADAS-2;*

[5], *judgement of imprecision was based on consideration of the 95% confidence intervals of test sensitivity as this was considered to be the primary measure of interest because a false negative – missing vascular invasion – risks understaging (and hence a potentially avoidable death), whilst a false positive – indicating vascular invasion where there is none - leads to overstaging (and hence potentially avoidable surgery or other treatment such as chemotherapy). Studies were considered to be of high sensitivity (and not imprecise) if the 95% CI was above 0.9 or of low specificity if it was below 0.75. Studies were assessed as subject to serious imprecision if the 95% CI crossed either 0.75 or 0.9, or subject to very serious imprecision if the 95%CI crossed both 0.75 and 0.9;*

[6], *summary positive and negative likelihood ratios calculated from meta-analysis;*

[7], *it was not possible to represent the 95% prediction region on the summary ROC curve. However, the sensitivity estimates ranged from 0.48 to 0.91;*

[8], *95% CI of sensitivity crosses 0.75.*

Table 72: Summary of other imaging studies on vascular invasion

Study[1]	N	Risk of bias[2]	Inconsistency[3]	Indirectness[4]	Imprecision[5]	Point estimates of sensitivity (95% CI)	Point estimates of specificity (95% CI)	Positive likelihood ratio (95% CI)[6]	Negative likelihood ratio (95% CI)[6]	Overall quality
Abdominal US										
Klek et al. 2004	126	Not serious	n/a	Not serious	Serious[7]	0.91 (0.8-0.97)	0.96 (0.88-0.99)	21.52 (7.09-65.32)	0.09 (0.04-0.22)	MODERATE
EUS										
Soriano et al. 2004	52	Not serious	n/a	Not serious	Not serious	0.42 (0.2-0.67)	0.97 (0.84-1.0)	13.89 (1.88-102.75)	0.6 (0.4-0.88)	HIGH
Tellez-Avila et al. 2012	50	Not serious	n/a	Not serious	Serious[7]	0.61 (0.36-0.83)	0.9 (0.73-0.98)	6.11 (1.96-19.01)	0.43 (0.24-0.78)	MODERATE
Overall	102	Not serious	Serious[8]	Not serious	Serious[9]					LOW
MRI										
Soriano et al. 2004	53	Not serious	n/a	Not serious	Not serious	0.59 (0.46-0.72)	0.84 (0.74-0.94)	3.66 (1.53-8.79)	0.49 (0.29-0.82)	HIGH

Study[1]	N	Risk of bias[2]	Inconsistency[3]	Indirectness[4]	Imprecision[5]	Point estimates of sensitivity (95% CI)	Point estimates of specificity (95% CI)	Positive likelihood ratio (95% CI)[6]	Negative likelihood ratio (95% CI)[6]	Overall quality
PET/CT										
Lemke et al. 2004	104	Serious[10]	n/a	Not serious	Serious[7]	0.68 (0.52-0.81)	0.67 (0.09-0.99)	2.0 (0.41-10.26)	0.48 (0.19-1.19)	LOW

[1], *positive test result corresponds to vascular invasion according to the relevant index test;*

[2], *risk of bias evaluated using risk of bias items of QUADAS-2 checklist;*

[3], *Inconsistency was assessed by inspection of the 95% prediction region in a summary ROC plot if a diagnostic meta-analysis was conducted. If between 2 and 3 studies, inconsistency was assessed by visual inspection of the point estimates of sensitivity and specificity. If only one study, then inconsistency is not applicable;*

[4], *indirectness was evaluated using the applicability items of QUADAS-2;*

[5], *judgement of imprecision was based on consideration of the 95% confidence intervals of test sensitivity as this was considered to be the primary measure of interest because a false negative – missing vascular invasion – risks understaging (and hence a potentially avoidable death), whilst a false positive – indicating vascular invasion where there is none - leads to overstaging (and hence potentially avoidable surgery or other treatment such as chemotherapy). Studies were considered to be of high sensitivity (and not imprecise) if the 95% CI was above 0.9 or of low specificity if it was below 0.75. Studies were assessed as subject to serious imprecision if the 95% CI crossed either 0.75 or 0.9, or subject to very serious imprecision if the 95%CI crossed both 0.75 and 0.9;*

[6], *positive and negative likelihood ratios calculated from raw diagnostic test accuracy data if not already reported; 95% CIs calculated using log method (see Chapter 4.3.3.2.2 for details);*

[7], *95% CI crosses 0.9;*

[8], *estimated sensitivity ranged from 0.42 to 0.61;*

[9], *range of 95% CI is from 0.2 to 0.83;*

[10], *unclear risk of bias due to insufficient information about index test and reference standard.*

7.4.7 Tests for indicating laparoscopic resectability

Table 73: Summary of CA19-9 studies to improve staging laparoscopy in patients with potentially resectable pancreatic cancer and who had had prior imaging[1]

Study	N	Threshold (kU/ml)	Risk of bias[2]	Inconsistency[3]	Indirectness[4]	Imprecision[5]	Point estimates of sensitivity (95% CI)	Point estimates of specificity (95% CI)	Positive likelihood ratio (95% CI)[6]	Negative likelihood ratio (95% CI)[6]	Overall quality
		≤150		n/a	Not serious	Not serious	0.44	0.88	3.56	0.63	

Study	N	Threshold (kU/ml)	Risk of bias[2]	Inconsistency[3]	Indirectness[4]	Imprecision[5]	Point estimates of sensitivity (95% CI)	Point estimates of specificity (95% CI)	Positive likelihood ratio (95% CI)[6]	Negative likelihood ratio (95% CI)[6]	Overall quality
Connor et al. 2005[7]	159		Not serious				(0.36-0.53)	(0.68-0.97)	(1.21-10.42)	(0.51-0.79)	HIGH
		≤150 (or ≤300 If bilirubin level >35µmol/l)[8]				Not serious	0.61 (0.52-0.69)	0.8 (0.56-0.94)	3.04 (1.25-7.39)	0.49 (0.36-0.67)	
		≤300 If bilirubin level >35µmol/l[9]				Not serious	0.3 (0.18-0.44)	0.94 (0.73-1.0)	5.43 (0.77-38.13)	0.74 (0.6-0.91)	
Maithel et al. 2008[7]	262	≤130	Not serious	n/a	Not serious	Not serious	0.5 (0.43-57)	0.75 (0.6-0.86)	1.95 (1.2-3.18)	0.67 (0.55-0.83)	HIGH

[1], *positive test result corresponds to resectability according to the relevant CA 19-9 threshold where lower than the threshold indicates resectability;*

[2], *risk of bias evaluated using risk of bias items of QUADAS-2 checklist;*

[3], *Inconsistency was assessed by inspection of the 95% prediction region in a summary ROC plot if a diagnostic meta-analysis was conducted. If between 2 and 3 studies, inconsistency was assessed by visual inspection of the point estimates of sensitivity and specificity. If only one study, then inconsistency is not applicable;*

[4], *indirectness was evaluated using the applicability items of QUADAS-2;*

[5], *judgement of imprecision was based on consideration of the 95% confidence intervals of test sensitivity as this was considered to be the primary measure of interest because a false negative – missing a resectable tumour – risks understaging (and hence a potentially avoidable death), whilst a false positive – indicating a tumour is resectable when it is not - leads to overstaging (and hence potentially avoidable surgery or other treatment such as chemotherapy. Studies were considered to be of high sensitivity (and not imprecise) if the 95% CI was above 0.9 or of low specificity if it was below 0.75. Studies were assessed as subject to serious imprecision if the 95% CI crossed either 0.75 or 0.9, or subject to very serious imprecision if the 95%CI crossed both 0.75 and 0.9;*

[6], *positive and negative likelihood ratios calculated from raw diagnostic test accuracy data if not already reported; 95% CIs calculated using log method (see Chapter 4.3.3.2.2 for details);*

[7], *Connor et al. 2005 had prior CT, whilst Maithel et al. 2008 had prior CT or MRI;*

[8], *n=145 because bilirubin levels were not available for 14 patients);*

9, n=71 jaundiced patients only.

7.5 Economic evidence

7.5.1 Systematic literature review

The literature search of previous economic evidence identified one economic evaluation relevant to this topic. Morris et al. (2015) compared diagnostic laparoscopy, to assess the resectability of a tumour, performed at an appointment prior to laparotomy to direct laparotomy with no diagnostic work-up in people with pancreatic or periampullary cancer which has been identified as resectable through CT scanning.

The study took a UK NHS and PSS perspective and was deemed to only have minor methodological issues. The effectiveness side of the model was based almost entirely on one Cochrane review (16 studies, n=1146) which matched the decision problem considered by the model. All costs were obtained from NHS reference costs. The utilities for the model were taken from patient responses to the EQ-5D questionnaire scored using the UK population weightings they were drawn from a different patient group (hepatic colorectal metastases). The model considered both pancreatic and periampullary cancer although the model was rerun separately for each disease and reported similar results for the combined and pancreatic cancer models, although this analysis was not presented in detail.

The model concluded that a diagnostic laparoscopy would be both cost saving and health improving if held at an appointment prior to surgery and thus wasted operating theatre time could be averted in patients subsequently identified as having unresectable tumours. However, the cost savings (£10) and health improvements (0.009 QALYS) per patient were small.

Both deterministic and probabilistic sensitivity analysis were undertaken. The results were sensitive to alternate assumptions around key variables especially around the proportion of patients with unresectable disease sent to surgery and the post-test probability of unresectable disease. The preferred option changed to no further diagnostic work-up prior to laparotomy for values less than 36% and greater than 22% for these two variables respectively. Both of these values were plausible and within the 95% confidence intervals estimated in the Cochrane review. The uncertainty around the preferred option was further supported by the probabilistic sensitivity analysis which showed diagnostic laparoscopy cost effective a £20,000 willingness to pay per QALY only having a 63.2% probability of being the preferred option.

References to all included studies and evidence tables for all economic evaluations included in the systematic literature review of the economic evidence are presented in Appendix L. Economic evidence profiles of these studies are presented in Appendix K.

7.6 Evidence statements

7.6.1 Tests for overall TMN Staging

Staging accuracy

High quality evidence from 1 prospective cohort study (n=62) found that CT had the best accuracy of 46% in people with suspected pancreatic cancer who had had prior ultrasound, compared to an accuracy of 40% for EUS and 36% for MRI. Computed tomography also understaged the least number of people (46%), followed by EUS and MRI (56% and 57% respectively). However, CT overstaged the most number of people (8%), followed by MRI (7%) and EUS (5%).

Low quality evidence from 1 prospective cohort study (n=48) found that MRI had an accuracy of 75% in people with confirmed pancreatic cancer, compared to 71% for EUS-FNA. MRI also both understaged and overstaged the least number of people (25% and 0% respectively) closely followed by EUS-FNA (27% and 2%).

7.6.2 Tests for resectability

Staging accuracy of CT

Very low quality evidence from a meta-analysis of 12 observational studies (n=766) found that CT had a moderate pooled sensitivity of 0.89 (95% CI, 0.76-0.95) and a low pooled specificity of 0.74 (95% CI, 0.44-0.91) in determining pancreatic tumour resectability in adults. The positive likelihood ratio of 3.4 (95% CI, 1.29-9.86) suggests that a positive result for resectability is not particularly useful for ruling it in, though there is uncertainty in the estimate. The negative likelihood ratio of 0.15 (0.06-0.36) suggests that a negative result for resectability is moderately useful for ruling it out, though there is substantial uncertainty in the estimate.

A subgroup analysis by whether the participants had had prior imaging (prior imaging versus no prior imaging) showed that there was no significant difference between the two groups in the estimated pooled sensitivity (0.86 [95% CI, 0.71-0.94] vs 0.91 [95% CI, 0.64-0.98] respectively) and estimated pooled specificity (0.76 [95% CI, 0.3-0.96] vs 0.62 [95% CI, 0.29-0.89]). Similarly, the positive likelihood ratios of 3.61 (95% CI, 0.86-15.14) and 2.58 (95% CI, 0.89-7.5) suggest that a positive result for resectability is not particularly useful for ruling it in, though there is substantial uncertainty in the estimates. The negative likelihood ratios of 0.18 (95% CI, 0.1-0.35) and 0.13 (95% CI, 0.02-1.0), suggest– in line with the main meta-analysis – that a negative result for resectability is moderately useful for ruling it out, though there is substantial uncertainty in the estimates.

High quality evidence from 1 prospective cohort study (n=57) found that three-dimensional computed tomography (CT-3D) had a high sensitivity of 1.0 (95% CI, 0.91-1.0) and a high specificity of 1.0 (95% CI, 0.82-1.0) in determining pancreatic tumour resectability in adults with confirmed pancreatic cancer. However, the positive likelihood ratio of 39.49 (95% CI, 2.56-609.84) suggests that a positive result for resectability is very useful for ruling it in, though there is substantial uncertainty in the estimate. The negative likelihood ratio of 0 suggests that a negative result for resectability is very useful for ruling it out.

Staging accuracy of abdominal ultrasound

Low quality evidence from 1 prospective cohort study (n=64) found that abdominal ultrasound had a moderate sensitivity of 0.89 (95% CI, 0.65-0.99) and moderate specificity of 0.76 (95% CI, 0.55-0.91) in determining pancreatic tumour resectability in adults with suspected pancreatic cancer. The positive likelihood ratio of 3.7 (95% CI, 1.81-7.58) suggests that a positive result for resectability is not particularly useful for ruling it in, though there is uncertainty in the estimate. The negative likelihood ratio of 0.15 (95% CI, 0.04-0.55) suggests that a negative result for resectability is moderately useful for ruling it out, though there is substantial uncertainty in the estimate.

Staging accuracy of combined computed tomography and EUS

Moderate quality evidence from 1 prospective cohort study (n=52) found that combined computed tomography and EUS had a low sensitivity of 0.73 (95% CI, 0.5-0.89) and a high specificity of 0.97 (95% CI, 0.83-1.0) in determining pancreatic tumour resectability in adults. The positive likelihood ratio of 21.82 (95% CI, 3.12-152.43) suggests that a positive result for resectability is very useful for ruling it in, though there is substantial uncertainty in the estimate. The negative likelihood ratio of 0.28 (95% CI, 0.14-0.56) suggests that a negative

result for resectability is not particularly useful for ruling it out, though there is uncertainty in the estimate.

Moderate quality evidence from 1 prospective cohort study (n=59) found that combined CT and EUS only if resectable on CT had a high sensitivity of 0.98 (95% CI, 0.89-1.0) and moderate specificity of 0.8 (95% CI, 0.28-0.99) in determining pancreatic tumour resectability in adults. The positive likelihood ratio of 4.89 (95% CI, 0.85-28.26) suggests that a positive result for resectability is not particularly useful for ruling it in, though there is substantial uncertainty in the estimate. The negative likelihood ratio of 0.03 (95% CI, 0-0.19) suggests that a negative result for resectability is very useful for ruling it out, though there is uncertainty in the estimate.

Staging accuracy of EUS

Very low quality evidence from 2 prospective cohort studies (n=139) in adults with suspected or confirmed pancreatic cancer though no prior imaging found that EUS had a moderate sensitivity ranging from 0.82 to 0.88 and low specificity ranging from 0.43 to 0.68 in determining pancreatic tumour resectability. The positive likelihood ratios of 1.44 (95% CI, 0.74-2.79) and 2.74 (95% CI, 1.57-4.78) suggest that a positive result for resectability is not particularly useful for ruling it in. The negative likelihood ratios of 0.18 (95% CI, 0.06-0.53) and 0.42 (95% CI, 0.13-1.34) suggest that a negative result for resectability is either moderately useful or not particularly useful for ruling it out, though there is substantial uncertainty in the estimates. By contrast, high quality evidence from 1 prospective cohort study (n=52) in adults with suspected pancreatic cancer who had had prior ultrasound found that EUS had a low sensitivity of 0.23 (95% CI, 0.08-0.45) and high specificity of 1.0 (95% CI, 0.88-1.0). The positive likelihood ratio of 14.83 (0.86-254.88) suggests that a positive result for resectability is very useful after prior ultrasound for ruling it in, though there is substantial uncertainty in the estimate. The negative likelihood ratio of 0.77 (95% CI, 0.62-0.97) suggests that a negative result for resectability is not particularly useful for ruling it out.

Moderate quality evidence from 1 prospective cohort study (n=52) in adults with suspected pancreatic cancer found that combined EUS and CT only if resectable on EUS had a low sensitivity of 0.63 (95% CI, 0.38-0.84) and high specificity of 0.97 (95% CI, 0.84-1.0) in determining pancreatic tumour resectability in adults. The positive likelihood ratio of 20.84 (95% CI, 2.93-148.02) suggests that a positive result for resectability is very useful for ruling it in, though there is substantial uncertainty in the estimate. The negative likelihood ratio of 0.38 (95% CI, 0.21-0.69) suggests that a negative result for resectability is not particularly useful for ruling it out.

Staging accuracy of laparoscopy with laparoscopic ultrasound

Moderate quality evidence from a meta-analysis of 6 observational studies (n=278) found that laparoscopy with laparoscopic ultrasound had a high sensitivity of 0.98 (95% CI, 0.93-0.99) and a low specificity of 0.67 (95% CI, 0.44-0.83) in determining pancreatic tumour resectability. The positive likelihood ratio of 3.0 (95% CI, 1.74-5.59) suggests that a positive result for resectability is not particularly useful for ruling it in, though there is uncertainty in the estimate. The negative likelihood ratio of 0.04 (95% CI, 0.01-0.11) suggests that a negative result for resectability is very useful for ruling it out, though there is uncertainty in the estimate.

Staging accuracy of magnetic resonance imaging

Low quality evidence from 3 studies (n=102) in adults with suspected pancreatic cancer who had had prior imaging found that MRI had a low to moderate sensitivity ranging from 0.57 to 0.83 and a moderate specificity ranging from 0.78 to 0.9 in determining pancreatic tumour resectability. The positive likelihood ratios were 3.18 (95% CI,0.9-11.2), 4.72 (95% CI, 1.59-14.01) and 5.65 (95% CI, 1.82-17.53) suggesting that a positive result for resectability is

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either moderately useful or not particularly useful for ruling it in, though there is substantial uncertainty in the estimates. The negative likelihood ratios were 0.2 (95% CI, 0.03-1.23), 0.38 (95% CI, 0.17-0.85) and 0.48 (95% CI, 0.3-0.78) suggesting that a negative result for resectability is not particularly useful for ruling it out, though there is substantial uncertainty in the estimates.

7.6.3 Tests for T-Staging

T-Staging accuracy

Moderate quality evidence from 1 prospective cohort study (n=49) compared the ability of CT and EUS to determine the size and extent of a primary tumour in adults with suspected or recently diagnosed pancreatic cancer and found that EUS was more accurate than CT (67% vs 41% respectively). EUS overstaged 18% and understaged 14% of the sample, compared with 14% and 45%, respectively, for CT.

High quality evidence from 1 prospective cohort study (n=27) compared the ability of CT and EUS to determine the size and extent of a primary tumour in adults with confirmed pancreatic cancer who had previous CT or ultrasound and found that EUS was more accurate than CT (89% vs 59%, respectively). Both EUS and CT overstaged 7% of the sample, whilst EUS only understaged 4% compared to 33% of the sample for CT.

High quality evidence from 1 prospective cohort study (n=53 to 59) compared the ability of CT, EUS and MRI to determine the size and extent of a primary tumour in adults with suspected pancreatic cancer who had had prior ultrasound and found that CT was more accurate than either EUS or MRI (73%, 63% and 62%, respectively). CT also understaged the least amount of the sample followed by MRI and EUS (25%, 32% and 37%, respectively). By contrast EUS did not overstage any of the sample, whilst CT and MRI overstaged 2% and 6%, respectively, of the sample.

7.6.4 Tests for N-Staging

N-Staging accuracy of CT

Very low quality evidence from a meta-analysis of 6 prospective cohort studies (n=329) found that computed tomography has a low sensitivity of 0.38 (95% CI, 0.26-0.52) and a moderate specificity of 0.87 (95% CI, 0.7-0.95) in detecting whether a pancreatic tumour has spread to the lymph nodes in adults. The positive likelihood ratio of 2.86 (95% CI, 0.91-8.97) suggests that a positive result for nodal involvement is not particularly useful for ruling it in, though there is uncertainty in the estimate. The negative likelihood ratio of 0.71 (95% CI, 0.52-0.98) suggests that a negative result for nodal involvement is not particularly useful for ruling it in and ruling it out.

A subgroup analysis by whether the participants had had prior imaging (prior imaging [1 study, n=58] vs no prior imaging [5 studies, n=271]) showed that there was no significant difference (t=0.05, p=0.96) between the two groups in the estimated pooled sensitivity (0.38 [95% CI, 0.19-0.59] vs 0.39 [95% CI, 0.25-0.56] respectively). Similarly, there was no significant difference (t=0.55, p=0.58) in the estimated pooled specificity between the two groups (0.79 [95% CI, 0.62-0.91] vs 0.88 [95% CI, 0.67-0.96]). The positive likelihood ratios of 1.82 (95% CI, 0.79-4.21) and 3.3 (95% CI, 0.78-13.93) suggests that a positive result for nodal involvement, regardless of whether prior imaging has been conducted, is not particularly useful for ruling it in, though there is substantial uncertainty in the latter estimate. The negative likelihood ratios of 0.79 (95% CI, 0.55-1.12) for the single study in the prior imaging group and 0.69 (95% CI, 0.47-1.01) in the no prior imaging group suggests that a negative result for nodal involvement is not particularly useful for ruling it out regardless of whether prior imaging has occurred

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High quality evidence from 1 prospective cohort study (n=9, 40 lymph nodes) that calculated accuracy of CT for detecting nodal involvement according to the number of detected lymph nodes (rather than number of patients) found that it had low sensitivity of 0.14 (95% CI, 0-0.58) and a moderate specificity of 0.85 (95% CI, 0.68-0.95) in adults with confirmed pancreatic cancer. The positive likelihood ratio of 0.94 (95% CI, 0.13-6.87) suggests that a positive result for nodal involvement is not particularly useful for ruling it in, though there is uncertainty in the estimate. The negative likelihood ratio of 1.01 (95% CI, 0.72-1.41) suggests that a negative result for nodal involvement is not particularly useful for ruling it out.

N-Staging accuracy of abdominal ultrasound

Low quality evidence from 1 prospective cohort study (n=126) found that abdominal ultrasound had a moderate sensitivity of 0.75 (95% CI, 0.53-0.9) and a high specificity of 0.91 (95% CI, 0.79-0.98) in detecting whether a pancreatic tumour has spread to the lymph nodes in adults with suspected pancreatic cancer. The positive likelihood ratio of 8.62 (95% CI, 3.29-22.63) suggests that a positive result for nodal involvement is moderately useful for ruling it in, though there is substantial uncertainty in the estimate. The negative likelihood ratio of 0.27 (95% CI, 0.14-0.55) suggests that a negative result for nodal involvement is not particularly useful for ruling it out, though there is uncertainty in the estimate.

N-Staging accuracy of EUS

Moderate to high quality evidence from 3 prospective cohort studies (n=187) found that EUS had a low sensitivity ranging from 0.25 to 0.36 and a moderate to high specificity ranging from 0.87 to 0.93 in detecting whether a pancreatic tumour has spread to the lymph nodes in adults with suspected pancreatic cancer who had had prior ultrasound. The positive likelihood ratios were 2.73 (95% CI, 0.94-7.93), 3.25 (95% CI, 0.45-23.45) and 4.69 (95% CI, 0.62-35.63) suggesting that a positive result for nodal involvement is not particularly useful for ruling it in, though there is substantial uncertainty in the estimates. The negative likelihood ratios were 0.73 (95% CI, 0.52-1.04), 0.74 (95% CI, 0.52-1.05) and 0.81 (95% CI, 0.63-1.05) suggesting that a negative result for nodal involvement is not particularly useful for ruling it out.

N-Staging accuracy of MRI

High quality evidence from 1 prospective cohort study (n=53) found that MRI had a low sensitivity of 0.15 (95% CI, 0.03-0.38) and a high specificity of 0.93 (95% CI, 0.78-0.99) in detecting whether a pancreatic tumour has spread to the lymph nodes in adults with suspected pancreatic cancer who had had prior ultrasound. The positive likelihood ratio of 2.25 (95% CI, 0.41-12.28) suggests that a positive result for nodal involvement is not particularly useful for ruling it in, though there is substantial uncertainty in the estimate. The negative likelihood ratio of 0.91 (95% CI, 0.74-1.12) suggests that a negative result for nodal involvement is not particularly useful for ruling it out.

N-Staging accuracy of PET/CT

Moderate quality evidence from 1 prospective cohort study (n=100) found that standard PET/CT had a low sensitivity of 0.32 (95% CI, 0.17-0.51) and a moderate specificity of 0.75 (95% CI, 0.48-0.93) in detecting whether a pancreatic tumour has spread to the lymph nodes in adults with suspected pancreatic cancer. The positive likelihood ratio of 1.29 (95% CI, 0.48-3.47) and negative likelihood ratio of 0.9 (95% CI, 0.62-1.31) suggest that neither a positive nor negative result for nodal involvement is particularly useful for ruling it in and ruling it out.

Low quality evidence from 1 retrospective review of a prospective database compared standard PET/CT (n=52) with contrast-enhanced PET/CT (n=43) and found that both had a moderate sensitivity (ranging from 0.73 to 0.83) and a high specificity of 0.9 in detecting

whether a pancreatic tumour has spread to the lymph nodes in adults with confirmed pancreatic cancer. The positive likelihood ratio was 7.45 (95% CI, 2.75-20.24) for standard PET/CT and 8.61 (95% CI, 2.85-25.99) for contrast-enhanced PET/CT suggesting that a positive result on either test for nodal involvement is moderately useful for ruling it in, though there is substantial uncertainty in the estimates. The negative likelihood ratio ranged from 0.18 (95% CI, 0.05-0.66) for contrast-enhanced PET/CT and 0.3 (95% CI, 0.11-0.8) for standard PET/CT suggesting that a negative result for nodal involvement in the former test is moderately useful for ruling it out but that a negative result in the latter test is not particularly useful for ruling it out, though there is uncertainty in both estimates.

7.6.5 Tests for M Staging

M-Staging accuracy of CT

Low to moderate quality evidence from 2 observational studies (n=141; 1 prospective cohort and 1 retrospective review of a prospective database) found that CT had a low sensitivity ranging from 0.55 to 0.57 and a high specificity ranging from 0.92-0.96 in detecting whether a pancreatic tumour has metastasised in adults with suspected pancreatic cancer. The positive likelihood ratios were 6.67 (95% CI, 2.68-16.6) and 13.09 (95% CI, 3.04-56.37) suggesting that a positive result for metastases is either moderately or very useful for ruling it in, though there is substantial uncertainty in the estimates. By contrast, the negative likelihood ratios were 0.47 (95% CI, 0.25-0.91) and 0.48 (95% CI, 0.3-0.76) suggesting that a negative result for metastases is not particularly useful for ruling it out.

M-Staging accuracy of EUS

High quality evidence from 1 prospective cohort study (n=52) found that EUS had a high specificity of 1.0 (95% CI, 0.92-1.0) in detecting whether a pancreatic tumour has metastasised in adults with suspected pancreatic cancer who had had prior ultrasound. The positive likelihood ratio of 5.0 (95% CI, 0.11-235.93) suggest that a positive result for metastases is moderately useful for ruling it in, though there is substantial uncertainty in the estimate. The negative likelihood ratio of 1.0 (95% CI, 1.0-1.0) suggests that a negative result for metastases is not particularly useful ruling it out.

M-Staging accuracy of MRI

High quality evidence from 1 prospective cohort study (n=53) found that MRI had a low sensitivity of 0.3 (95% CI, 0.07-0.65) and a high specificity of 0.95 (95% CI, 0.84-0.99) in detecting whether a pancreatic tumour has metastasised in adults with suspected pancreatic cancer who had had prior ultrasound. The positive likelihood ratio of 6.45 (95% CI, 1.24-33.64) suggests that a positive result for metastases is moderately useful for ruling it in, though there is substantial uncertainty in the estimate. The negative likelihood ratio of 0.73 (95% CI, 0.49-1.11) suggests that a negative result for metastases is not particularly useful for ruling it out.

M-Staging accuracy of PET/CT

Low quality evidence from 1 retrospective review of a prospective database (n=82) found that standard PET/CT had a low sensitivity of 0.61 (95% CI, 0.39-0.8) and a high specificity of 1.0 (95% CI, 0.94-1.0) in detecting whether a pancreatic tumour has metastasised in adults with suspected pancreatic cancer. The positive likelihood ratio of 72.5 (95% CI, 4.5-1167.71) suggest that a positive result for metastases is very useful for ruling it in, though there is substantial uncertainty in the estimate. The negative likelihood ratio of 0.39 (95% CI, 0.24-0.65) suggests that a negative result for metastases is not particularly useful for ruling it out.

Low quality evidence from 1 retrospective review of a prospective database compared standard PET/CT (n=52) with contrast-enhanced PET/CT (n=43) and found the former had a moderate sensitivity of 0.76 (95% CI, 0.53-0.92) and moderate specificity of 0.84 (95% CI, 0.66-0.95), whilst the latter had a high sensitivity of 0.9 (95% CI, 0.7-0.98) and a high specificity of 0.91 (95% CI, 0.71-0.99), in detecting whether a pancreatic tumour has metastasised in adults with confirmed pancreatic cancer. The positive likelihood ratios of 4.72 (95% CI, 2.04-10.92) for standard PET/CT and 9.95 (95% CI, 2.64-37.58) for contrast-enhanced PET/CT suggest that a positive result for metastases using the former is not particularly useful for ruling it in, whilst a positive result using the latter is moderately useful for ruling it in, though there is substantial uncertainty in both estimates. The negative likelihood ratios of 0.28 (95% CI, 0.13-0.62) for standard PET/CT and 0.1 (95% CI, 0.03-0.39) for contrast-enhanced PET/CT suggest that a negative result for metastases using the former is not particularly useful for ruling it in, whilst a negative result using the latter is moderately useful for ruling it out, though there is uncertainty in both estimates.

M-Staging accuracy of combined CT and PET/CT

Very low quality evidence from 1 retrospective review of a prospective database (n=82) found that combined CT and PET/CT had a moderate sensitivity of 0.87 (95% CI, 0.66-0.97) and a high specificity of 0.92 (95% CI, 0.81-0.97) in detecting whether a pancreatic tumour has metastasised in adults with suspected pancreatic cancer. The positive likelihood ratio of 10.26 (95% CI, 4.37-24.09) suggests that a positive result for metastases is very useful for ruling it in, whilst the negative likelihood ratio of 0.14 (95% CI, 0.05-0.41) suggests that a negative result for metastases is moderately useful for ruling it out, though there is substantial uncertainty in both estimates.

M-Staging accuracy of diagnostic laparoscopy

High quality evidence from 1 retrospective review of a prospective database (n=74 CT-unresectable or locally advanced pancreatic cancer participants) found that 34% of the sample had pancreatic tumours that had metastasised and that the negative predictive value was 0.66.

High quality evidence from 1 retrospective review of a prospective database (n=90 CT-resectable or locally advanced pancreatic cancer participants) found that 23% of the sample had pancreatic tumours that had metastasised and that the negative predictive value was 0.77. The diagnostic yield was 18% (NPV=0.82) for CT-resectable participants (n=45), whilst it was 24% (NPV=0.76) for CT-locally advanced participants (n=55).

7.6.6 Tests for vascular invasion

Vascular invasion accuracy of CT

Low quality evidence from a meta-analysis of 5 prospective cohort studies (n=419) found that CT had a low pooled sensitivity of 0.70 (95% CI, 0.49-0.85) and high specificity of 0.92 (95% CI, 0.86-0.96) in detecting whether a pancreatic tumour has spread to the arteries and/or veins in adults with suspected or confirmed pancreatic cancer. The positive likelihood ratio of 9.5 (95% CI, 4.47-17.8) suggests that a positive result for vascular invasion is moderately useful for ruling it in, though there is substantial uncertainty in the estimate. The negative likelihood ratio of 0.33 (95% CI, 0.17-0.55) suggests that a negative result for vascular invasion is not particularly useful for ruling it out, though there is uncertainty in the estimate.

Vascular invasion accuracy of abdominal ultrasound

Moderate quality evidence from 1 prospective cohort study (n=126) found that abdominal ultrasound had a high sensitivity of 0.91 (95% CI, 0.8-0.97) and a high specificity of 0.96

(95% CIU, 0.88-0.99) in detecting whether a pancreatic tumour has spread to the arteries and/or veins in adults with suspected pancreatic cancer. The positive likelihood ratio of 21.52 (95% CI, 7.09-65.32) suggests that a positive result for vascular invasion is very useful for ruling it in, though there is uncertainty in the estimate. The negative likelihood ratio of 0.09 (95% CI, 0.04-0.22) suggests that a negative result for vascular invasion is very useful for ruling it out, though there is substantial uncertainty in the estimate.

Vascular invasion accuracy of EUS

Moderate to high quality evidence from 2 prospective cohort studies (n=102) found that EUS had a low sensitivity ranging from 0.42 to 0.61 and a high specificity ranging from 0.9 to 0.97 in detecting whether a pancreatic tumour has spread to the arteries and/or veins in adults with suspected pancreatic cancer who had had prior imaging tests. The positive likelihood ratios were 6.11 (95% CI, 1.96-19.01) and 13.89 (95% CI, 1.88-102.75) suggesting that a positive result for vascular invasion is either very useful or moderately useful for ruling it in, though there is substantial uncertainty in both estimates. The negative likelihood ratios were 0.43 (95% CI, 0.24-0.78) to 0.6 (95% CI, 0.4-0.88) suggesting that a negative result for vascular invasion is not particularly useful for ruling it out.

Vascular invasion accuracy of MRI

High quality evidence from 1 prospective cohort study (n=53) found that MRI had a low sensitivity of 0.59 (95% CI, 0.46-0.72) and moderate specificity of 0.84 (95% CI, 0.74-0.94) in detecting whether a pancreatic tumour has spread to the arteries and/or veins in adults with suspected pancreatic cancer who had had prior ultrasound. The positive likelihood ratio of 3.66 (95% CI, 1.53-8.79) suggests that a positive result for vascular invasion is not particularly useful for ruling it in, though there is uncertainty in the estimate. The negative likelihood ratio of 0.49 (95% CI, 0.29-0.82) suggests that a negative result for vascular invasion is not particularly useful for ruling it out.

Vascular invasion accuracy of PET/CT

Low quality evidence from 1 prospective cohort study (n=104) found that standard PET/CT had a low sensitivity of 0.68 (95% CI, 0.52-0.81) and a low specificity of 0.67 (95% CI, 0.09-0.99) in detecting whether a pancreatic tumour has spread to the arteries and/or veins in adults with suspected pancreatic cancer. The positive likelihood ratio of 2.05 (95% CI, 0.41-10.26) suggests that a positive result for vascular invasion is not particularly useful for ruling it in, though there is substantial uncertainty in the estimate. The negative likelihood ratio of 0.48 (95% CI, 0.19-1.19) suggests that a negative result for vascular invasion is not particularly useful for ruling it out, though there is uncertainty in the estimate.

7.6.7 Tests for indicating laparoscopic resectability

Laparoscopic resectability accuracy of CA 19-9 ≤ 150 kU/ml or ≤ 300 kU/ml

High quality evidence from 1 retrospective review of a prospective database (n=159) found that a CA 19-9 level of 150 kU/ml or less for indicating laparoscopic resectability had a low sensitivity of 0.44 (95% CI, 0.36-0.53) and a moderate specificity of 0.88 (95% CI, 0.68-0.97) in adults with suspected pancreatic cancer. The positive likelihood ratio of 3.56 (95% CI, 1.21-10.42) suggests that a positive result for indicating laparoscopic resectability according to this threshold is not particularly useful for ruling it in, though there is substantial uncertainty in the estimate. The negative likelihood ratio of 0.63 (95% CI, 0.51-0.79) suggest that a negative result for indicating laparoscopic resectability according to this threshold is not particularly useful for ruling it out.

High quality evidence from the same study (n=145) found that a CA 19-9 level of 150 kU/ml in people with a bilirubin level of less than 35 µmol/l and a CA 19-9 level of 300 kU/ml or less in people with a bilirubin level greater than 35 µmol/l for indicating laparoscopic resectability had a low sensitivity of 0.61 (95% CI, 0.52-0.69) and a moderate specificity of 0.8 (95% CI, 0.56-0.94) in adults with suspected pancreatic cancer with or without obstructive jaundice. The positive likelihood ratio of 3.04 (95% CI, 1.25-7.39) suggests that a positive result for indicating laparoscopic resectability according to these thresholds is not particularly useful for ruling it in, though there is uncertainty in the estimate. The negative likelihood ratio of 0.49 (95% CI, 0.36-0.67) suggests that a negative result for indicating laparoscopic resectability according to these thresholds is not particularly useful for ruling it out.

High quality evidence from the same study (n=71) found that a CA 19-9 level of 300 kU/ml or less in people with a bilirubin level greater than 35 µmol/l for indicating laparoscopic resectability had a low sensitivity of 0.29 (95% CI, 0.18-0.43) and a high specificity of 0.94 (95% CI, 0.7-1.0) in adults with suspected pancreatic cancer and obstructive jaundice. The positive likelihood ratio of 5.43 (95% CI, 0.77-38.13) suggests that a positive result for indicating laparoscopic resectability according to these thresholds is moderately useful for ruling it in, though there is substantial uncertainty in the estimate. The negative likelihood ratio of 0.74 (95% CI, 0.6-0.91) suggests that a negative result for indicating laparoscopic resectability according to these thresholds is not particularly useful for ruling it out.

Laparoscopic resectability accuracy of CA 19-9 ≤ 130 kU/ml

High quality evidence from 1 retrospective review of a prospective database (n=262) found that a CA 19-9 level of 130 kU/ml or less for indicating laparoscopic resectability had a low sensitivity of 0.5 (95% CI, 0.43-0.57) and a moderate specificity of 0.75 (95% CI, 0.6-0.86) in adults with potentially resectable pancreatic cancer. The positive likelihood ratio of 1.95 (95% CI, 1.2-3.18) and negative likelihood ratio of 0.67 (95% CI, 0.55-0.83) suggest that neither a positive nor negative result for indicating laparoscopic resectability according to this threshold is particularly useful for ruling it in and ruling it out.

7.7 Recommendations

17. For people with newly diagnosed pancreatic cancer who have not had a pancreatic protocol CT scan, offer a pancreatic protocol CT that includes the chest, abdomen and pelvis.

18. If there are abnormal findings on CT, consider one or more of the following if the test results will change the clinical management the person receives:

- MRI, for suspected liver metastases
- PET-CT, if MRI is contraindicated or there are suspected metastases outside the liver
- endoscopic ultrasound, if more information is needed for tumour and node staging
- laparoscopy with laparoscopic ultrasound, for suspected small-volume peritoneal and/or liver metastases if resectional surgery is contemplated possibility.

See recommendation 16 on how care should be agreed and delivered.

7.8 Evidence to recommendations

7.8.1 Relative value placed on the outcomes considered

Diagnostic accuracy (sensitivity, specificity, positive predictive value and negative predictive value) for T staging, N staging, M staging, resectability and vascular invasion, and adverse events were considered the critical outcomes for this question.

Resectability was reported for most studies. Staging information and vascular invasion were reported for about half the studies. No studies reported adverse events.

7.8.2 Quality of evidence

Evidence was identified on CT, CT-3D, abdominal ultrasound, EUS, CT + EUS, laparoscopy with laparoscopic ultrasound, MRI, PET-CT, EUS-FNA, CA 19-9 and diagnostic laparoscopy + CT.

The quality of the evidence for the critical outcomes was as follows:

- resectability ranged from very low for CT and EUS, to low for abdominal US and moderate for laparoscopy with LUS and combination CT and EUS
- overall TNM staging was low (for EUS-FNA and MRI) or high (for CT, EUS and MRI)
- T staging ranged from moderate to high quality studies
- N staging ranged from very low for CT, low for abdominal US, low or moderate for PET/CT and moderate or high for EUS and MRI
- M staging ranged from low for PER/CT, low or moderate for CT, and high for EUS, MRI and diagnostic laparoscopy
- Vascular invasion ranged from low for CT and PET/CT, moderate for abdominal US, moderate or high for EUS, and high for MRI.

The committee noted that in the Klek study, most of the participants have had a prior ultrasound which had proven insufficient to stage the cancer. The committee considered that the use of abdominal ultrasound for staging was inadequate in that it does not have the ability to detect metastases outside of the abdomen and is operator dependent. Therefore, they did not use the data from this study when making their recommendations.

The committee noted that many of the studies in this review included people with periampullary cancers as well as pancreatic cancer. Where possible, the data for these 2 groups had been reported separately. However, in instances where they had been reported together, the committee agreed that it was still appropriate to use this data to make recommendations because it is not always possible to determine the primary origin of cancer in the head of the pancreas.

7.8.3 Consideration of clinical benefits and harms

The committee noted, based on the evidence, that CT had good sensitivity and specificity for T staging and identifying vascular invasion. They noted, based on their experience, that CT is widely available, non-invasive and allows both local and distant sites to be imaged. The committee agreed that the diagnostic accuracy of CT for N staging and M staging was not as good as for some other investigations and, therefore, CT was not as good at picking up smaller deposits and low volume disease in the liver, lymph nodes and peritoneum. However, the committee agreed that the advantages of using CT, in terms of accessibility, non-invasiveness and ability to image local and distant sites, made it the best choice for the initial staging investigation.

Given the limitations of CT for N and M staging, the committee agreed that it would be prudent to make additional recommendations on what other investigations should be used if the CT identified abnormal findings that needed further clarification. Based on the evidence, they noted that MRI had good specificity for M staging and would, therefore, be a useful additional investigation if the CT scan showed abnormal findings suggestive of liver metastases, as MRI has better resolution for detecting smaller metastases that would be found in the liver.. The committee noted that PET-CT also had good specificity for M staging and considered that it would be a useful additional investigation if MRI was contraindicated or if the CT indicated potential metastatic disease outside of the liver. The committee noted that EUS had good sensitivity for T and N staging and it is possible to obtain histology and cytology so agreed it was a useful supplementary investigation to perform. The committee agreed that PET-CT and MRI do not have good enough resolution to pick up small volume metastases in the peritoneum and liver. Laparoscopy with laparoscopic ultrasound would be a useful test if resectional surgery was being contemplated.

The committee agreed, based on the evidence available, that CA 19-9 did not appear to be a useful staging investigation for pancreatic cancer. However, they noted that this evidence was low quality and came from a limited number of studies. Therefore, they did not make any recommendations about CA 19-9.

The committee agreed that the potential benefits of the recommendations made would be a more effective and streamlined sequence of staging investigations for pancreatic cancer. This would lead to improved staging and people getting the correct treatment. The committee considered that the potential harms would be the risks associated with invasive investigative procedures. However, they considered these risks were likely to be minimal compared with the potential for benefit.

7.8.4 Consideration of economic benefits and harms

The committee agreed that by streamlining staging investigations unnecessary, repeated staging investigations would be avoided which would potentially result in a cost saving. They considered that improved staging would result in correct management, thereby avoiding the costs of inappropriate treatments. Therefore, the committee agreed that there were unlikely to be any significant resource implications from the recommendations made.

7.8.5 Other considerations

The committee were aware that a HTA report was likely to include evidence relevant to this section of the guideline. However, the final report was not published when this guideline went out for consultation. It was agreed that if the report was published in time, the committee would review it after the guideline consultation, and amend the recommendations if needed.

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8 Support needs

8.1 Psychological support needs

Review question: What are the specific psychological support needs (including information) of adults who are diagnosed with pancreatic cancer and their families or carers (as appropriate) throughout the care pathway?

8.1.1 Introduction

People and their families or carers are often left devastated by a diagnosis of pancreatic cancer particularly when they learn that there are limited treatment options for the disease and often a poor prognosis. This means they can have significant psychological information and support needs to help them cope with the diagnosis of a life limiting disease and the impact this has on them and their families.

The disease and treatment for the disease can also leave people feeling very unwell and they may experience a range of symptoms that can impact on their quality of life and ability to take part in normal daily activities. These symptoms can include pain, anxiety, depression, fatigue, bowel or digestive problems, loss of appetite, itchiness and nausea. People and their families and carers need timely access to psychological, physical, practical and spiritual information and support to help them cope with these symptoms and side effects and maintain as good a quality of life as possible for as long as possible.

The NICE guideline 'Supportive and palliative care for adults with cancer' contains a recommendation that 'Assessment and discussion of peoples' needs for physical, psychological, social, spiritual and financial support should be undertaken at key points (such as at diagnosis; at commencement, during, and at the end of treatment; at relapse; and when death is approaching). NHS England in their guidance document implementing the cancer taskforce recommendations for commissioning person centred care for people affected by cancer (2016) stated that everyone with cancer should be offered a holistic needs assessment and care plan. However, feedback to national charities and from the National Cancer Patient Experience Survey suggests that this may not always be happening for pancreatic cancer patients and it is important that these assessments cover the specific needs of people with pancreatic cancer.

People and families and carers also need access to information and support to help them understand their diagnosis, the treatment and care options available and to fully participate in shared decision making.

Unfortunately, pancreatic cancer patients currently do not always get access to the support and information they need. National Patient Experience Surveys have shown that pancreatic cancer patients experience a worse experience of treatment and care than those with other cancer types. In particular, there are problems with how people receive their diagnosis and a lack of communication about diagnosis, type of cancer, treatment options and what to expect following discharge from hospital.

Access to a clinical nurse specialist has also been shown to improve patient experience through National Patient Experience Surveys and feedback to patient organisations. The NICE guidance 'Supportive and palliative care for adults with cancer' recommends that 'Teams may wish to consider nominating (with the agreement of each patient) a person to act as 'key worker'; this person might be, for instance, a community nurse, allied health professional, nurse specialist or social worker, and the role might involve orchestrating assessments to ensure patients' needs are elicited, ensuring care plans have been agreed with patients, ensuring findings from assessments and care plans are communicated to

others involved in a patient's care and ensuring patients know who to contact when help or advice is needed'.

Research has identified that pancreatic cancer patients can have significant unmet needs in the areas of psychological wellbeing, anxiety and depression, as well as the psychological impact of pain, decreased energy or tiredness, fatigue and coping with bowel or digestive problems caused by pancreatic cancer on daily living and quality of life. The diagnosis of pancreatic cancer and the impact of the disease can also have a psychological impact on carers or family members.

Guidance is needed on the specific psychological support needs of people with pancreatic cancer and their families or carers.

8.1.1.1 Review protocol summary

The review protocol summary used for this question can be found in Table 74. Full details of the review protocol can be found in Appendix C.

Table 74: Clinical review protocol summary for the review of specific psychological support needs

Population	Adults with pancreatic cancer and their carers or family members
Context	• Psychological support needs/information: • Pain • Bowel/digestive problems • Nutritional concerns • Anxiety • Depression • Fatigue • Timing
Outcomes	• Health Related Quality of Life • Patient satisfaction • Patient/family/carer understanding of disease impact • Patient reported outcomes • Patient experience

8.1.2 Description of Clinical Evidence

The evidence for this topic was drawn from a total of fourteen studies employing primarily qualitative methodologies to investigate the information and support needs of patients with pancreatic cancer or the family and/or care-givers of people with pancreatic cancer. A summary of the included studies is presented in Table 75.

Two studies (Arthur et al. 2016; Sun et al. 2016) assessed the effectiveness of specific interventions designed to help meet the needs of pancreatic cancer patients. Arthur et al. (2016) collected data to inform the development of a specific exercise and diet intervention while Sun et al. (2016) conducted a pilot study to assess the feasibility of an interdisciplinary supportive care planning intervention which included the development of tailored care plans for patients and specific focus groups for information delivery.

Five studies (Chapple et al. 2012; Coleman et al. 2005; D'Angelica et al. 1998; Grant et al. 2015; Petrin et al. 2009) reported information and patient feedback around the source of information and support and mode of delivery of information.

Three studies (Beesley et al. 2016a; Beesley et al. 2016b; Uitdehaag et al. 2015) reported on the unmet needs of pancreatic cancer patients.

Two studies (Akizuki et al. 2016l; Boyd et al. 2012) reported on depression and pancreatic cancer.

The remaining two studies (Andersson et al. 2012; Schildmann et al. 2013) reported patients' perceptions and opinions about their experiences following a pancreatic cancer diagnosis.

Given the qualitative nature of the evidence, a modified CASP checklist was used (see methodology chapter).

Further information about the search strategy can be found in Appendix D. See study selection flow chart in Appendix E, study evidence tables in Appendix F and list of excluded studies in Appendix G.

8.1.3 Summary of included studies

A summary of the studies that were included in this review are presented in Table 75.

Table 75: Summary of included studies

Study	Sample Country	Type of psychological support	Measures	Outcomes
Akizuki 2016	110 pancreatic cancer patients Japan	n/a	Structured interviews (SCID-III-R)/questionnaires	Presence of depression and anxiety, time of onset
Andersson 2012	13 pancreatic or periampullary resected patients Sweden	n/a	Interviews	Qualitative analysis of lived experience post-recovery
Arthur 2016	51 survivors of resectable pancreatic cancer USA	Healthy lifestyle program to aid patients to manage their diet and exercise	Telephone survey	Interest in, preference for, perceived barriers and facilitators to participating in intervention program Acceptability and comfort of technology-based intervention using face-to-face applications (e.g. Skype)
Beesley, Janda et al. 2016	136 patients with suspected or confirmed pancreatic cancer Australia	Support services	Self-report questionnaire	Patient need and use of support services
Beesley, Wockner 2016	116 patients with pancreatic cancer Australia	Support services	Self-report questionnaire	Current and future patient need and use of support services
Boyd 2012	22 patients with confirmed pancreatic cancer USA	n/a	Questionnaires (PHQ9/PSWQ, UMSAQ)	Screening for depressive symptoms, general anxiety, sleep disturbance
Chapple 2012	40 patients, or relatives of people,	Internet	Interview	Use of internet

Study	Sample Country	Type of psychological support	Measures	Outcomes
	with pancreatic cancer UK			
Coleman 2005	600 postings on pancreatic cancer patient/family internet chatroom USA	FAQ module on PC website	Qualitative and quantitative analysis of chat room conversations	Pre- and post- qualitative and quantitative changes in chat room conversations
D'Angelica 1998	48 pancreatic resected patients USA	Information and emotional support	Questionnaire	Short- and long-term surgeon-patient communication, surgeon's role in providing emotional support
Grant 2015	Convenience sample of users of pancreatic cancer website USA	Palliative care nurse practitioner	Questionnaire	Use of PC website
Petrin 2009	First-degree relatives of people with pancreatic cancer USA	n/a	Interview	Relatives' experience of communicating about and adjusting to relative with PC
Schildmann 2013	12 confirmed pancreatic cancer with ≥1 CT regimen Germany	n/a	Interview	Qualitative analysis of perception/views of information and treatment decision making
Sun 2016	11 confirmed pancreatic cancer USA	Supportive care + education	Questionnaires (FACT-Hep, service use, financial burden	Quality of life, service use, financial burden, satisfaction with intervention
Uitdehaag 2015	57 oesophageal or pancreaticobiliary cancer Netherlands	n/a	Questionnaires (PNPCQ, EORTC QLQ-PAN26)	Problems, needs, quality of life

1 *Abbreviations: CT, chemotherapy; EORTC QLQ-PAN26, The European Organization for Research and Treatment of Cancer PAN26 ; FACT Hep, Functional Assessment of*

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Cancer Therapy-Hepatobiliary questionnaire; n/a, not applicable; PHQ9, Personal Health Questionnaire 9; PSWQ, Penn State Worry Questionnaire; PNPCQ, Problems and Needs for Palliative Care Questionnaire; QoL, quality of life; SCID III R, structured clinical interview for DSM III-R; University of Michigan Sleep Assessment Questionnaire

8.1.4 Clinical evidence profile

The methodologies in the majority of studies employed some form of questionnaire or interview to assess patient opinion and experience. In most cases, these were pre-existing, validated tools designed for the purpose of the study. Limitations of each study were assessed using a modified CASP Qualitative checklist and are detailed below in Table 76.

Table 76: Summary of clinical evidence for psychological support needs/information

Study	Population and methods	Risk of Bias	Study Quality
Akizuki et al. (2016)	Results of the study are based on a survey conducted >10 years ago	Unclear: new chemotherapy agents have been introduced which may give longer survival times however pancreatic cancer still has one of the poorest prognoses.	-
	Duration between baseline the follow-up assessment may have been too short.	Unclear: may not have been long enough to assess the predictive factors however given the poor prognosis for pancreatic cancer information regarding depression and anxiety in the1-2 months post diagnosis is important.	-
Anderss on et al. (2012)	Participants were recruited from the same hospital so the results are not generalisable to a wider pancreatic population	Unclear: the participants varied with regard to age, gender and follow-up time and the type of surgery is generally only carried out in specialist centres and likely to be only in a highly selected group of patients, so not clear what impact including patients from other centres would have on the results.	-
	Credibility of results	Low: to prevent retrospective distortion or misinterpretation, participants statements were followed up by additional questions	
Arthur et al. (2016)	93% of participants were diagnosed with stage 1 or 2 pancreatic cancer	High: Bias towards more healthy survivors with longer survival times	-
	Small sample size	Low: pancreatic cancer is a rare cancer type	
	Methodology was not mixed methods	Unclear: Pilot study and there appeared to be consistency in the results	
Beesley et al. (2016a)	Analysis was cross-sectional and included patients with a wide variation in the time from diagnosis to questionnaire completion	Unclear: Not possible to determine temporal associations between access to services and supportive care needs	-

Study	Population and methods	Risk of Bias	Study Quality
	Higher proportion of people with resectable disease than would be found in the overall population	Unclear: likely to have underestimated the level of unmet need	
	Measure of supportive care needs was validated for patients with a mixture of prognoses	Unclear: possible there are other needs specific to palliation that have not been identified.	
Beesley et al. (2016b)	Small sample size	Low: appropriate analysis used to detect significant effects	–
	Participants in this study had better overall prognosis compared with the general overall population	Unclear: possible underestimation of supportive care needs particularly with increasing as the population in this study was indicative of increasing needs over time in patients with advanced cancer	
	Considerable intermittent missing data and attrition due to death/incapacity	Possible underestimation of the level of unmet needs as those who withdrew due to sickness were significantly less likely to have had a resection and non-curative disease was associated with higher odds of future needs	
Boyd et al. (2012)	Study carried out in a referral centre so patients likely to have had an initial diagnosis prior to clinic visit	Unclear: possible impact on the baseline depression measures, participants may have had depression prior to malignant diagnosis	–
	Protocol may have created opportunity for participant exclusion	Unclear: treating clinicians assessed suitability for inclusion and immediate referrals were made for severely depressed or anxious patients.	
	No data collected on the use of psychotropic drugs	Unclear	
Chapple et al. (2012)	No specific limitations	n/a	+
Coleman et al. (2005)	Convenience sample of patients, families and friends dealing with advanced cancer	Unclear: results cannot be generalised to all patients, family or friends dealing with non-life threatening forms of cancer	-
	No way to track the number of individual people who posted the 600 messages	High: possible unequal representation of the type of posters in this sample as some posters may post more than once	
	Assumption that posts are truthful and representative of people dealing with pancreatic cancer	Unclear: no way to know if people are misrepresenting themselves/experiences	
D'Angelica et al. (1998)	Survey conducted by medical personnel from the treating institution	Unclear: possible response bias as patients may be more likely to respond positively fear of insulting/upsetting the source of their life prolonging medical care	-

Study	Population and methods	Risk of Bias	Study Quality
	Patients are a select sample of elderly, white, middle to upper class patients being treated in a specialist centre	Unclear: possible selection bias meaning the results are not generalisable	
	Of the original cohort, 43% of patients had died and 16% of patients refused to take part	Unclear: possible only satisfied patients were surveyed although this is unlikely as dissatisfied often find surveys the ideal opportunity to express their feeling.	
Grant et al. (2015)	Small sample size of patients who had not read the webpage before responding and sample drawn from one site	Unclear: difficult to generalise the results as patients accessing other websites may have had different questions	-
	The modified CMSNS questions on the online survey were not validated for this population	Unclear	
Petrin et al. (2009)	Limitations not reported	Unclear risks of bias	-
Schildmann et al. (2013)	Selective memory and socially desirable answers may have influenced the narratives	Unclear risk of recall bias	-
	Patients not receiving chemotherapy were excluded Small sample of patients selected from a single institution	Unclear risk of selection bias. Results cannot be generalised to the wider pancreatic population	
Sun et al. (2016)	Small sample size and heterogeneous population regarding stage of disease and type of treatments	Unclear risk of selection bias. Results may not be generalised to the wider pancreatic population	-
Ultdehaag et al. (2015)	Cross-sectional design measuring results at a single time point	Unclear: possible patients responses may change over time	-
	Patients were excluded if they were too ill to participate	Possible underestimation of certain problems and needs in pancreatic cancer patients	
	Small sample size	Unclear risk of selection bias	
	Symptoms analysed individually	Unclear: possible that symptom clusters should be analysed as some symptoms are related to each other	

8.1.5 Economic evidence

A literature review of published cost effectiveness analyses did not identify any relevant studies for this topic. Although there were potential implications for resource use associated with making recommendations in this area, other topics in the guideline were agreed as a higher economic priority. Consequently, bespoke economic modelling was not done for this topic.

8.1.6 Evidence Statements

8.1.6.1 Common information and support needs of pancreatic cancer patients and their families and friends

In one low quality (-) study, the most commonly reported symptom in a chat room was pain and this was the case both before and after the addition of a frequently asked questions (FAQ) section. By comparison, questions relating to fatigue decline 3-fold after the introduction of the FAQ section. Postings made describing end of life symptoms indicated a lack of awareness that death was near. (Coleman et al. 2005).

In one low quality (-) study, messages sent via a website to a Palliative Care Nurse Practitioner included questions relating to pain, gastrointestinal symptoms, post-operative complications and nutrition (Grant et al. 2015).

In one low quality (-) study, 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%) (Uitdehaag et al. 2015).

In one low quality (-) study, pain, fatigue and overall treatment side effects were the most commonly discussed physical themes at interdisciplinary meetings while the most common psychological concerns included anxiety, changes in appearance, feeling sad and the inability to work or undertake normal activities (Sun et al. 2016).

Reasons for seeking information and support varied across the studies however the common themes emerging included seeking information on their diagnosis in relation to treatment, survival or symptoms and seeking information on how to tell family or friends.

In one low quality (-) study, seeking information was one of the most commonly reported coping strategies (Petrin et al. 2009).

“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, how did he know he was even sick? I mean, what was he feeling? You know, I just needed to know everything.”

In one low quality (-) study, patients reported a strong desire to return to normal daily routine but had an awareness of the need for a recovery period (Andersson et al. 2012). In relation to recapturing everyday life, food and drink were associated with negative experiences due to symptoms such as altered taste. Eating was no longer pleasant and considered merely necessary for the recovery process. And as a result of difficulties with food intake, weight did not stabilise for a while and bodily changes resulted in various emotional problems (Andersson et al. 2012):

“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”

"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"

Prior to discharge participants in the same study had access to healthcare professionals continuously providing them with attention and care. It was a shock to some participants that they no longer had someone to rely on post discharge or to discuss their self-care experiences with (Andersson et al. 2012):

"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 healthcare staff after discharge as they felt it gave them a chance to discuss symptom management and self-care needs (Andersson et al. 2012):

"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."

In another low quality (-) study, patients expected professional care to help deal with pain, the fear of physical suffering, fatigue and lack of appetite but did not feel they needed professional care for issues relating to employment/study, inability to continue usual activities, the frustration that they can do less or their dependency on others (Uitdehaag et al. 2015).

For the participants of one low quality (-) study, being healthy did not equate to being symptom free with participants who experienced debilitating symptoms coping by using successful symptom management (Andersson et al. 2012):

"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"

In another low quality (-) study, patients reported feeling as though they had no choice and having limited interest in the details of treatment related information but that trust in the physician was paramount (Schildmann et al. 2013):

"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 life 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."

8.1.6.2 Interventions to meet specific needs of pancreatic cancer patients

In one low quality (-) qualitative study (Arthur et al. 2016), a telephone survey was conducted and data from 12 patients previously treated for resectable pancreatic cancer to inform the development of an exercise and diet intervention was collected. The study reported that 69% of participants indicated an interest in participating in a non-research exercise and diet intervention and 32% of participants perceived there to be no barriers to program participation. In relation to intervention preferences, 50% of participants indicated a preference to exercise alone and 30% indicated a preference for supervised exercise. In terms of information provision, 34% of participants indicated a preference to have exercise information provided personally while 48% indicated a preference to have diet/nutrition advice delivered personally.

One low quality (-) pilot study (Sun et al. 2016) assessed a nurse-led intervention to determine the feasibility of an interdisciplinary supportive care planning intervention in 10 patients with pancreatic cancer. The intervention included a care plan completed by the nurse and discussed at interdisciplinary meetings where care coordination recommendations were made by the team which were tailored to individual patient need. Participants were also invited to attend education sessions designed to educate patients on quality of life concerns. There was a high level of satisfaction with 70% of patients rating the intervention as 'excellent' and 30% rating the intervention as 'very good'. 80% of participants considered the time spent in the education sessions to be the right amount however 70% of participants considered there to be too much information in the written manuals provided.

8.1.6.3 Depression in pancreatic cancer

Two low quality (-) studies (Akizuki et al. 2016; Boyd et al. 2012) reported on depression and anxiety in patients diagnosed with pancreatic cancer. Boyd et al. (2012) assessed 22 patients with pancreatic cancer to investigate the association between symptoms of depression and anxiety and sleep disturbances. The study reported a total of 60% of participants reported mild (32%), moderate (23%) or moderately severe depressive symptoms (5%). 40% of participants reported no symptoms of depression and no participants reported severe depressive symptoms. In relation to 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) and 5% (n=1) participant reported an anxiety score indicative of a likely anxiety disorder (score >60).

In relation to sleep disturbances, 45% of participants reported no sleep disturbances, 41% of participants recorded scores indicative of a potential sleep problem and 10% (n=2) recorded scores indicative of a sleep problem. No correlation was observed between the scores for depression or anxiety and sleep disturbances. There is a possible link between depressive symptoms and sleep disturbances though this correlation was not significant (p=0.009). It was estimated that 16% of the depressive score is explained by the SQ scores. Similarly, 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.

Akizuki et al. (2016) reported 15 (13.6%) patients were diagnosed with depression and anxiety at baseline; 12 of these patients experienced their first psychiatric symptoms concomitant with or after onset of somatic symptoms (median=1 month after onset). Twelve of these patients were assessed at follow-up and 4 of them continued to have psychiatric disorders.

8.1.6.4 Unmet needs

Two low quality (-) studies (Beesley et al. 2016a; Beesley et al. 2016b) explored the unmet needs of 136 patients with pancreatic cancer and how those needs changed over time. Beesley et al. (2016a) reported that 32% of respondents described moderated to high unmet needs relating to help with health system/information, 21% reported moderated to high unmet patient care needs with no significant difference between patients following a palliative care pathway or a surgical resection pathway. The most commonly reported 'moderate to high' unmet need was 'participants not being able to do what they used to' (41%) and 'concerns about the worries of those close to them' (37%). Beesley et al. (2016b) reported no significant change in the proportion of patients reporting moderate to high unmet needs over time (70% at baseline versus 75% at four months: OR=0.9, 95% CI, 0.3-2.1). There was an indication of a reduction in needs over time for patients who had complete surgical resection (71%-63%) and an increase in needs for patients with locally advanced disease (73%-85%) and metastatic disease (66%-88%).

Pancreatic cancer patients (n=33) in one low quality (-) study completed questionnaires exploring problems and needs for palliative care and reported inadequate professional care for their fear of physical suffering (34%), lack of written information (28%) and fatigue (22%) (Uitdehaag et al. 2015).

One low quality (-) study (D'Angelica et al. 1998) investigated the experiences of 48 patients regarding the face-to-face patient-surgeon communication relating to preparation for surgery and information about the surgery. 94% of respondents did not require more time with their surgeon and 92% were satisfied with the information provided and had no more questions following their initial meeting. A total of 88% of respondents remembered their surgeon discussing the necessity and explaining the surgical procedure and mean understanding reported by patients was 4.7 (5 being complete understanding).

8.1.6.5 The internet as a source of information and support

Three studies (Chapple et al. 2012; Coleman et al. 2005; Grant et al. 2015) explored the role of the internet as a source of information for pancreatic cancer patients and the families and friends of pancreatic cancer patients. One high quality (+) study (Chapple et al. 2012) reported that 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. One low quality (-) study (Grant et al. 2015) reported an average of 62 visits per week to a specific pancreatic cancer website where patients could interact with a palliative care nurse and ask questions.

One low quality (-) study (Coleman et al. 2005) explored the effect off adding an FAQ section to a pancreatic cancer website and found that a greater proportion of chat room users were seeking information after the addition of the FAQ section and the chat room was most likely to be accessed by family members with only 7% of postings coming from pancreatic cancer patients.

Reasons reported for using the internet included 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 or to raise awareness of pancreatic cancer (Chapple et al. 2012). 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."

Some participants used the internet to confirm the information they were being given by doctors (Chapple et al. 2012):

"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 (Chapple et al. 2012):

"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."

8.1.6.6 Use of technology

Three low-quality (-) studies reported on the use of technology. Beesley et al. (2016b) reported that only 10% of the patients used a tablet to enter their own data into the system with 90% of participants filling out the paper forms and the data were entered by research staff.

Arthur et al. (2016) investigated the level of comfort of participants with using technology to aid the delivery of an exercise and nutrition intervention. 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 technology such as Skype™ and FaceTime®.

From one study in which 39 participants completed an online survey, responses to the modified computer mediated social network scale (CMSNS) showed that use of social networks varied; 35.9% did not use them for gaining information on pancreatic cancer while 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 (Grant et al. 2015).

8.1.7 Recommendations

19. Throughout the person's care pathway, specifically assess the psychological impact of pancreatic cancer on:

- fatigue
- pain
- gastrointestinal symptoms (including changes to appetite)
- nutrition
- anxiety
- depression.

20. Provide people and their family members or carers (as appropriate) with information and support to help them manage the psychological impact of pancreatic cancer on their lives and daily activities. This should be:

- available on an ongoing basis
- relevant to the stage of the person's condition
- tailored to the person's needs.

For more guidance on providing information and support, see the NICE guideline on patient experience in adult NHS services.

8.1.8 Evidence to recommendations

8.1.8.1 Relative value placed on the outcomes considered

Health related quality of life, patient satisfaction, patient, family or carer understanding of disease impact, patient reported outcomes and patient experience were the critical outcomes for this question. All of these outcomes were reported qualitatively.

8.1.8.2 Quality of evidence

The committee noted that the majority of studies included in the evidence employed some form of questionnaire or interview to assess patient opinion and experience. In most cases, these were pre-existing, validated tools designed for the purpose of the study. There is, therefore, the possibility that the study populations were highly selected and, in some studies, were convenience samples. The committee noted that most studies had small sample sizes.

The committee noted that there was very little evidence about the effective information and support interventions to address the psychological needs of people with pancreatic cancer. They, therefore, agreed to recommend further research in this area.

8.1.8.3 Consideration of clinical benefits and harms

The committee noted, based on the evidence, that people with pancreatic cancer have a variety of psychological support needs. Common support needs reported by the evidence included dealing with pain, fatigue and gastrointestinal symptoms and also issues around food and nutrition. Based on the evidence, people with pancreatic cancer also often report anxiety and depression.

The committee were aware, based on both the evidence and their knowledge of information from national charities and National Patient Experience Surveys, that these psychological support needs are often not met. They, therefore, made recommendations that information should be provided in the areas that had been highlighted by the evidence. This will ensure that the impact of these issues on people with pancreatic cancer is properly addressed. Based on their experience, the committee noted that provision of support has traditionally been associated with having advanced disease, but that all people with pancreatic cancer were likely to have some psychological support needs. They, therefore, agreed to recommend provision of information and support throughout the patient pathway.

However, the committee were aware, based on the evidence and their experience, that people have individualised requirements for information and support. What information may be enough for one person, may be too much or too little for someone else. They, therefore, recommended that peoples' needs in these specific support areas, and those of their families and carers, should be assessed in order to determine what level of information and support they require.

8.1.8.4 Consideration of economic benefits and harms

The committee noted that no relevant published economic evaluations had been identified and no additional economic analysis had been undertaken in this area.

They agreed that assessing peoples' need for support would require formalised time with a healthcare professional and there were likely to be costs associated with doing this. However, this would not all be additional costs as assessments are currently carried out, just not necessarily this early in the pathway. Overall, the committee agreed these recommendations were unlikely to have a significant resource impact as most of the costs are already being incurred. The assessments will happen at a different time point to what happens currently. This will mean earlier identification of issues and a reduction in the need for later support requirements and healthcare professional time.

8.1.8.5 Other considerations

The committee noted that the NICE guidance on Patient experience in NHS adult services makes recommendations on improving care in some areas such as good communication, provision of information, treating the person as an individual and shared decision making which are applicable to the care of people with pancreatic cancer. They, therefore, agreed it was important to cross reference this guidance.

8.1.9 Research recommendations

2. A qualitative study should be undertaken to evaluate information and support interventions to address psychological needs at different points in the care pathway for people with pancreatic cancer.

People with pancreatic cancer often have unmet psychological support needs that impact on their quality of life. These can be related to anxiety and depression, and to the psychological impact of fatigue, pain, gastrointestinal symptoms (particularly changes to appetite) and nutritional status. There has been very little research into the information and support interventions that would meet these needs. Research would help identify effective information and support interventions that would improve quality of life for people with pancreatic cancer and their family members or carers. Outcomes of interest are:

- quality of life
- psychological wellbeing
- ability to carry out normal activities
- patient experience and patient-reported outcome measures.

8.1.10 References

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8.2 Pain

Review question: What is the role of interventional techniques in the management of pain from pancreatic cancer?

8.2.1 Introduction

Pain is the commonest symptom reported by people with pancreatic cancer. Standard pain management involves individualised titration of medication according to the World Health Organisation (WHO) analgesic ladder. It is often necessary to combine different classes of pharmacotherapy, including opioid and adjuvant analgesics, to successfully manage the pain and reduce side effects.

Occasionally, various interventional techniques are employed to palliate the pain experienced by some individuals. These procedures are targeted at the nerve supply to the pancreas.

Methods involve injection with a drug and/or ethanol with the intention of nerve block or neurolysis. Neurolysis can also be achieved by direct destruction of the nerve with surgical techniques.

These interventional techniques can be performed by differing approaches. Percutaneous radiological guidance (plain film, CT, MRI), endoscopic ultrasound and laparoscopic, thorascopic or open surgery have all been utilised.

Uncertainty remains over which of these procedures and techniques is the most effective and appropriate to palliate the pain in people with pancreatic cancer. Currently the methods used can depend upon local expertise.

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The appropriate timing in the administration of these techniques is also unclear. Current variation in practice includes applying these techniques during the diagnostic process or later during the illness trajectory.

Interventional techniques are often considered if adequate pain control is elusive for the individual, or in an attempt to reduce the pharmacotherapy used and relieve unacceptable side effects the individual is experiencing.

Guidance is needed on the role of interventional techniques to manage pain in people with pancreatic cancer.

8.2.1.1 Review protocol summary

The review protocol summary used for this question can be found in Table 77. Full details of the review protocol can be found in Appendix C.

Table 77: Clinical review protocol summary for the review of interventional techniques for the management of pain

Population	Patients with pancreatic cancer
Intervention	• Sympathectomy (splanchnicectomy) • Neurolytic Techniques (nerve block/ablation, celiac plexus block/ablation, coeliac ganglion block/ablation, superior hypogastric block/ablation)
Comparison	• Each Other • Other methods of pain management
Outcomes	• Reduction in opioid medication • Pain Relief/ improved analgesia (pain scores) • Duration of effect/ duration of relief • Adverse Events (Diarrhoea, reduction in Opioid induced side effects) • HRQoL (functional domains) • Patient experience • PROMS • Overall survival

8.2.2 Description of Clinical Evidence

Six RCTs (Amr et al. 2013; Gao et al. 2014; Johnson et al. 2009; LeBlanc et al. 2011; Süleyman et al. 2004; Wyse et al. 2011) and one systematic review (Arcidiacono et al. 2011) involving 6 RCTs (Kawamata et al. 1996; Lillemoe et al. 1993; Mercadante 1993; Polati et al. 1998; Wong et al. 2004; Zhang et al. 2008) were included in the review. A summary of the included studies is presented in Table 78.

Three RCTs (Gao et al. 2014; Johnson et al. 2009; Wyse et al. 2011) and 1 systematic review (Arcidiacono et al. 2011) compared the efficacy and safety of conventional analgesic pain medication with or without neurolytic celiac plexus blockade (NCPB) in patients with pancreatic cancer (n=619).

One RCT (Amr et al. 2013) compared the efficacy and safety of controlling severe pain with medication followed by performing a celiac block with performing the celiac block first followed by medication for controlling severe pain in patients with pancreatic cancer (n=60).

One RCT (Johnson et al. 2009) compared the efficacy of NCPB plus medical management versus thoracic splanchnicectomy plus medical management in adults with pancreatic cancer (n=65). The same study compared the efficacy of thoracic splanchnicectomy plus medical management with medical management alone in adults with pancreatic cancer.

One RCT (LeBlanc et al. 2011) compared pain relief given as 1 versus 2 injections during EUS-guided NCPB in patients with pancreatic cancer (n=50).

One RCT (Süleyman-Ozyalcin et al. 2004) compared the efficacy of NCPB and splanchnic neurolytic blockade on pain caused by pancreatic cancer in the body and tail of the pancreas (n=39).

Where possible data were extracted from the included systematic review (Arcidiacono et al. 2011). Where there was not enough detail included in the review, the full copy of the original studies (included in the review) were checked for accuracy and completeness.

AMSTAR (A Measurement Tool to Assess Systematic Reviews) was used for assessing the methodological quality of systematic reviews; the Cochrane Collaboration's 'Risk of bias' tool was used for assessing risk of bias of RCTs. Where possible, the risk of bias information was taken from the systematic review (Arcidiacono et al. 2011) though in some cases, where there was not enough detail included in the review, the original studies were used to determine risk of bias.

Further information about the search strategy can be found in Appendix D. See study selection flow chart in Appendix E, forest plots in Appendix H, GRADE tables in Appendix I, study evidence tables in Appendix F and list of excluded studies in Appendix G.

8.2.3 Summary of included studies

A summary of the studies that were included in this review is presented in Table 78.

Table 78: Summary of included studies

Study	Study Type	Population	Intervention	Comparison	Outcomes
Amr et al. (2013)	Unblinded RCT Duration: One year	N=60 patients randomised	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).	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).	Reduction in opioid medication Pain Relief/ improved analgesia (pain scores) Adverse Events (Diarrhoea, reduction in Opioid induced side effects)
Arcidiacono et al. (2011)	Cochrane review (CR) Searches up to December 2010.	This CR includes 6 RCTs: Lillemoe et al. 1993: N=137; Mercadante et al. 1993: N=20; Polati et al. 1998: N=24; Kawamata et al. 1996: N=21; Wong et al. 2004: N=100; Zhang et al. 2008: N=56;	SR: CPB, the surgical approach, and EUS-guided neurolysis Included studies: Lillemoe et al. 1993: NCPB (chemical splanchnicectomy - Intraoperative bilateral 20 mL 50% ethanol) Mercadante et al. 1993: NCPB (X-ray posterior bilateral 25 ml 75% alcohol) Polati et al. 1998: Fluoroscopy posterior bilateral 7 mL 100% ethanol) Kawamata et al. 1996: NCPB (X-ray posterior bilateral 15 to 20 ml 80% ethanol) Wong et al. 2004: NCPB (Fluoroscopy posterior bilateral 10 mL 100% ethanol)	SR: NSAIDs and morphine Included studies: Lillemoe et al. 1993: analgesic therapy (NSAID, morphine). Mercadante et al. 1993: analgesic therapy (NSAID, morphine - saline). Polati et al. 1998: analgesic therapy (NSAID, morphine). Kawamata et al. 1996: analgesic therapy (NSAID, morphine) Wong et al. 2004: analgesic therapy (NSAID, morphine). Zhang et al. 2008: analgesic therapy (MS Contin - oral controlled-release morphine)	SR: Reduction in pain intensity using a visual analogue scale (VAS) or other pain relief scales (during the procedure the patients are usually sedated, so no discomfort will be reported). Consumption of analgesics. Included studies: Where possible data was extracted from the Cochrane SR. The full copy of the study was checked for accuracy and completeness. additional outcomes extracted from primary studies Lillemoe et al. 1993

Study	Study Type	Population	Intervention	Comparison	Outcomes
			Zhang et al. 2008: NCPB (CT-guided posterior bilateral block with 20 ml 100% ethanol)		Pain Relief (VAS pain scores) Adverse effect Overall survival Mercadante et al. 1993 Reduction in opioid medication Pain Relief (VAS pain scores) Adverse effect Polati et al. 1998 Reduction in opioid medication Adverse effect Kawamata et al. 1996 Pain Relief (VAS pain scores) Reduction in opioid medication Adverse effect Health Related Quality of Life (functional domains) PROS Wong et al. 2004 Pain Relief (VAS pain scores) Reduction in opioid medication Adverse effect Overall survival Zhang et al. 2008 Reduction in opioid medication

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Study	Study Type	Population	Intervention	Comparison	Outcomes
					Pain Relief (VAS pain scores) Adverse effect HRQoL (functional domains)
Suleyman Ozyalcin et al. (2004)	Outcomes' assessor blinded RCT Duration: 18 weeks	N=39 patients randomised	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)	SNB (Splanchnic nerves neurolytic blockade – 6 ml of 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)	Reduction in opioid medication Pain Relief/ improved analgesia (pain scores)
LeBlanc et al. (2011)	Single (patients) blinded RCT Duration: not clear	N=50 patients randomised	EUS-NCPB (1 injections) All patients received the same amount of medication (20 mL 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.	EUS-NCPB (2 injections) In the G2, half of the medication was injected into both sides of the celiac trunk	Reduction in pain medication Pain Relief
Wyse et al. (2011)	Double blinded RCT Duration: 3 months	N=96 patients randomised	EUS-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.	Conventional pain management	Reduction in opioid medication Pain Relief/ improved analgesia (pain scores)

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Study	Study Type	Population	Intervention	Comparison	Outcomes
Johnson et al. (2009)	Open RCT Duration: 2 months	N=65 patients (58 with PC) were randomised (18 withdrew)	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) MM + thoracoscopic splanchnicectomy-TS (patient positioned prone under general anaesthesia with a single lumen endotracheal tube, and partial lung collapse induced by pneumothorax)	MM – medical management (oral morphine-or other opioid-was prescribed according to standard practice at each centre)	Pain Relief/ improved analgesia (pain scores)
Gao et al. (2014)	Blinded RCT Duration: 2 months	N=100 patients randomised	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)	Reduction in opioid medication Pain Relief/ improved analgesia (pain scores) HRQoL (functional domains) PROS

CPB: Celiac plexus block; SR: Cochrane review; EUS: Endoscopic ultrasound; MM: Medical management; NCPB: Neurolytic celiac plexus block; NSAID: Non-steroidal anti-inflammatory drugs; PC: Pancreatic cancer; RCT: Randomised controlled trial; SNB: Splanchnic nerves neurolytic blockade; TS: Thoracic splanchnicectomy; VAS: Visual Analogue Scale; WHO: World Health Organization.

8.2.4 Clinical evidence profile

The clinical evidence profiles for this review question are presented in Table 79 to Table 84.

Table 79: Summary clinical evidence profile for neurolytic celiac plexus blockade versus medical management alone in adults with pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Medical management (MM)	NCPB				
Overall Survival Follow-up: 6 months	Median time: 6.1 (n.r.) months	Median time: 5.5 (n.r.) months	HR 0.80 (0.50 to 1.28	100 (1 study[6])	⊕⊕⊕⊖ moderate[24]	
Reduction in opioid medication: Opioid use at 2 weeks Follow-up: 2 weeks		The mean reduction in opioid medication: opioid use at 2 weeks in the intervention groups was 64.52 lower (99.45 to 29.59 lower)		76 (2 studies[1])	⊕⊕⊖⊖ low[2,3]	
Reduction in opioid medication: Opioid use at 4 weeks		The mean reduction in opioid medication: opioid use at 4 weeks in the intervention groups was 51.07 lower (82.71 to 19.43 lower)		120 (4 studies[4])	⊕⊕⊖⊖ low[3]	
Reduction in opioid medication: Opioid use the day before to death		The mean reduction in opioid medication: opioid use the day before to death in the intervention groups was 48.52 lower (68.82 to 28.22 lower)		111 (4 studies[4])	⊕⊕⊖⊖ low[5]	
Reduction in opioid medication: Percentage change in		The mean reduction in opioid medication: percentage		100 (1 study[6])	⊕⊕⊕⊖ moderate[7]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Medical management (MM)	NCPB				
analgesic medications use and 3 months - NSAIDs		change in analgesic medications use and 3 months - nsaids in the intervention groups was 54.6 lower (54.82 to 54.38 lower)				
Reduction in opioid medication: Percentage change in analgesic medications use and 3 months - Morphine		The mean reduction in opioid medication: percentage change in analgesic medications use and 3 months - morphine in the intervention groups was 76.6 lower (76.8 to 76.4 lower)		100 (1 study[6])	⊕⊕⊕⊖ moderate[7]	
Reduction in opioid medication: Percentage change in analgesic medications use and 3 months - Oxycodone		The mean reduction in opioid medication: percentage change in analgesic medications use and 3 months - oxycodone in the intervention groups was 68.4 lower (68.7 to 68.1 lower)		100 (1 study[6])	⊕⊕⊕⊖ moderate[7]	
Reduction in opioid medication: Absolute change in morphine use at 1 month		The mean reduction in opioid medication: absolute change in morphine use		98 (1 study[6])	⊕⊖⊖⊖ very low[8,9]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Medical management (MM)	NCPB				
		at 1 month in the intervention groups was 1 lower (48.5 lower to 46.5 higher)				
Reduction in opioid medication: Absolute change in morphine use at 3 months		The mean reduction in opioid medication: absolute change in morphine use at 3 months in the intervention groups was 50 lower (118.52 lower to 18.52 higher)		98 (1 study[10])	⊕⊖⊖⊖ very low[8,9]	
Pain Relief/ improved analgesia: Pain scores at 2 weeks		The mean pain relief/ improved analgesia: pain scores at 2 weeks in the intervention groups was 0.34 standard deviations lower (1.09 lower to 0.4 higher)		109 (3 studies[11])	⊕⊕⊖⊖ low[2,12]	SMD -0.34 (-1.09 to 0.4)
Pain Relief/ improved analgesia: Pain scores at 4 weeks		The mean pain relief/ improved analgesia: pain scores at 4 weeks in the intervention groups was 0.43 lower (0.73 to 0.14 lower)		173 (4 studies[13])	⊕⊕⊕⊖ moderate[14]	
Pain Relief/ improved analgesia: Pain scores at 8 weeks		The mean pain relief/ improved analgesia: pain scores at 8 weeks in the		279 (6 studies[10,13,15])	⊕⊕⊖⊖ low[9,14]	SMD -1.09 (-2.33 to 0.15)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Medical management (MM)	NCPB				
		intervention groups was 1.09 standard deviations lower (2.33 lower to 0.15 higher)				
Patients reporting effective pain management - 2 weeks	316 per 1000	357 per 1000 (114 to 704)	RR 1.13 (0.43 to 2.97)	33 (1 study[15])	⊕⊖⊖⊖ very low[16,17,18]	
Patients reporting effective pain management - 8 weeks	417 per 1000	554 per 1000 (183 to 875)	RR 1.33 (0.55 to 3.24)	21 (1 study[15])	⊕⊖⊖⊖ very low[16,17,18]	
Absolute Change in Pain score at 1 and 3 months - 1 Month		The mean absolute change in pain score at 1 and 3 months - 1 month in the intervention groups was 1 lower (1.73 to 0.27 lower)		98 (1 study[10])	⊕⊕⊕⊖ moderate[19]	
Absolute Change in Pain score at 1 and 3 months - 3 months		The mean absolute change in pain score at 1 and 3 months - 3 months in the intervention groups was 2.3 lower (3.09 to 1.51 lower)		98 (1 study[10])	⊕⊕⊕⊖ moderate[19]	
Adverse effects: constipation	525 per 1000	199 per 1000 (131 to 310)	RR 0.38 (0.25 to 0.59)	161 (6 studies[20])	⊕⊕⊕⊖ moderate[21]	
Adverse effects: diarrhoea	33 per 1000	108 per 1000 (32 to 371)	RR 3.25 (0.95 to 11.13)	121 (4 studies22)	⊕⊕⊖⊖ low[23,24]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Medical management (MM)	NCPB				
QOL scores at 1 month - Appetite		The mean QOL scores at 1 month - appetite in the intervention groups was 0.3 higher (0.57 lower to 1.17 higher)		56 (1 study[25])	⊕⊖⊖⊖ very low[18,26]	
QOL scores at 1 month - Sleep		The mean QOL scores at 1 month - sleep in the intervention groups was 0.5 higher (0.55 lower to 1.55 higher)		56 (1 study[25])	⊕⊖⊖⊖ very low[18,26]	
QOL scores at 1 month - communication		The mean QOL scores at 1 month - communication in the intervention groups was 1.1 lower (2.27 lower to 0.07 higher)		56 (1 study[25])	⊕⊕⊖⊖ low[24,26]	
QOL scores at 3 months - Appetite		The mean QOL scores at 3 months - appetite in the intervention groups was 0.3 lower (1.48 lower to 0.88 higher)		56 (1 study[25])	⊕⊖⊖⊖ very low[18,25]	
QOL scores at 3 months - Sleep		The mean QOL scores at 3 months - sleep in the intervention groups was 0.2 higher (1 lower to 1.4 higher)		56 (1 study[25])	⊕⊖⊖⊖ very low[18,26]	
QOL scores at 3 months - Communication		The mean QOL scores at 3 months - communication in the		56 (1 study[25])	⊕⊖⊖⊖ very low[18,26]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Medical management (MM)	NCPB				
		intervention groups was 0.4 higher (0.65 lower to 1.45 higher)				
QOL scores at 3 months - Physical function		The mean QOL scores at 3 months - physical function in the intervention groups was 11.6 higher (8.26 to 14.94 higher)		100 (1 study[6])	⊕⊕⊕⊖ moderate[7]	
QOL scores at 3 months - Role function		The mean QOL scores at 3 months - role function in the intervention groups was 1.6 higher (1.77 lower to 4.97 higher)		100 (1 study[6])	⊕⊖⊖⊖ very low[7,18]	
QOL scores at 3 months - Emotional function		The mean QOL scores at 3 months - emotional function in the intervention groups was 18 higher (14.53 to 21.47 higher)		100 (1 study[6])	⊕⊕⊕⊖ moderate[7]	
QOL scores at 3 months - Cognitive function		The mean QOL scores at 3 months - cognitive function in the intervention groups was 2.9 higher (3.76 lower to 9.56 higher)		100 (1 study[6])	⊕⊖⊖⊖ very low[7,18]	
QOL scores at 3 months - Social function		The mean QOL scores at 3 months - social function in the intervention groups was		100 (1 study[6])	⊕⊖⊖⊖ very low[7,18]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Medical management (MM)	NCPB				
		1 higher (3.57 lower to 5.57 higher)				
QOL scores - Digestive Disease questionnaire-15: 1 month		The mean QOL scores - digestive disease questionnaire-15: 1 month in the intervention groups was 8 higher (0.07 to 15.93 higher)27		98 (1 study[10])	⊕⊕⊖⊖ low[8,24]	
QOL scores - Digestive Disease questionnaire-15: 3 months		The mean QOL scores - digestive disease questionnaire-15: 3 months in the intervention groups was 1 higher (9.73 lower to 11.73 higher)27		98 (1 study[10])	⊕⊕⊖⊖ low[8,24]	
QOL scores – Global quality at 3 months		The mean QOL scores – global quality at 3 months in the intervention groups was 14.3 higher (14.1 to 14.5 higher)28		100 (1 study[6])	⊕⊕⊖⊖ low[7]	
QOL scores – Symptom at 3 months - Fatigue		The mean QOL scores – symptom at 3 months - fatigue in the intervention groups was 16.7 higher (11.97 to 21.43 higher)28		100 (1 study[6])	⊕⊕⊖⊖ low[7]	
QOL scores – Symptom at 3 months -		The mean QOL scores – symptom at 3		100 (1 study[6])	⊕⊖⊖⊖ very low[7,18]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Medical management (MM)	NCPB				
Nausea/vomiting		months - nausea/vomiting in the intervention groups was 1.6 higher (2.59 lower to 5.79 higher)28				
QOL scores – Symptom at 3 months - Pain		The mean QOL scores – symptom at 3 months - pain in the intervention groups was 33.9 lower (38.64 to 29.16 lower)28		100 (1 study[6])	⊕⊕⊖⊖ low[7]	
QOL scores – Symptom at 3 months - Dyspnea		The mean QOL scores – symptom at 3 months - dyspnea in the intervention groups was 0.3 higher (7.15 lower to 7.75 higher)28		100 (1 study[6])	⊕⊖⊖⊖ very low[7,18]	
QOL scores – Symptom at 3 months - Insomnia		The mean QOL scores – symptom at 3 months - insomnia in the intervention groups was 40.9 lower (46.6 to 35.2 lower)28		100 (1 study[6])	⊕⊖⊖⊖ very low[7,18]	
QOL scores – Symptom at 3 months - Appetite loss		The mean QOL scores – symptom at 3 months - appetite loss in the intervention groups was 28.8 lower (35.28 to 22.32 lower)28		100 (1 study[6])	⊕⊕⊖⊖ low[7]	
QOL scores – Symptom at 3		The mean QOL scores –		100 (1 study[6])	⊕⊖⊖⊖ very low[7,18]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Medical management (MM)	NCPB				
months - Constipation		symptom at 3 months - constipation in the intervention groups was 1.2 higher (7.12 lower to 9.52 higher)28				
QOL scores – Symptom at 3 months - Financial difficulties		The mean QOL scores – symptom at 3 months - financial difficulties in the intervention groups was 1.1 lower (3.03 lower to 0.83 higher)28		100 (1 study[6])	⊕⊖⊖⊖ very low[7,18]	
QOL scores – Symptom 3 months - Diarrhoea		The mean QOL scores – symptom 3 months - diarrhoea in the intervention groups was 0.7 lower (2.12 lower to 0.72 higher)28		100 (1 study[6])	⊕⊖⊖⊖ very low[7,18]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes.*

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

1 Mercadante et al. 1993 and Zhang et al. 2010
2 Evidence was downgraded by 1 due to unclear selection bias in all studies and potential risk of performance bias (no blinding of outcome assessors) in Mercadante et al. 1993
3 Serious inconsistency: I2=80%
4 Mercadante et al,1993; Kawamata et al,1996; Polati et al. 1998; Zhang et al. 2008
5 Evidence was downgraded by 1 due to potential risk of performance bias (no blinding of outcome assessors) in 2 studies (Mercadante et al,1993; Kawamata et al,1996) and potential selection bias in all studies
6 Gao et al. 2014
7 The quality of the evidence was downgraded because of the uncertain risk of selection and potential risk of performance bias (no blinding of outcome assessors)
8 The quality of the evidence was downgraded due to potential risk of contamination bias: 2 patients from the control group received open-label CPN at 43 and 52 days
9 The quality of the evidence was further downgraded from moderate to low due to imprecision in the effect size estimates (95%CI crossed two default MIDs)
10 Wyse et al. 2011
11 Jonshon 2009; Mercadante et al. 1993; Zhang et al. 2008.

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Medical management (MM)	NCPB				

12 Serious inconsistency: I2=71%
13 Kamawata et al. 1996, Wong 1994; Mercadante et al. 1993; Zhang et al. 2008.
14 The quality of the evidence was downgraded from high to moderate because of the unclear risk of selection bias in two studies (Mercadante et al. 1993; and Zhang et al. 2008) and potential risk of performance bias (Kamawata et al. 1996; Mercadante et al. 1993)
15 Johnson et al. 2009
16 The quality of the evidence was downgraded from high to moderate because of the potential risk of performance bias (no blinding of outcome assessors) and unclear risk of attrition bias
17 The quality of the evidence was further downgraded from moderate to low due to indirectness in Johnson et al. 2009 (the cohort included 65 patients (only 58 with PC)
18 Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs
19 The quality of the evidence was downgraded due to potential risk of contamination bias: 2 patients from the control group received open-label CPN at 43 and 52 days
20 Kawamata et al. 1996; Lillimoe 1993; Mercadante et al. 1993; Polati et al. 1998; Wong et al. 2004; Zhang et al. 2008
21 Evidence was downgraded by 1 due to performance bias: no blinding of outcome assessors in 2 studies (Mercadante et al. 1993; Kawamata et al. 1996) and unclear selection bias in 5 studies (Lillemoe et al. 1993; Mercadante et al. 1993; Polati et al. 1998; Kawamata et al. 1996; Zhang et al. 2008)
22 Kawamata et al. 1996; Mercadante et al. 1993; Polati et al. 1998; Zhang et al. 2008
23 Evidence was downgraded by 1 due to performance bias: no blinding of outcome assessors in 2 studies (Mercadante et al. 1993; Kawamata et al. 1996) and unclear selection bias in all studies (Mercadante et al. 1993; Polati et al. 1998; Kawamata et al. 1996; Zhang et al. 2008)
24 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. This outcome was therefore downgraded for imprecision by one level as it was not statistically significant.
25 Zhang et al. 2008
26 The quality of the evidence was downgraded from high to moderate because of the potential risk of attrition bias and unclear risk of selection bias
27 The QOL scores were collected by means of the Digestive Disease questionnaire-15
28 The QOL scores were collected by means of the questionnaire "Changes in function and symptom scores on European Organization for Research and Treatment of Cancer QLQ-C30"

Table 80: Summary clinical evidence profile for early NCPB versus late NCPB in adults with pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Late NCPB	Early NCPB				
Reduction in opioid medication: Oral morphine use at 16 weeks		The mean reduction in opioid medication: oral morphine use at 16 weeks in the intervention groups was 55.82 higher (40.91 to 70.73 higher)		23 (1 study[1])	⊕⊕⊕⊖ moderate[2]	
Reduction in opioid medication: Oral morphine use at 24 weeks		The mean reduction in opioid medication: oral morphine use at 24 weeks in the intervention groups		22 (1 study[1])	⊕⊕⊕⊖ moderate[2]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Late NCPB	Early NCPB				
		was 62.41 higher (46.07 to 78.75 higher)				
Reduction in opioid medication: Oral Tramadol Hydrochloride use at 16 weeks		The mean reduction in opioid medication: oral tramadol hydrochloride use at 16 weeks in the intervention groups was 209.68 higher (143.2 to 276.16 higher)		21 (1 study[1])	⊕⊕⊕⊖ moderate[2]	
Reduction in opioid medication: Oral Tramadol Hydrochloride use at 24 weeks		The mean reduction in opioid medication: oral tramadol hydrochloride use at 24 weeks in the intervention groups was 160 higher (1.9 to 318.1 higher)		12 (1 study[1])	⊕⊕⊖⊖ low[2,4]	
Pain Relief/ improved analgesia: Pain scores at 16 weeks		The mean pain relief/ improved analgesia: pain scores at 16 weeks in the intervention groups was 21.3 higher (18.88 to 23.72 higher)5		60 (1 study[1])	⊕⊕⊕⊖ moderate[2]	
Pain Relief/ improved analgesia: Pain scores at 24 weeks		The mean pain relief/ improved analgesia: pain scores at 24 weeks in the intervention groups was 26 higher (22.34 to 29.66 higher)5		60 (1 study[1])	⊕⊕⊕⊖ moderate[2]	
Adverse effects: nausea	33 per 1000	333 per 1000 (45 to 1000)	RR 10 (1.36 to 73.33)	60 (1 study[1])	⊕⊕⊖⊖ low[2,6]	
Adverse effects: constipation	267 per 1000	533 per 1000 (269 to 1000)	RR 2 (1.01 to 3.95)	60 (1 study[1])	⊕⊕⊖⊖ low[2,4]	
Adverse effects: pluritus	33 per 1000	100 per 1000 (11 to 908)	RR 3 (0.33	60 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Late NCPB	Early NCPB				
			to 27.23)			

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes.*

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

1 Amr et al. 2013
2 The quality of the evidence was downgraded from high to moderate due to potential indirectness (as the randomised trial was conducted in Egypt and the outcomes may not be transferrable to the UK settings)
3 Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs
4 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed 1 default MID
5 Pain relief was assessed using the visual analogue scale (VAS) pain score
6 The low sample size doesn't allow for precision in the effect estimates

Table 81: Summary clinical evidence profile for NCPB plus medical management versus thoracic splanchnicectomy plus medical management in adults with pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Thoracic splanchnicectomy + MM	NCPB + MM				
Pain Relief/ improved analgesia: Pain scores at 2 weeks		The mean pain relief/ improved analgesia: pain scores at 2 weeks in the intervention groups was 0.16 higher (1.31 lower to 1.63 higher)1		28 (1 study[2])	⊕⊖⊖⊖ very low[3,4,5]	
Pain Relief/ improved analgesia: Pain scores at 8 weeks		The mean pain relief/ improved analgesia: pain scores at 8 weeks in the intervention groups was 1.02 lower (2.95 lower to 0.91 higher)1		18 (1 study[2])	⊕⊖⊖⊖ very low[3,4,5]	
Patients reporting effective pain management at 2 weeks	286 per 1000	357 per 1000 (100 to 731)	RR 1.25 (0.35 to 2.56)[6]	28 (1 study[2])	⊕⊖⊖⊖ very low[3,4,5]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Thoracic splanchnicectomy + MM	NCPB + MM				
Patients reporting effective pain management at 2 months	364 per 1000	556 per 1000 (171 to 884)	RR 1.53 (0.47 to 2.43)[6]	20 (1 study[2])	⊕⊖⊖⊖ very low[3,4,5]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes.*

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

1 Pain scores were assessed using a 4-point Likert scale
2 Jonshon et al. 2009
3 The quality of the evidence was downgraded from high to moderate because of the potential risk of performance bias (no blinding of outcome assessors) and unclear risk of attrition bias
4 The quality of the evidence was further downgraded from moderate to low due to indirectness in the study population (the cohort included 65 patients (only 58 with PC)
5 Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs
6 Patients reporting effective pain relief was assessed as one or more of the following: (i) a Brief Pain Inventory (BPI) 'worst' pain rated over the last week as 0-4 (none or mild), (ii) a reduction of >50% between the mean of the three BPI items ('worst', 'least' and 'average') obtained at the baseline assessment and that obtained at the 2-month assessment, (iii) a decrease from baseline to 2 months of at least 2 points in the response to the question 'During the past week, have you had pain?'.

Table 82: Summary clinical evidence profile for thoracic splanchnicectomy plus medical management versus medical management alone in adults with pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	MM	Thoracic splanchnicectomy + MM				
Pain Relief/ improved analgesia: Pain scores at 2 and 8 weeks - Pain scores at 2 weeks		The mean pain relief/ improved analgesia: pain scores at 2 and 8 weeks - pain scores at 2 weeks in the intervention groups was 0.3 lower (1.81 lower to 1.21 higher)		33 (1 study[1])	⊕⊖⊖⊖ very low[2,3,4]	
Pain Relief/ improved analgesia: Pain scores at 2 and 8 weeks - Pain		The mean pain relief/ improved analgesia: pain scores at 2 and 8 weeks - pain scores at 8 weeks in the		22 (1 study[1])	⊕⊖⊖⊖ very low[2,3,4]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	MM	Thoracic splanchnicectomy + MM				
scores at 8 weeks		intervention groups was 0.52 lower (2.11 lower to 1.07 higher)				
Patients reporting effective pain management at 2 and 8 weeks - At 2 months	316 per 1000	287 per 1000 (82 to 644)	RR 0.91 (0.26 to 2.04)5	33 (1 study[1])	⊕⊖⊖⊖ very low[2,3,4]	
Patients reporting effective pain management at 2 and 8 weeks - At 8 months	417 per 1000	362 per 1000 (96 to 754)	RR 0.87 (0.23 to 1.81)5	23 (1 study[1])	⊕⊖⊖⊖ very low[2,3,4]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes.*

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

1 Johnson et al. 2009
2 The quality of the evidence was downgraded from high to moderate because of the potential risk of performance bias (no blinding of outcome assessors) and unclear risk of attrition bias
3 The quality of the evidence was further downgraded from moderate to low due to indirectness in study population (the cohort included 65 patients (only 58 with PC)
4 Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs
5 Patients reporting effective pain relief was assessed as one or more of the following: (i) a Brief Pain Inventory (BPI) 'worst' pain rated over the last week as 0-4 (none or mild), (ii) a reduction of >50% between the mean of the three BPI items ('worst', 'least' and 'average') obtained at the baseline assessment and that obtained at the 2-month assessment, (iii) a decrease from baseline to 2 months of at least 2 points in the response to the question 'During the past week, have you had pain?'.

Table 83: Summary clinical evidence profile for EUS-guided NCPB - 1 injection versus 2 injections in adults with pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	EUS-guided NCPB: 2 injections	EUS- guided NCPB: 1 injection				
Reduction in pain medication	333 per 1000	310 per 1000 (120 to 600)	RR 0.93 (0.36 to 1.8)	50 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Patients with pain relief	810 per 1000	688 per 1000 (372 to 890)	RR 0.85	50 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	EUS-guided NCPB: 2 injections	EUS- guided NCPB: 1 injection				
			(0.46 to 1.1)			
Patients reporting a block effective (subjective)	619 per 1000	687 per 1000 (409 to 879)	RR 1.11 (0.66 to 1.42)	50 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Patient with a complete pain relief	95 per 1000	69 per 1000 (10 to 365)	RR 0.72 (0.1 to 3.83)	50 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes.*

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

1 LeBlanc et al. 2013
2 The quality of the evidence was downgraded from high to moderate because of the unclear risk of attrition bias (insufficient reporting of attritions/exclusions), the unclear risk of performance bias (no details given on blinding of outcome assessors) and the high risk of selective reporting bias (All outcomes of interest [Pain score and analgesic use overtime] are reported completely, but no details about the time frame of the outcome measurement)
3 Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs

Table 84: Summary clinical evidence profile for NCPB versus splanchnic neurolytic blockade in adults with pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Splanchnic nerve blocks	NCPB				
Reduction in opioid medication: total daily codeine consumption	See comment	See comment	Not estimable[1]	39 (1 study[2])	⊕⊖⊖⊖ very low[3,4,5]	
Pain Relief/ improved analgesia: Pain scores (VAS)	See comment	See comment	Not estimable[6]	39 (1 study[2])	⊕⊖⊖⊖ very low[3,4,5]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes.*

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

1 Data are reported as medians (mg - COD consumption) and p values overtime: "There are significant

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Splanchnic nerve blocks	NCPB				

*differences between two groups at 2nd (4 weeks), 4th (8 weeks), and 5th (10 weeks) controls (respectively; p=0.041, p=0.021, p=0.028). **There are highly significant differences between two groups at 1st (2 weeks), 3rd (6 weeks), controls (respectively; p=0.003, p=0.005)"*
2 Suleyman Ozyalcin et al. 2004
3 The quality of the evidence was downgraded from high to moderate because of the unclear risk of attrition bias (insufficient reporting of attritions/exclusions) and the high risk of selective reporting bias (all outcomes of interest [Pain score, analgesic use overtime and survival rates] are reported incompletely)
4 The quality of the evidence was downgraded from moderate to low due to potential indirectness (as the randomised trial was conducted in Turkey and the outcomes may not be transferrable to the UK settings)
5 The quality of evidence was further downgraded from low to very low due to imprecision in the effect estimates (not possible to estimate how precise the effect estimates: no information regarding uncertainty of the estimates reported)
*6 Data reported as medians (VAS scores) and p values overtime: "*There are significant differences between two groups at 2nd (4 weeks), 4th (8 weeks), and 5th (10 weeks) controls (respectively; p=0.041, p=0.021, p=0.028). **There are highly significant differences between two groups at 1st (2 weeks), 3rd (6 weeks), controls (respectively; p=0.003, p=0.005)"*

8.2.5 Economic evidence

A literature review of published cost effectiveness analyses did not identify any relevant studies for this topic. Although there were potential implications for resource use associated with making recommendations in this area, other topics in the guideline were agreed as a higher economic priority. Consequently, bespoke economic modelling was not done for this topic.

8.2.6 Evidence Statements

8.2.6.1 NCPB versus medical management alone

Reduction in medication use

Low quality evidence from a meta-analysis of 2 RCTs (n=76) showed a clinically important difference favouring NCPB on opioid usage (in mg/day oral morphine) compared to medical management (analgesic therapy: non-steroid anti-inflammatory drugs [NSAIDs] and morphine) at 2 weeks follow-up in adults with pancreatic cancer: MD -64.52 (95% CI 99.45 to -29.59).

Low quality evidence from a meta-analysis of 4 RCTs (n=120) showed a clinically important difference favouring NCPB on opioid usage (in mg/day oral morphine) compared to medical management (analgesic therapy: non-steroid anti-inflammatory drugs [NSAIDs] and morphine) at 4 weeks follow-up in adults with pancreatic cancer: MD -51.07 (95% CI -82.71 to -19.43).

Moderate quality evidence from a meta-analysis of 4 RCTs (n=111) showed a clinically important difference favouring NCPB on opioid usage (in mg/day oral morphine) compared to medical management (analgesic therapy: non-steroid anti-inflammatory drugs [NSAIDs] and morphine) until the day before death in adults with pancreatic cancer: MD -48.52 (95% CI -68.82 to -28.22).

Moderate quality evidence from 1 RCT (n=100) showed a clinically important difference favouring NCPB on change [percentage] in analgesic medications usage (NSAIDs, morphine, and oxycodone) compared to medical management (analgesic therapy: non-steroid anti-inflammatory drugs [NSAIDs] and morphine) at 3 months follow-up in adults with

pancreatic cancer: NSAIDs: MD -54.60 (95% CI -54.82 to -54.38); morphine: MD -76.60 (95% CI -76.80 to -76.40); and oxycodone: MD -68.40 (95% CI -68.70 to -68.10).

Very low quality evidence from 1 RCT (n=98) showed no clinically important difference between NCPB and medical management (analgesic therapy: non-steroid anti-inflammatory drugs [NSAIDs] and morphine) on morphine consumption at 1 month (MD -1.00 [95% CI -48.50 to 46.50]) and 3 months (MD -50.00 [95% CI -118.52 to 18.52]) follow-up in adults with pancreatic cancer, where MD less than 0 favours the NCPB arm.

Pain relief/improved analgesia

Low quality evidence from a meta-analysis of 3 RCTs (n=109) showed no clinically important difference between NCPB and medical management (analgesic therapy: non-steroid anti-inflammatory drugs [NSAIDs] and morphine) on pain scores at 2 weeks follow-up in adults with pancreatic cancer: SMD -0.34 (95% CI -1.09 to 0.40), where SMD less than 0 favours the NCPB arm.

Moderate quality evidence from a meta-analysis of 4 RCTs (n=174) showed a clinically important difference favouring NCPB on VAS pain scores compared to medical management (analgesic therapy: non-steroid anti-inflammatory drugs [NSAIDs] and morphine) at 4 weeks follow-up in adults with pancreatic cancer: MD -0.43 (95% CI -0.73 to -0.14).

Low quality evidence from a meta-analysis of 6 RCTs (n=279) showed no clinically important difference between NCPB and medical management (analgesic therapy: non-steroid anti-inflammatory drugs [NSAIDs] and morphine) on pain scores at 8 weeks follow-up in adults with pancreatic cancer: SMD -1.09 (95% CI -2.33 to 0.15), where SMD less than 0 favours the NCPB arm.

Very low quality evidence from a multicentre RCT (n=33) showed no clinically important difference between NCPB and medical management (analgesic therapy: non-steroid anti-inflammatory drugs [NSAIDs] and morphine) in the number of people reporting “effective pain relief” at 2 weeks (RR 1.13 [95% CI 0.43 to 2.97]) and 2 months (RR 1.33 [95% CI 0.55 to 3.24]) follow-up in adults with pancreatic cancer, where RR less than 1 favours the NCPB arm.

Moderate quality evidence from 1 RCT (n=98) showed a clinically important difference favouring NCPB on VAS pain scores (absolute change) compared to medical management (analgesic therapy: non-steroid anti-inflammatory drugs [NSAIDs] and morphine) at 1 month (MD -1.00 [95% CI -1.73 to -0.27]) and 3 months (MD -2.30 [95% CI -3.09 to -1.51]) follow-up in adults with pancreatic cancer.

Duration of effect/ duration of relief

No evidence was identified to inform this outcome

Adverse events

Moderate quality evidence from a meta-analysis of 6 RCTs (n=161) showed a clinically important difference favouring NCPB on constipation-related adverse effects compared to medical management (analgesic therapy: non-steroid anti-inflammatory drugs [NSAIDs] and morphine) in adults with pancreatic cancer: RR 0.38 (95% CI 0.25-0.59)

Low quality evidence from a meta-analysis of 4 RCTs (n=121) showed no clinically important difference between NCPB and medical management (analgesic therapy: non-steroid anti-inflammatory drugs [NSAIDs] and morphine) on diarrhoea-related adverse effects in adults with pancreatic cancer: RR 3.25 (95% CI 0.95 to 11.13), where RR less than 1 favours the NCPB arm.

Health related quality of life (functional domains)

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Low and very low quality evidence from 1 RCT (n=56) showed no clinically important difference between NCPB and medical management (analgesic therapy: non-steroid anti-inflammatory drugs [NSAIDs] and morphine) in QOL scores (as interference with appetite, sleep, and communication) at 1 month and 3 months follow-up in adults with pancreatic cancer.

Moderate quality evidence from 1 RCT (n=100) showed a clinically important difference favouring NCPB on QOL scores (including physical and emotional functions) compared to medical management (analgesic therapy: non-steroid anti-inflammatory drugs [NSAIDs] and morphine) at 3 months follow-up in adults with pancreatic cancer: physical function: MD 11.60 (95% CI 8.26 to 14.94); emotional function: RR = 18.00 (95% CI 14.53 to 21.47). The same trial showed no clinically important difference between NCPB and medical management on QOL scores, regarding role (MD 1.60 [95% CI 1.77 to 4.97]), cognitive (MD 2.90 [95% CI -3.76 to 9.56]) and social functions (MD 1.00 [95% CI -3.57 to 5.57]) in adults with pancreatic cancer, where MD higher than 0 favours the NCPB arm.

Moderate quality evidence from 1 RCT (n=98) showed no clinically important difference between NCPB and medical management (analgesic therapy: non-steroid anti-inflammatory drugs [NSAIDs] and morphine) in QOL scores (percentage change measured using the Digestive Disease questionnaire-15) between patients treated with NCPB and those treated with standard analgesic care at 1 month (MD 8.00 [95% CI 0.07 to 15.93]) or 3 months (MD 1.00 [95% CI -9.73 to 11.73]) follow-up in adults with pancreatic cancer, where MD higher than 0 favours the NCPB arm.

Low quality evidence from 1 RCT (n=100) showed a clinically important difference favouring NCPB on global QOL scores compared to medical management (analgesic therapy: non-steroid anti-inflammatory drugs [NSAIDs] and morphine) at 3 month follow-up in adults with pancreatic cancer: MD 14.30 (95% CI 14.10 to 14.50).

Very low quality evidence from 1 RCT (n=100) showed:

- a clinically important difference favouring NCPB on QOL scores (including self-assessed scores for pain (MD -33.90 [95% CI -38.64 to -29.16]), insomnia (MD -40.90 [95% CI -46.60 to –35.20]) and appetite loss symptoms (MD -28.80 [95% CI -35.28 to -22.32]) compared to medical management (analgesic therapy: non-steroid anti-inflammatory drugs [NSAIDs] and morphine) at 3 month follow-up in adults with pancreatic cancer.
- a clinically important difference favouring medical management (analgesic therapy: non-steroid anti-inflammatory drugs [NSAIDs] and morphine) on QOL scores (including fatigue symptoms) compared to NCPB at 3 month follow-up in adults with pancreatic cancer: MD 16.70 (95% CI 11.97 to 21.43)
- no clinically important difference between NCPB and medical management in QOL scores, regarding the following symptoms nausea/vomiting: MD 1.6 (95% CI -2.59 to 5.79); dyspnoea MD 0.3 (95% CI -7.15 to 7.75); constipation MD 1.2 (95% CI -7.12 to 9.52); financial difficulties -1.1 (95% CI -3.03 to 0.83) and diarrhoea MD -0.70 (95% CI -2.12 to 0.72), where MD less than 0 favours the NCPB arm.

Patient experience

No evidence was identified to inform this outcome

PROMS

No evidence was identified to inform this outcome

Overall survival

Moderate quality evidence from 1 RCT (n=100) showed no clinically important difference between neurolytic celiac plexus blockade (NCPB) and medical management (analgesic therapy: non-steroid anti-inflammatory drugs [NSAIDs] and morphine) on overall survival in

adults with pancreatic cancer: HR=0.80 (95% CI 0.50 to 1.28), where HR less than 1 favours the NCPB arm.

8.2.6.2 Early NCPB versus late NCPB

Reduction in opioid medication

Moderate quality evidence from 1 RCT (n=23) showed a clinically important difference favouring late NCPB [analgesics were given first to control pain and the NCPB was performed only when the patients reported a VAS score <40] on oral morphine sulphate consumption compared to early NCPB [the NCPB was performed first and then the analgesic therapy] in adults with pancreatic cancer at 16 weeks (MD 55.82 [95% CI 40.91 to 70.73]) and 24 weeks (MD 62.41 [95% CI 46.07 to 78.75]) follow-up.

Moderate to low quality evidence from 1 RCT (n=21) showed a clinically important difference favouring late NCPB [analgesics were given first to control pain and the NCPB was performed only when the patients reported a VAS score <40] on oral tramadol consumption compared to early NCPB [the NCPB was performed first and then the analgesic therapy] in adults with pancreatic cancer at 16 weeks follow-up: MD 209.68 (95% CI 143.20 to 276.16). The same trial showed no clinically important difference between late and early NCPB on oral tramadol consumption at 24 weeks follow-up: MD 160.00 (95% CI 1.90 to 318.10), where MD less than 0 favours the early NCPB arm.

Pain relief/ improved analgesia

Moderate quality evidence from 1 RCT (n=60) showed a clinically important difference favouring late NCPB [analgesics were given first to control pain and the NCPB was performed only when the patients reported a VAS score <40] in pain scores compared to early NCPB [the NCPB was performed first and then the analgesic therapy] in adults with pancreatic cancer both at 16 weeks (MD 21.30 [95% CI 18.88 to 23.72]) and 24 weeks (MD 26.00 [95% CI 22.34 to 29.36]) follow-up.

Duration of effect/ duration of relief

No evidence was identified to inform this outcome

Adverse Events

Moderate quality evidence from 1 RCT (n=60) showed a clinically important difference favouring late NCPB [analgesics were given first to control pain and the NCPB was performed only when the patients reported a VAS score <40] on opioid adverse effects (nausea) compared to early NCPB [the NCPB was performed first and then the analgesic therapy] in adults with pancreatic cancer: RR 10.00 (95% CI 1.36 to 73.33).

The same RCT showed no clinically important difference between late and early NCPB on opioid adverse effects (including constipation (RR 2.00 [95% CI 1.01 to 3.95]) and pluritus (RR 3.00 [95% CI 0.33 to 27.3]) in adults with pancreatic cancer, where RR less than 1 favours the early NCPB arm.

Health related quality of life (functional domains)

No evidence was found for this outcome.

Patient experience

No evidence was identified to inform this outcome

PROMS

No evidence was identified to inform this outcome

.

Overall survival

No evidence was identified to inform this outcome

8.2.6.3 NCPB plus medical management versus thoracic splanchnicectomy plus medical management

Reduction in opioid medication

No evidence was identified to inform this outcome

Pain Relief/ improved analgesia

Very low quality evidence from a multicentre RCT (n=28) showed no clinically important difference between NCPB + medical management and thoracoscopic splanchnicectomy + medical management on pain scores at 2 weeks (MD 0.16 [95% CI -1.31 to 1.63]) and 2 months (MD -1.02 [95% CI -2.95 to 0.91]) follow-up in adults with pancreatic cancer, where MD less than 0 favours the NCPB + medical management arm.

Very low quality evidence from a multicentre RCT (n=28) showed no clinically important difference between NCPB + medical management and thoracoscopic splanchnicectomy + medical management on the number of people reporting “effective pain relief” at 2 weeks (RR 1.25 [95% CI 0.42 to 3.70]) and 2 months (RR 1.53 [95% CI 0.58 to 4.05]) follow-up in adults with pancreatic cancer, where RR less than 1 favours the NCPB + medical management arm.

Duration of effect/ duration of relief

No evidence was identified to inform this outcome

Adverse events

No evidence was identified to inform this outcome

Health related quality of life (functional domains)

No evidence was identified to inform this outcome

Patient experience

No evidence was identified to inform this outcome

PROMS

No evidence was identified to inform this outcome

Overall survival

No evidence was identified to inform this outcome

8.2.6.4 Thoracic splanchnicectomy plus medical management versus medical management alone

Reduction in opioid medication

No evidence was identified to inform this outcome

Pain Relief/ improved analgesia

Low quality evidence from a multicentre RCT (n=33) showed no clinically important difference between thoracic splanchnicectomy + medical management and medical management alone on pain scores at 2 weeks (n=33) (MD -0.30 [95% CI -1.81 to 1.21]) and

2 months (n=22) (MD -0.52 [95% CI -2.11 to 1.07]) follow-up in adults with pancreatic cancer, where MD less than 0 favours the thoracic splanchnicectomy + medical management arm.

Very low quality evidence from a multicentre RCT (n=33) showed no clinically important difference between thoracic splanchnicectomy + medical management and medical management alone on the number of people reporting “effective pain relief” at 2 weeks (RR 0.90 [95% CI 0.31 to 2.61]) and 2 months (RR 0.87 [95% CI 0.31 to 2.44]) follow-up in adults with pancreatic cancer, where RR less than 1 favours the thoracic splanchnicectomy + medical management arm.

Duration of effect/ duration of relief

No evidence was identified to inform this outcome

Adverse Events

No evidence was identified to inform this outcome

Health related quality of life (functional domains)

No evidence was identified to inform this outcome

Patient experience

No evidence was identified to inform this outcome

PROMS

No evidence was identified to inform this outcome

Overall survival

No evidence was identified to inform this outcome

8.2.6.5 EUS- guided NCPB: 1 injection versus EUS- guided NCPB: 2 injections

Reduction in opioid medication

Very low quality evidence from 1 RCT (n=50) showed no clinically important difference between EUS-guided NCPB performed with 1 or 2 injections on the usage of pain medication in adults with pancreatic cancer: RR 0.93 (95% CI 0.41-2.10), where RR less 1 favours the 1 injection arm.

Pain Relief/ improved analgesia

Very low quality evidence from 1 RCT (n=50) showed no clinically important difference between EUS-guided NCPB performed with 1 or 2 injections on pain relief in adults with pancreatic cancer: RR 0.85 (95% CI 0.62-1.17), where RR less 1 favours the 1 injection arm.

Very low quality evidence from 1 RCT (n=50) showed no clinically important difference between EUS-guided NCPB performed with 1 or 2 injections on the number of people reporting complete pain relief in adults with pancreatic cancer: RR 0.72 (95% CI 0.11-4.74), where RR less 1 favours the 1 injection arm.

Very low quality evidence from 1 RCT (n=50) showed no clinically important difference between EUS-guided NCPB performed with 1 or 2 injections on the number of people reporting an effective block in adults with pancreatic cancer: RR 1.11 (95% CI 0.74-1.69), where RR less 1 favours the 1 injection arm.

Duration of effect/ duration of relief

No evidence was identified to inform this outcome

.

Adverse Events

No evidence was identified to inform this outcome

Health related quality of life (functional domains)

No evidence was identified to inform this outcome

Patient experience

No evidence was identified to inform this outcome

PROMS

No evidence was identified to inform this outcome

Overall survival

No evidence was identified to inform this outcome

8.2.6.6 NCPB versus splanchnic nerve blocks

Reduction in opioid medication

Very low quality evidence from 1 RCT (n=39) suggests clinically important differences favouring splanchnic nerve blocks on total daily codeine consumption compared to NPCB at 2, 4, 6, 8, and 10 weeks follow-up in adults with pancreatic cancer [Relative effect not estimable].

Pain Relief/ improved analgesia

Very low quality evidence from 1 RCT (n=39) showed a clinically important difference favouring splanchnic nerve blocks on VAS pain scores when compared to those treated with NPCB at 2, 4, 6, 8, 10 and 12 weeks follow-up in adults with pancreatic cancer [Relative effect not estimable].

Duration of effect/ duration of relief

No evidence was identified to inform this outcome

Adverse Events

No evidence was identified to inform this outcome

Health related quality of life (functional domains)

No evidence was identified to inform this outcome

Patient experience

No evidence was identified to inform this outcome

PROMS

No evidence was identified to inform this outcome

Overall survival

No evidence was identified to inform this outcome

.

8.2.7 Recommendations

21. Consider EUS-guided or image-guided percutaneous neurolytic coeliac plexus block to manage pain for people with pancreatic cancer who:

- have uncontrolled pancreatic pain or
- are experiencing unacceptable opioid adverse effects or
- are receiving escalating doses of analgesics.

22. Do not offer thoracic splanchnicectomy to people with pancreatic cancer.

8.2.8 Evidence to recommendations

8.2.8.1 Relative value placed on the outcomes considered

Reduction in opioid medication, pain relief or improved analgesia, duration of effect, adverse events, overall survival, health-related quality of life, patient experience and PROMS were considered the critical outcomes for this question.

Patient experience was not reported for any comparisons of interest. Health related quality of life and PROMs were only reported for the comparison of neurolytic coeliac plexus blockade (NCPB) against medical management alone. Duration of effect or duration of relief was reported for the comparison of endoscopic ultrasound (EUS)-guided NCPB with one injection against EUS-guided NCPB with 2 injections. Adverse events were only reported for the comparison of neurolytic coeliac plexus blockade (NCPB) against medical management alone and for early versus late NCPB. Reduction in opioid medication, pain relief and overall survival were reported for the majority of the included comparisons.

The committee noted that as most patients were in the palliative setting, overall survival was not a useful outcome on which to base recommendations.

8.2.8.2 Quality of evidence

The quality of the evidence was assessed by GRADE, the Cochrane risk of bias checklist for individual studies and the AMSTAR (A Measurement Tool to Assess Systematic Reviews) checklist was used to assess the methodological quality of systematic reviews.

No evidence was found comparing either EUS-guided NCPB with percutaneous NCPB or late EUS-guided NCPB with early EUS-guided NCPB.

The quality of the evidence for NCPB versus medical management ranged from moderate to very low. The committee noted that the evidence base included non-UK studies. It was not possible to determine whether the RCT evidence was adequately randomised or blinded and for the outcome of overall survival, the studies were not exclusively on people with pancreatic cancer. The committee acknowledged that there were some limitations with the evidence, but agreed that it was possible to make recommendations for clinical practice as there was moderate quality evidence for some outcomes.

The committee noted that NCPB can be done by either percutaneous or by EUS guidance, but the evidence did not demonstrate superiority for any particular route. The committee considered making a research recommendation to compare the effectiveness of percutaneous NCPB with EUS-guided NCBP. However, they agreed that this would be unlikely to be picked up because EUS-guidance is becoming the preferred technique in most UK centres.

The quality of the evidence for the comparison of early versus late NCPB was moderate for all reported outcomes. The committee noted, based on the evidence, that opioid medication

usage, pain relief and opioid adverse effects (nausea and constipation) improved with late NCPB, for example for people in whom the NCPB was performed after the analgesic therapy. However, the committee noted that the evidence for this comparison consisted of only one study and that this study was not transferrable to the UK setting. They, therefore, agreed not to make any recommendations for clinical practice in this area. Instead, they recommended further research comparing early NCPB with late NCPB in order to establish the most effective time point for this intervention.

The quality of evidence for thoracic splanchnicectomy ranged from low to very low for the outcomes of interest. The committee noted that only one study had been found and that this study was not exclusively in people with pancreatic cancer. Also, very few of the outcomes of interest had been reported. However, the committee noted that for pain relief, the evidence did not show any meaningful clinical benefit. They, therefore, agreed it was important to make recommendations about this intervention.

The quality of the evidence for the comparison of one EUS-guided NCPB injection versus two injections was very low quality for all outcomes. The committee noted that, based on the evidence, opioid medication usage, pain relief, duration of effect and overall survival improved in people who received EUS-guided NCPB injections. However, there was no meaningful difference in these outcomes relative to the number of injections used. They were, therefore, unable to make any recommendations about the number of injections that was most effective.

The quality of evidence for the comparison of NCPB versus splanchnic nerve blocks was very low for all outcomes. The committee noted that, based on the evidence, opioid medication usage reduced and survival improved in people who underwent splanchnic nerve blocks. However, due to the limitations in the evidence, the committee agreed not to make any recommendations for clinical practice on the use of splanchnic nerve blocks.

8.2.8.3 Consideration of clinical benefits and harms

The committee did not make clinical practice recommendations for several of the comparisons of interest as they considered the quality of the evidence to be insufficient to allow them to adequately evaluate the benefits and harms for people.

The committee noted that current practice for pain management in people with pancreatic cancer is medical management with analgesics. If these analgesics do not adequately control the pain or the person has difficulties with the side effects of the analgesia then NCPB may be considered. It was also noted that people with pancreatic cancer often have issues with poorly-controlled pain and would like to be aware of other options if the medical management does not work. However, NCPB is often under-used due to a lack of expertise and/or awareness of it.

The committee noted, based on the evidence, that medication or opioid usage, pain relief, constipation and quality of life appeared to improve for people treated with NCPB. They agreed that NCPB should be considered for pain management for those people who have uncontrolled pancreatic pain, are receiving escalating doses of analgesia or are experiencing unacceptable opioid adverse effects as these were the groups from the evidence who showed a benefit from this intervention.

The committee considered that the potential benefit of the recommendation to use NCPB was that people with pancreatic cancer would be made aware of this intervention, which is effective in managing pain. As a result of its use, the use of opioids, and their resulting side effects, would likely be reduced. However, the committee noted that the evidence for the side effects or complications of NCPB was limited. Thus, they only recommended NCPB in those people in whom conventional analgesia is suboptimal.

Based on their clinical experience, the committee noted that thoracic splanchnicectomy is an invasive technique that needs to be done under general anaesthetic. This procedure is not currently in widespread use in UK centres and, consequently, is only being done in small numbers. Given the lack of evidence showing any effectiveness of thoracic splanchnicectomy, particularly for pain relief, the committee agreed to recommend that this procedure should not be performed. The committee considered that the benefits of the recommendation on thoracic splanchnicectomy would be to stop a practice that was shown to be ineffective.

8.2.8.4 Consideration of economic benefits and harms

The committee noted that no relevant published economic evaluations had been identified and no additional economic analysis had been undertaken in this area.

The committee agreed that the recommendations made were unlikely to result in a substantial increase in costs. This was because the number of people involved would not be large. Moreover, EUS facilities and the expertise to perform EUS-guided procedures would already be available at all pancreatic resectional centres. Peripheral hospitals would also be able to send people to the centres for this procedure. With more widespread use of NCPB, the requirement for analgesia would be reduced, which would contribute to cost saving.

8.2.9 Research recommendations

3. A randomised trial should be undertaken comparing early endoscopic ultrasound-guided neurolytic coeliac plexus (EUS-guided NCP) interventions with on-demand EUS-guided NCP interventions in people with unresectable pancreatic cancer.

There is a limited number of randomised trials in this area, and the methods used to perform NCP intervention are heterogeneous. It is not clear if early NCP intervention is superior to on-demand NCP intervention in terms of the important outcomes for the patient and duration of effect of the procedure. On-demand NCP intervention may benefit people with uncontrolled pain, people receiving escalating doses of analgesia, people experiencing unacceptable analgesic side effects, and others. However, people who receive early NCP intervention may not need on-demand NCP intervention later on. Further research should clarify if the timing of the intervention confers any advantage. The outcomes of interest are:

- reduction in pain
- patient experience (including nutritional status)
- health-related quality of life
- adverse events
- analgesic use
- survival.

8.2.10 References

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8.3 Nutritional Interventions

Review question: What nutritional interventions are effective for patients with newly diagnosed or recurrent pancreatic cancer?

8.3.1 Introduction

Malnutrition, sarcopenia and cachexia are common in pancreatic cancer. There is considerable variation in the nutritional input received by people with pancreatic cancer in different parts of the country (and in some cases between local hospitals or GPs and tertiary centres). This has been reported to be an area of confusion for people with pancreatic cancer, their families and some professionals, meaning that some people continue to experience symptoms that have a negative impact on their quality of life. Good nutritional input can improve quality of life for people with pancreatic cancer and, potentially improve their ability to undergo oncological treatment and survival.

There is a high incidence of pancreatic exocrine insufficiency (not producing or secreting enough digestive enzymes from the pancreas for adequate digestion) in those with pancreatic cancer, this is treated with pancreatic enzyme replacement therapy (PERT). However, there is variation in the amount of specialist information people receive on how to

take PERT effectively, which means they may continue to experience the symptoms and consequences of poor digestion and not get the full benefit of this intervention.

Many people with pancreatic cancer benefit from dietary counselling to increase their nutritional intake. Most can consume adequate nutrition with advice on modifying food choices and preparation methods and some require additional measures such as oral nutritional supplements. However, there is variation in the level and type of information given and the route nutrition is provided. There is uncertainty over what are the most effective interventions and route for providing nutrition.

Guidance is needed on the nutritional interventions that are effective for people with pancreatic cancer.

8.3.1.1 Review protocol summary

The review protocol summary used for this question can be found in Table 85. Full details of the review protocol can be found in Appendix C.

Table 85: Clinical review protocol summary for the review of nutritional interventions

Population	Patients with: • Resectable pancreatic cancer (pre and post-operative) • Unresectable or metastatic pancreatic cancer
Intervention	• Pancreatic Enzyme replacement therapy +/- Proton Pump Inhibitors • Oral nutritional supplements • Fish oils (Omega 3 fatty acids, DHA, EPA) • Glycaemic control • Enteral/ parenteral/oral nutrition
Comparison	• No intervention • Each other
Outcome	• Overall Survival • Treatment related morbidity • Health Related Quality of Life • Symptom control • Nutritional status (weight, BMI, lean body mass, strength test/ muscle function, sarcopenia, percentage weight change) • Adverse events • Patient experience

8.3.2 Description of Clinical Evidence

Eleven randomised trials involving nine comparisons were included in the review. A summary of the included studies is presented in Table 86.

2 RCTs (Hamza et al., 2015; Gianotti et al. 2000) compared enteral immunonutrition with standard enteral nutrition on nutritional outcomes in patients with pancreatic cancer (n=181). One RCT focused on patients before and after surgery for pancreatic cancer (Hamza et al. 2015). In the other RCT (Gianotti et al. 2000) the intervention was implemented and evaluated after surgery.

One RCT (Gade et al. 2016) compared the effect of supplementary enteral immunonutrition seven days before surgery for pancreatic cancer against standard nutrition on postoperative complications and body weight (n=35).

2 RCTs (Gianotti et al. 2000; Liu et al. 2011) compared the effectiveness of parenteral nutrition with standard enteral nutrition on nutritional outcomes in patients who underwent surgery for pancreatic cancer (n=126).

One RCT (Gianotti et al. 2000) compared the effectiveness of parenteral nutrition against enteral immunonutrition to evaluate whether the route of administration and the composition of the post-operative nutritional support could affect the immunometabolic response and outcome in patients with pancreatic cancer (n=139).

One RCT (Brennan et al. 1994) assessed the impact of adjuvant parenteral nutrition after surgery for patients with pancreatic cancer (n=117).

Two RCTs (Fearon et al. 2003; Moses et al. 2013) compared a protein and energy dense supplement enriched with n-3 fatty acids with an isocaloric-isonitrogenous supplement (without n-3 fatty acids) for their effects on nutritional outcomes and physical capability in patients with unresectable pancreatic cancer (n=224).

One RCT (Kraft et al. 2012) examined the role of oral L-Carnitine supplementation on cancer cachexia in pancreatic cancer (n=72).

Two RCTs (Bruno et al. 1998; Woo et al. 2016) compared pancreatic enzyme replacement therapy (PERT) with placebo in reducing or preventing weight loss in patients with unresectable pancreatic cancer (n=101).

One RCT (Satoi et al. 2016) compared the effectiveness of pancrelipase replacement therapy against conventional PERT on protecting against non-alcoholic fatty liver disease (NAFLD) development after surgery in patients with pancreatic cancer (n=39).

The Cochrane Collaboration's 'Risk of bias' tool was used for assessing risk of bias of randomised trials. Further information about the search strategy can be found in Appendix D. See study selection flow chart in Appendix E, forest plots in Appendix H, GRADE tables in Appendix I, study evidence tables in Appendix F and list of excluded studies in Appendix G.

8.3.31 Summary of included studies

2 A summary of the studies that were included in this review is presented in Table 86.

3 **Table 86: Summary of included studies**

Study	Study Type	Population	Aim	Intervention	Comparison	Outcomes
Brennan et al. 1994	Design: Un-blinded RCT Randomization method: not stated Duration: not stated	N=117 patients with PC after surgery	To analyse the impact of adjuvant PN after major resection for PC.	PN (n=60)	No intervention (n=57)	Overall Survival at median follow up of 18 months Treatment related morbidity Major complications Minor complications Overall complications
Bruno et al. 1998	Design: Double blinded RCT Randomization method: not stated Duration: 8 weeks	N=24 patients with unresectable PC	To assess the role of pancreatic PERT in combination with dietary counselling in reducing/preventing weight loss in patients with unresectable PC with occlusion of the pancreatic duct.	PERT (n=11)	Placebo (n=10)	Nutritional status at 8 weeks follow-up Change in body weight (%) Change in body weight (Kg) Daily dietary intake of total calories (MJ)
Fearon et al. 2003	Design: Double blind RCT Randomization method: computer generated random assignments and sealed envelopments Duration: 8 weeks	N=200 losing weight patients with unresectable PC	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.	EPA enriched oral supplement (n=95)	Identical supplement without EPA (n=105)	Health Related Quality of Life at 8 weeks Nutritional status at 4/8 weeks Change in Lean body mass Change Weight

Study	Study Type	Population	Aim	Intervention	Comparison	Outcomes
Gade et al. 2016	Design: Personnel-blind RCT Randomization method: unclear Duration: 1 month	N=35 patients with PC after surgery	To examine the effect of supplementary per oral EIN seven days before surgery for PC on postoperative complications, length of hospital stay, functional capability and body weight.	E IN (n=19)	No intervention –habitual diet (n=16)	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
Gianotti et al. 2000	Design: Assessors-blind RCT Randomization method: randomization was performed using sealed envelopes Duration: 8 days post-surgery	N=220 patients with PC after surgery	To evaluate whether early SEN may be a suitable alternative to PN for patients with PC undergoing surgery, and whether EIN could improve outcome in these patients.	PN (n = 68) SNT(n = 73)	G3: EIN (n=71)	Treatment related morbidity Patients with infectious complications Patients with non-infectious complications Total patients with complications Postoperative mortality SEN versus EIN side effects
Hamza et al. 2015	Design: Un-blind RCT Randomization method: randomization was performed using sequential series of 4 per block of 10 patients Duration: 3 weeks (2 weeks before and 1 week after surgery)	N=37 patients with resectable PC	To compare the effects of perioperative EIN versus SEN on systemic and mucosal immunity in patients undergoing surgery for periampullary cancer.	EIN (n=17)	SEN (n=20)	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

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Study	Study Type	Population	Aim	Intervention	Comparison	Outcomes
						BMI strength test/ muscle function: midarm circumference, corrected arm muscle area
Kraft et al. 2012	Design: Double-blind RCT Randomization method: randomization was performed using sequential series of 4 per block, sealed envelopes, and computer generated randomization code Duration: 12 weeks	N=72 patients with unresectable PC	To investigate the role of oral L-Carnitine supplementation on cancer cachexia in pancreatic cancer.	Oral nutritional supplement: L-Carnitine (n = 38)	Placebo (n = 34)	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)
Liu et al. 2011	Design: Un-blind RCT Randomization method: randomization was performed according to the smallest imbalance index scheme Duration: 14 days post-surgery	N=58 patients with PC after surgery	To determine the effects of PN and SEN on clinical outcomes in pancreatic cancer patients who underwent surgery.	PN (n=30)	SEN (n=28)	Treatment related morbidity Total patients with postoperative complications Postoperative mortality
Moses et al. 2004	Design: Double-blind RCT Randomization method: randomization was performed using a sequential series of numbered, sealed, opaque envelopes containing computer-	N=24 patients with advanced PC	To determine whether the decreased TEE and 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 EPA.	GJJ – n=18 (GJJ was open-n = 16, or laparoscopic-n = 2, and either antecolic-n = 12, or retrocolic-n = 6)	Duodenal stent placement (Enteral Wallstent) – n=21	Nutritional status Change in weight (kg) at 8 weeks Change in lean body mass at 8 weeks TEE and PAL Change in TEE at 8 weeks Change in REE at 8 weeks

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Study	Study Type	Population	Aim	Intervention	Comparison	Outcomes
	generated random assignments Duration: 8 weeks					Change in PAL at 8 weeks
Satoi et al. 2016	Design: Un-blind RCT Randomization method: no stated Duration: 12 months	N=39 patients randomised	To evaluate the role of pancrelipase replacement therapy on NAFLD after surgery in patients with pancreatic cancer in comparison with conventional PERT.	Pancrelipase replacement therapy (n = 29)	Conventional PERT (n = 28)	Treatment related morbidity NAFLD at 1 year follow-up Nutritional status BMI at 6 and 12 months follow-up
Woo et al. 2016	Design: Double-blind phase II randomised 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	N=77 patients with unresectable PC	To assessed whether pancreatic PERT could reduce or prevent weight loss in patients with unresectable PC.	PERT (n=34)	Placebo (n=33)	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

TEE: Total energy expenditure; PAL: Physical activity level; EPA: N-3 fatty acid eicosapentaenoic acid; NAFLD: Non-alcoholic fatty liver disease; EIN: Enteral immunonutrition; SEN: Standard enteral nutrition; PN: Parenteral nutrition; BMI: Body mass index; PERT: Pancreatic enzyme replacement therapy; REE: Resting energy expenditure.

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8.3.4 Clinical evidence profile

The clinical evidence profiles for this review question are presented in Table 87 to Table 96.

Table 87: Summary clinical evidence profile for standard enteral nutrition versus enteral immunonutrition before and after surgery

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Enteral immunonutrition (EIN) versus Standard Enteral nutrition (SEN) before and after surgery				
Treatment related morbidity - postoperative complications - Patients with infectious complications	400 per 1000	332 per 1000 (128 to 860)	RR 0.83 (0.32 to 2.15)	30 (1 study[1])	⊕⊖⊖⊖ very low[3,4]	
Treatment related morbidity - postoperative complications - Patients with non-infectious complications	400 per 1000	400 per 1000 (168 to 960)	RR 1 (0.42 to 2.4)	30 (1 study[1])	⊕⊖⊖⊖ very low[2,3,4]	
Health Related Quality of Life - Karnofsky score at 2 weeks after surgery, change from baseline		The mean health related quality of life - Karnofsky score at 2 weeks after surgery, change from baseline in the intervention groups was 2 lower (7.33 lower to 3.33 higher)		37 (1 study[1])	⊕⊖⊖⊖ very low[2,3,4]	
Nutritional status at 2 weeks after surgery - BMI (kg/m2), change from baseline		The mean nutritional status at 2 weeks after surgery - BMI (kg/m2), change from baseline in the intervention groups was 1.5 standard deviations lower (3.93 lower to 0.93 higher)		37 (1 study[1])	⊕⊖⊖⊖ very low[2,3,4]	
Nutritional status at 2 weeks after surgery - mid-arm		The mean nutritional status at 2 weeks after surgery - mid-		37 (1 study[1])	⊕⊖⊖⊖ very low[2,3,4]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Enteral immunonutrition (EIN) versus Standard Enteral nutrition (SEN) before and after surgery				
circumference (cm), change from baseline		arm circumference (cm), change from baseline in the intervention groups was 0.6 lower (2.92 lower to 1.72 higher)				
Nutritional status at 2 weeks after surgery - corrected arm muscle area (cm2), change from baseline		The mean nutritional status at 2 weeks after surgery - corrected arm muscle area (cm2), change from baseline in the intervention groups was 1.6 lower (7.09 lower to 3.89 higher)		37 (1 study[1])	⨁⊖⊖⊖ very low[2,3,4]	

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio;

1 Hamza et al. 2015
2 Evidence was downgraded by 1 due to attrition bias (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, missing data were judged to affect the true outcome of the trial) and unclear risk of performance bias
3 Evidence was downgraded by 1 due to indirectness of the study population (only 26 of 47 particpiants had PC)
4 Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs

Table 88: Summary clinical evidence profile for standard enteral nutrition versus enteral immunonutrition after surgery

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Enteral immunonutrition (EIN) versus Standard Enteral nutrition (SEN) after surgery				
Treatment related morbidity - postoperative	151 per 1000	84 per 1000 (33 to 217)	RR 0.56 (0.22	144 (1 study[1])	⨁⨁⊖⊖ low[2]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Enteral immunonutrition (EIN) versus Standard Enteral nutrition (SEN) after surgery				
complications - Patients with infectious complications			to 1.44)			
Treatment related morbidity - postoperative complications - Patients with non-infectious complications	288 per 1000	253 per 1000 (147 to 434)	RR 0.88 (0.51 to 1.51)	144 (1 study[1])	⊕⊕⊖⊖ low[2]	
Treatment related morbidity - postoperative mortality	14 per 1000	28 per 1000 (3 to 304)	RR 2.06 (0.19 to 22.18)	144 (1 study[1])	⊕⊕⊖⊖ low[2]	
Treatment related morbidity - Jejunostomy and enteral nutritional related complications - Tube clogging/kinking	68 per 1000	42 per 1000 (10 to 171)	RR 0.62 (0.15 to 2.49)	144 (1 study[1])	⊕⊕⊖⊖ low[2]	
Treatment related morbidity - Jejunostomy and enteral nutritional related complications - Tube dislodgment	14 per 1000	28 per 1000 (3 to 304)	RR 2.06 (0.19 to 22.18)	144 (1 study[1])	⊕⊕⊖⊖ low[2]	
Treatment related morbidity - Jejunostomy and enteral nutritional related complications - Tube breakage	14 per 1000	5 per 1000 (0 to 113)	RR 0.34 (0.01 to 8.27)	144 (1 study[1])	⊕⊕⊖⊖ low[2]	
Treatment related morbidity - Jejunostomy and enteral nutritional related complications - Local skin infection	14 per 1000	5 per 1000 (0 to 113)	RR 0.34 (0.01 to 8.27)	144 (1 study[1])	⊕⊕⊖⊖ low[2]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Enteral immunonutrition (EIN) versus Standard Enteral nutrition (SEN) after surgery				
Treatment related morbidity - Jejunostomy and enteral nutritional related complications - Abdominal cramps	151 per 1000	140 per 1000 (63 to 310)	RR 0.93 (0.42 to 2.06)	144 (1 study[1])	⊕⊕⊖⊖ low[2]	
Treatment related morbidity - Jejunostomy and enteral nutritional related complications - Abdominal distention	123 per 1000	141 per 1000 (60 to 325)	RR 1.14 (0.49 to 2.64)	144 (1 study[1])	⊕⊕⊖⊖ low[2]	
Treatment related morbidity - Jejunostomy and enteral nutritional related complications - Vomiting	27 per 1000	6 per 1000 (0 to 115)	RR 0.21 (0.01 to 4.21)	144 (1 study[1])	⊕⊕⊖⊖ low[2]	
Treatment related morbidity - Jejunostomy and enteral nutritional related complications - Diarrhoea	123 per 1000	99 per 1000 (38 to 250)	RR 0.8 (0.31 to 2.03)	144 (1 study[1])	⊕⊕⊖⊖ low[2]	

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio;

1 Gianotti et al. 2000
2 Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs

Table 89: Summary clinical evidence profile for enteral immunonutrition versus standard nutrition after surgery

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Enteral immunonutrition (EIN) versus no intervention (standard nutrition) after surgery				
Treatment related morbidity - postoperative complications	See comment	See comment	Not estimable	35 (1 study[1])	⨁⨁⊖⊖ low[2]	"There was no difference between the two groups for postoperative complications graded with respect to severity"
Nutritional status at 30 days after surgery - Absolute change in weight (kg) from baseline		The mean nutritional status at 30 days after surgery - absolute change in weight (kg) from baseline in the intervention groups was 0.97 higher (1.37 lower to 3.32 higher)		31 (1 study[1])	⨁⊖⊖⊖ very low[3,4]	
PROMS - Satisfaction with nutritional treatment at 1 month after surgery		The mean proms - satisfaction with nutritional treatment at 1 month after surgery in the intervention groups was 0.04 higher (0.34 lower to 0.41 higher)		30 (1 study[1])	⨁⊖⊖⊖ very low[3,4]	

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio;

1 Gade et al. 2016
2 Evidence was downgraded by 2 due to selective outcome reporting bias (data were unclearly reported on the postoperative complications, so that it was not possible to judge the certainty of the evidence) and unclear risk of performance and selection bias
3 Evidence was downgraded by 1 due to unclear risk of performance and selection bias
4 Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs

Table 90: Summary clinical evidence profile for parenteral nutrition versus standard enteral nutrition after surgery

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Parenteral nutrition (PN) versus SEN after surgery				
Treatment related morbidity - postoperative complications - Patients with infectious complications	151 per 1000	220 per 1000 (108 to 446)	RR 1.46 (0.72 to 2.96)	141 (1 study[1])	⊕⊕⊖⊖ low[2]	
Treatment related morbidity - postoperative complications - Patients with non-infectious complications	288 per 1000	368 per 1000 (227 to 593)	RR 1.28 (0.79 to 2.06)	141 (1 study[1])	⊕⊕⊖⊖ low[2]	
Treatment related morbidity - postoperative complications - Total patients with complications (infectious+ non-infectious)	438 per 1000	587 per 1000 (425 to 815)	RR 1.34 (0.97 to 1.86)	141 (1 study[1])	⊕⊕⊖⊖ low[2]	
Treatment related morbidity - postoperative mortality	14 per 1000	59 per 1000 (7 to 513)	RR 4.29 (0.49 to 37.47)	199 (2 studies[3])	⊕⊕⊖⊖ low[2]	

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio;

1 Gianotti et al. 2000
2 Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs
3 Gianotti et al. 2000; Liu et al. 2011

Table 91: Summary clinical evidence profile for parenteral nutrition versus enteral immunonutrition after surgery

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Enteral immunonutrition (EIN) after surgery	Parenteral nutrition (PN)				
Treatment related morbidity - postoperative complications - Patients with infectious complications	85 per 1000	221 per 1000 (91 to 535)	RR 2.61 (1.08 to 6.33)	139 (1 study[1])	⊕⊕⊕⊖ moderate [2]	
Treatment related morbidity - postoperative complications - Patients with non-infectious complications	254 per 1000	368 per 1000 (221 to 611)	RR 1.45 (0.87 to 2.41)	139 (1 study[1])	⊕⊕⊕⊖ moderate [2]	
Treatment related morbidity - postoperative complications - Total patients with complications (infectious+ non-infectious)	338 per 1000	588 per 1000 (402 to 862)	RR 1.74 (1.19 to 2.55)	139 (1 study[1])	⊕⊕⊕⊖ moderate [2]	
Treatment related morbidity - Postoperative mortality	28 per 1000	59 per 1000 (11 to 311)	RR 2.09 (0.4 to 11.03)	139 (1 study[1])	⊕⊕⊖⊖ low[3]	

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio;

1 Gianotti et al. 2000
2 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed two default MID
3 Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs

Table 92: Summary clinical evidence profile for parenteral nutrition versus no intervention after surgery

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No Intervention	Parenteral nutrition (PN) after surgery				
Treatment related morbidity - major complications - Deep infection	70 per 1000	67 per 1000 (18 to 254)	RR 0.95 (0.25 to 3.62)	117 (1 study[1])	⊕⊖⊖⊖ very low[2,4]	
Treatment related morbidity - major complications - Fistula	88 per 1000	133 per 1000 (46 to 383)	RR 1.52 (0.53 to 4.37)	117 (1 study[1])	⊕⊖⊖⊖ very low[2,4]	
Treatment related morbidity - major complications - Abscess	35 per 1000	200 per 1000 (47 to 855)	RR 5.7 (1.33 to 24.36)	117 (1 study[1])	⊕⊕⊖⊖ low[2]	
Treatment related morbidity - major complications - Peritonitis	35 per 1000	117 per 1000 (25 to 538)	RR 3.33 (0.72 to 15.34)	117 (1 study[1])	⊕⊖⊖⊖ very low[2,4]	
Treatment related morbidity - major complications - Haemorrhage	35 per 1000	17 per 1000 (1 to 179)	RR 0.48 (0.04 to 5.1)	117 (1 study[1])	⊕⊖⊖⊖ very low[2,4]	
Treatment related morbidity - major complications - Intestinal obstruction	0 per 1000	0 per 1000 (0 to 0)	RR 8.56 (0.47 to 155.45)	117 (1 study[1])	⊕⊖⊖⊖ very low[2,4]	
Treatment related morbidity - major complications - Anastomotic breakdown	53 per 1000	117 per 1000 (32 to 429)	RR 2.22 (0.6 to 8.16)	117 (1 study[1])	⊕⊖⊖⊖ very low[2,4]	
Treatment related morbidity -	18 per 1000	6 per 1000 (0 to 134)	RR 0.32 (0.01 to 7.62)	117 (1 study[1])	⊕⊖⊖⊖	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No Intervention	Parenteral nutrition (PN) after surgery				
major complications - Aspiration					very low[2,4]	
Treatment related morbidity - major complications - Pneumonia	105 per 1000	83 per 1000 (27 to 258)	RR 0.79 (0.26 to 2.45)	117 (1 study[1])	⊕⊖⊖⊖ very low[2,4]	
Treatment related morbidity - major complications - Pulmonary embolus	18 per 1000	6 per 1000 (0 to 134)	RR 0.32 (0.01 to 7.62)	117 (1 study[1])	⊕⊖⊖⊖ very low[2,4]	
Treatment related morbidity - major complications - Myocardial infarction	18 per 1000	33 per 1000 (3 to 358)	RR 1.9 (0.18 to 20.38)	117 (1 study[1])	⊕⊖⊖⊖ very low[2,4]	
Treatment related morbidity - major complications - Reoperation	53 per 1000	100 per 1000 (26 to 381)	RR 1.9 (0.5 to 7.24)	117 (1 study[1])	⊕⊖⊖⊖ very low[2,4]	
Treatment related morbidity - major complications - Total major complications (excluding death)	211 per 1000	383 per 1000 (211 to 697)	RR 1.82 (1 to 3.31)	117 (1 study[1])	⊕⊕⊖⊖ low[2]	
Treatment related morbidity - minor complications - Superficial wound infection	18 per 1000	83 per 1000 (10 to 692)	RR 4.75 (0.57 to 39.42)	117 (1 study[1])	⊕⊖⊖⊖ very low[2,4]	
Treatment related morbidity - minor	0 per 1000	0 per 1000 (0 to 0)	RR 2.85 (0.12 to 68.62)	117 (1 study[1])	⊕⊖⊖⊖ very low[2,4]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No Intervention	Parenteral nutrition (PN) after surgery				
complications - Cellulitis						
Treatment related morbidity - minor complications - Prolonged ileus	88 per 1000	217 per 1000 (82 to 569)	RR 2.47 (0.94 to 6.49)	117 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Treatment related morbidity - minor complications - Gastric atony	18 per 1000	33 per 1000 (3 to 358)	RR 1.9 (0.18 to 20.38)	117 (1 study[1])	⊕⊖⊖⊖ very low[2,4]	
Treatment related morbidity - minor complications - Atelectasis	211 per 1000	251 per 1000 (128 to 486)	RR 1.19 (0.61 to 2.31)	117 (1 study[1])	⊕⊖⊖⊖ very low[2,4]	
Treatment related morbidity - minor complications - Pleural effusion	228 per 1000	201 per 1000 (100 to 401)	RR 0.88 (0.44 to 1.76)	117 (1 study[1])	⊕⊖⊖⊖ very low[2,4]	
Treatment related morbidity - minor complications - Catheter sepsis	18 per 1000	83 per 1000 (10 to 692)	RR 4.75 (0.57 to 39.42)	117 (1 study[1])	⊕⊖⊖⊖ very low[2,4]	
Treatment related morbidity - minor complications - Urinary tract infection	105 per 1000	66 per 1000 (20 to 224)	RR 0.63 (0.19 to 2.13)	117 (1 study[1])	⊕⊖⊖⊖ very low[2,4]	
Treatment related morbidity - minor complications - PN related complication	0 per 1000	0 per 1000 (0 to 0)	RR 4.75 (0.23 to 96.93)	117 (1 study[1])	⊕⊖⊖⊖ very low[2,4]	
Treatment related morbidity -	See comment	See comment	Not estimable	117 (1 study[1])	⊕⊖⊖⊖	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No Intervention	Parenteral nutrition (PN) after surgery				
minor complications - Liver function abnormality					very low[2,4]	
Treatment related morbidity - minor complications - Total minor complications	421 per 1000	535 per 1000 (362 to 783)	RR 1.27 (0.86 to 1.86)	117 (1 study[1])	⊕⊖⊖⊖ very low[2,4]	
Treatment related morbidity - Postoperative mortality	18 per 1000	67 per 1000 (8 to 579)	RR 3.8 (0.44 to 32.99)	117 (1 study[1])	⊕⊖⊖⊖ very low[2,4]	
Overall Survival at median follow up of 18 months	See comment	See comment	Not estimable	117 (1 study[1])	⊕⊕⊖⊖ low[2]	"The actuarial median survival is 24 months. (No difference between the two groups has been identified P=0.25)"

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio;

1 Brennan et al. 1994
2 The quality of the evidence was downgraded from high to low because of the unclear risk of detection, performance bias and of attrition bias (No details were given in the text)
3 Evidence was further downgraded by 1 due to serious imprecision as 95%CI crossed one default MID
4 Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs

Table 93: Summary clinical evidence profile for oral nutritional supplements (n-3 fatty acids) versus isocaloric-isonitrogenous supplement (without n-3 fatty acids)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Isocaloric-isonitrogenous supplement (No n-3 fatty acids)	Oral nutritional supplements (n-3 fatty acids)				
Nutritional status - Change in		The mean nutritional status - change in		110 (1 study[1])	⊕⊕⊖⊖ low[2,3]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Isocaloric-isonitrogenous supplement (No n-3 fatty acids)	Oral nutritional supplements (n-3 fatty acids)				
weight (kg/month) at 8 weeks		weight (kg/month) at 8 weeks in the intervention groups was 0.12 higher (0.09 lower to 0.33 higher)				
Nutritional status - Change in lean body mass (kg) at 8 weeks		The mean nutritional status - change in lean body mass (kg) at 4 and 8 weeks in the intervention groups was 0.15 higher (0.02 to 0.28 higher)		97 (1 study[1])	⊕⊕⊖⊖ low[2,3]	
Change in resting energy expenditure at 8 weeks		The mean change in resting energy expenditure at 8 weeks in the intervention groups was 14 higher (81.8 lower to 109.8 higher)		19 (1 study[4])	⊕⊕⊖⊖ low[5]	
Change in total energy expenditure at 8 weeks		The mean change in total energy expenditure at 8 weeks in the intervention groups was 187 higher (114.38 lower to 488.38 higher)		19 (1 study[4])	⊕⊕⊕⊖ moderate[3]	
Change in physical activity level at 8 weeks		The mean change in physical activity level at 8 weeks in the intervention groups was 0.17 higher (0.05 lower to 0.39 higher)		19 (1 study[4])	⊕⊕⊕⊖ moderate[3]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Isocaloric-isonitrogenous supplement (No n-3 fatty acids)	Oral nutritional supplements (n-3 fatty acids)				
Health Related Quality of Life at 8 weeks	See comment	See comment	Not estimable	110 (1 study[1])	⊕⊕⊖⊖ low[6]	"there were no significant differences in quality of life measures between the two groups" (data not shown)

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval;

1 Fearon et al. 2003
2 The quality of the evidence was downgraded from high to moderate because of the potential risk of attrition bias (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 affected)
3 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID
4 Moses et al. 2004
5 Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs
6 The quality of the evidence was downgraded from high to moderate because of the potential risk of attrition bias (see comment 2) and selective reporting for this outcome

Table 94: Summary clinical evidence profile for oral nutritional supplements (oral L-Carnitine therapy) versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Oral nutritional supplements (oral L-Carnitine therapy)				
Nutritional status - % change of BMI at 12 weeks		The mean nutritional status - % change of BMI at 12 weeks in the intervention groups was 4.9 higher (2.71 to 7.09 higher)		72 (1 study[1])	⊕⊕⊖⊖ low[2]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Oral nutritional supplements (oral L-Carnitine therapy)				
Nutritional status - % change of BCM at 12 weeks		The mean nutritional status - % change of BCM at 12 weeks in the intervention groups was 8.8 higher (7.20 to 10.40 higher)		72 (1 study[1])	⊕⊕⊖⊖ low[2]	
Health Related Quality of Life - EORTC-QLQ-C30/PAN26 - cognitive function at 6 weeks follow-up	See comment	See comment	Not estimable	72 (1 study[1])	⊕⊕⊖⊖ low[2]	There was a significant improvement in favour of the L-Carnitine group, p = 0.034
Health Related Quality of Life - EORTC-QLQ-C30/PAN26 - global health status at 12 weeks follow-up	See comment	See comment	Not estimable	72 (1 study[1])	⊕⊕⊖⊖ low[2]	There was a significant improvement in favour of the L-Carnitine group, p = 0.041
Overall Survival at follow up of 1500 days	See comment	See comment		72 (1 study[1])	⊕⊕⊖⊖ low[2]	No difference between intervention an control group (p value not reported, median 519 ± 50 days in the intervention group versus 399 ± 43 days with placebo)

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval;

1 Kraft et al. 2012
2 The quality of the evidence was downgraded from high to low because of the potential risk of attrition bias (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 randomised patients [59%] is still significant) and the selective reporting of findings.

Table 95: Summary clinical evidence profile for pancreatic enzyme replacement therapy versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Pancreatic enzyme replacement therapy (PERT)				
Nutritional status - Percentage change in body weight (%) at 8 weeks follow-up		The mean nutritional status - percentage change in body weight (%) at 8 weeks follow-up in the intervention groups was 2.89 higher (0.51 to 5.27 higher)		88 (2 studies[1])	⊕⊕⊕⊖ moderate [2]	
Nutritional status - Absolute change in body weight (Kg) at 8 weeks follow-up		The mean nutritional status - absolute change in body weight (kg) at 8 weeks follow-up in the intervention groups was 1.64 higher (0.7 lower to 3.98 higher)		88 (2 studies[1])	⊕⊕⊕⊖ moderate [2]	
Nutritional status - Daily dietary intake of total calories at 8 weeks follow-up		The mean nutritional status - daily dietary intake of total calories at 8 weeks follow-up in the intervention groups was 1.76 higher (0.19 to 3.33 higher)		21 (1 study[3])	⊕⊕⊖⊖ low[2,4]	
Health related quality of life - Global Health status EORTC-QLQ-C30 - Korean version Follow-up: 8 weeks		The mean health related quality of life - global health status in the intervention groups was 8.76 higher (2.63 lower to 20.15 higher)		62 (1 study[5])	⊕⊕⊖⊖ low[2,7]	
Health related quality of life - Functional scale EORTC-QLQ-C30 -		The mean health related quality of life - functional scale in the intervention groups was		62 (1 study[5])	⊕⊕⊖⊖ low[2,7]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Pancreatic enzyme replacement therapy (PERT)				
Korean version Follow-up: 8 weeks		6.93 higher (5.36 lower to 19.22 higher)				
Health related quality of life - Physical EORTC-QLQ-C30 - Korean version Follow-up: 8 weeks		The mean health related quality of life - physical in the intervention groups was 7.15 higher (5.89 lower to 20.19 higher)		62 (1 study[5])	⊕⊕⊖⊖ low[2,7]	
Health related quality of life - Role EORTC-QLQ-C30 - Korean version Follow-up: 8 weeks		The mean health related quality of life - role in the intervention groups was 9.7 higher (6.58 lower to 25.98 higher)		62 (1 study[5])	⊕⊕⊖⊖ low[2,7]	
Health related quality of life - Emotional EORTC-QLQ-C30 - Korean version Follow-up: 8 weeks		The mean health related quality of life - emotional in the intervention groups was 1.24 higher (12.78 lower to 15.26 higher)		62 (1 study[5])	⊕⊕⊖⊖ low[2,7]	
Health related quality of life - Cognitive EORTC-QLQ-C30 - Korean version Follow-up: 8 weeks		The mean health related quality of life - cognitive in the intervention groups was 7.18 higher (7.53 lower to 21.89 higher)		62 (1 study[5])	⊕⊕⊖⊖ low[2,7]	
Health related quality of life - Social EORTC-QLQ-C30 - Korean version Follow-up: 8 weeks		The mean health related quality of life - social in the intervention groups was 9.36 higher (1.21 lower to 19.93 higher)		62 (1 study[5])	⊕⊕⊖⊖ low[2,7]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Pancreatic enzyme replacement therapy (PERT)				
Health related quality of life - Symptom scale EORTC-QLQ-C30 - Korean version Follow-up: 8 weeks		The mean health related quality of life - symptom scale in the intervention groups was 4.67 lower (17.73 lower to 8.39 higher)		62 (1 study[5])	⊕⊕⊖⊖ low[2,7]	
Health related quality of life - Fatigue EORTC-QLQ-C30 - Korean version Follow-up: 8 weeks		The mean health related quality of life - fatigue in the intervention groups was 4.87 lower (19.51 lower to 9.77 higher)		62 (1 study[5])	⊕⊕⊖⊖ low[2,7]	
Health related quality of life - Nausea and vomiting EORTC-QLQ-C30 - Korean version Follow-up: 8 weeks		The mean health related quality of life - nausea and vomiting in the intervention groups was 7.44 lower (22.43 lower to 7.55 higher)		62 (1 study[5])	⊕⊕⊖⊖ low[2,7]	
Health related quality of life - Pain EORTC-QLQ-C30 - Korean version Follow-up: 8 weeks		The mean health related quality of life - pain in the intervention groups was 4.57 lower (20.73 lower to 11.59 higher)		62 (1 study[5])	⊕⊕⊖⊖ low[2,7]	
Health related quality of life - Dyspnea EORTC-QLQ-C30 - Korean version Follow-up: 8 weeks		The mean health related quality of life - dyspnea in the intervention groups was 3.25 higher (13.96 lower to 20.46 higher)		62 (1 study[5])	⊕⊕⊖⊖ low[2,7]	
Health related quality of life - Insomnia EORTC-		The mean health related quality of life - insomnia in the intervention		62 (1 study[5])	⊕⊕⊖⊖ low[2,7]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Pancreatic enzyme replacement therapy (PERT)				
QLQ-C30 - Korean version Follow-up: 8 weeks		groups was 2.99 lower (20.14 lower to 14.16 higher)				
Health related quality of life - Appetite loss EORTC-QLQ-C30 - Korean version Follow-up: 8 weeks		The mean health related quality of life - appetite loss in the intervention groups was 18.8 lower (36.51 to 1.09 lower)		62 (1 study[5])	⊕⊕⊖⊖ low[2,7]	
Health related quality of life - Constipation EORTC-QLQ-C30 - Korean version Follow-up: 8 weeks		The mean health related quality of life - constipation in the intervention groups was 1.2 higher (15.26 lower to 17.66 higher)		62 (1 study[5])	⊕⊕⊖⊖ low[2,7]	
Health related quality of life - Diarrhoea EORTC-QLQ-C30 - Korean version Follow-up: 8 weeks		The mean health related quality of life - diarrhoea in the intervention groups was 3.25 lower (19.52 lower to 13.02 higher)		62 (1 study[5])	⊕⊕⊖⊖ low[2,7]	
Health related quality of life - Financial difficulties EORTC-QLQ-C30 - Korean version Follow-up: 8 weeks		The mean health related quality of life - financial difficulties in the intervention groups was 4.53 lower (17.45 lower to 8.39 higher)		62 (1 study[5])	⊕⊕⊖⊖ low[2,7]	
Overall survival	See comment	See comment	Not estimable	62 (1 study[5])	⊕⊕⊖⊖ low[6,7]	Overall survival did not differ significantly between intervention groups (PERT group: 5.84 month;

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Pancreatic enzyme replacement therapy (PERT)				
						placebo: 8.13 months [p=0.774]).

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval;

1 Bruno et al. 1998; Woo et al. 2016
2 Evidence for this outcome was downgraded by 1 due to imprecision as 95%CI crossed one default MID
3 Bruno et al. 1998
4 Evidence was downgraded by 1 due indirectness (2 of the 24 participants did not have PC
5 Woo et al. 2016
6 Evidence for this outcome was downgraded by 1 due to potential selective reporting of findings.
7 The quality of the evidence was downgraded from moderate to low due to potential indirectness (as the randomised trial was conducted in Korea and the outcomes may not be transferrable to the UK settings).

Table 96: Summary clinical evidence profile for pancreatic enzyme replacement therapy versus pancrelipase replacement therapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Pancreatic enzyme replacement therapy (PERT) versus pancrelipase replacement therapy				
Nutritional status - BMI (kg/m2) at 6 and 12 months follow-up - at 6 months follow-up		The mean nutritional status - BMI (kg/m2) at 6 and 12 months follow-up - at 6 months follow-up in the intervention groups was 0.95 higher (0.68 lower to 2.58 higher)		57 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Nutritional status - BMI (kg/m2) at 6 and 12 months follow-up - at 12 months follow-up		The mean nutritional status - BMI (kg/m2) at 6 and 12 months follow-up - at 12 months follow-up in the intervention groups was 0.51 higher (1.11 lower to 2.13 higher)		57 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Treatment related morbidity -	393 per 1000	208 per 1000 (90 to 483)	RR 0.53 (0.23	57 (1 study[1])	⊕⊕⊖⊖ low[2,4]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Pancreatic enzyme replacement therapy (PERT) versus pancrelipase replacement therapy				
NAFLD at 1 year follow-up			to 1.23)			
The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). *CI: Confidence interval; RR: Risk ratio;*						
1 Satoi et al. 2016 *2 The quality of the evidence was downgraded from high to moderate because of the unclear risk of performance bias (no information blinding of outcome assessors) and unclear risk of selection bias* *3 Evidence was further downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs* *4 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID*						

8.3.5 Economic evidence

A literature review of published cost effectiveness analyses did not identify any relevant studies for this topic. Although there were potential implications for resource use associated with making recommendations in this area, other topics in the guideline were agreed as a higher economic priority. Consequently, bespoke economic modelling was not done for this topic.

8.3.6 Evidence Statements

8.3.6.1 Enteral immunonutrition versus Standard Enteral nutrition

8.3.6.1.1 Before and after surgery (perioperative)

Overall Survival

No evidence was identified to inform this outcome

Treatment related morbidity

Very low quality evidence from 1 RCT (n=30) showed no clinically important difference between enteral immunonutrition and standard enteral nutrition on either post-operative infectious complications (RR 0.83 [95% CI 0.32-2.15]) or post-operative non-infectious complications (RR 1.00 [95% CI 0.42-2.40]) in adults with resectable pancreatic cancer.

Health Related Quality of Life

Very low quality evidence from 1 RCT (n=37) showed no clinically important difference between enteral immunonutrition and standard enteral nutrition on mean Karnofsky score 2 weeks after surgery in adults with resectable pancreatic cancer: MD -2.00 (95% CI -7.33 to 3.33).

Symptom control

No evidence was identified to inform this outcome

Nutritional status

Very low quality evidence from 1 RCT (n=37) showed no clinically important difference between enteral immunonutrition and standard enteral nutrition on mean change on BMI from baseline (MD -1.50 kg/m^2 [95% CI -3.93 to 0.93]), mid-arm circumference (MD -0.60 cm [95% CI -2.92 to 1.72]), and corrected arm muscle area (MD -1.60 cm^2 [95% CI -7.09 to 3.89]) 2 weeks after surgery in adults with resectable pancreatic cancer.

Adverse events

No evidence was identified to inform this outcome

Patient experience

No evidence was identified to inform this outcome

8.3.6.1.2 After surgery (postoperative)

Overall Survival

No evidence was identified to inform this outcome

Treatment related morbidity

Low quality evidence from 1 RCT (n=144) showed no clinically important difference between enteral immunonutrition and standard enteral nutrition on either post-operative infectious complications (RR 0.56 [95% CI 0.22-1.44]) or post-operative non-infectious complications (RR 0.88 [95% CI 0.51-1.51]) in adults with pancreatic cancer after surgery.

Low quality evidence from 1 RCT (n=144) showed no clinically important difference between enteral immunonutrition and standard enteral nutrition on post-operative mortality in adults with pancreatic cancer after surgery: RR 2.06 (95% CI, 0.19-22.18).

Low quality evidence from 1 RCT (n=144) showed no clinically important difference between enteral immunonutrition and standard enteral nutrition on tube clogging/kinking (RR 0.62 [95% CI, 0.15-2.49]), tube dislodgment (RR 2.06 [95% CI, 0.19-22.18]), tube breakage (RR 0.34 [95% CI, 0.01-8.27]), local skin infection (RR 0.34 [95% CI, 0.01-8.27]), abdominal cramps (RR 0.93 [95% CI, 0.42-2.06]), abdominal distension (RR 1.14 [95% CI, 0.49-2.64]), diarrhoea (RR 0.8 [95% CI, 0.31-2.03]), and vomiting (RR 0.21 [95% CI, 0.01-4.21]) in adults with pancreatic cancer after surgery.

Health Related Quality of Life

No evidence was identified to inform this outcome

Symptom control

No evidence was identified to inform this outcome

Nutritional status

No evidence was identified to inform this outcome

Adverse events

No evidence was identified to inform this outcome

Patient experience

No evidence was identified to inform this outcome

8.3.6.2 Enteral immunonutrition versus Standard nutrition (no intervention)

Overall Survival

No evidence was identified to inform this outcome

Treatment related morbidity

Low quality evidence from 1 RCT (n=35) showed no statistically significant difference between enteral immunonutrition and standard nutrition (no intervention) on total post-operative infectious or non-infectious complications in adults with pancreatic cancer after surgery (the data was not reported).

Health Related Quality of Life

No evidence was identified to inform this outcome

Symptom control

No evidence was identified to inform this outcome

Nutritional status

Very low quality evidence from 1 RCT (n=35) showed no clinically important difference between enteral immunonutrition and standard nutrition (no intervention) on absolute change 30 days after surgery in weight from baseline in adults with pancreatic cancer: MD 0.97 kg (95% CI -1.37 to 3.32).

Adverse events

No evidence was identified to inform this outcome

Patient experience

Very low quality evidence from 1 RCT (n=35) showed no clinically important difference between enteral immunonutrition and standard nutrition (no intervention) on PROMS satisfaction with nutritional treatment 30 days after surgery in adults with pancreatic cancer: MD 0.04 (95% CI -0.34 to 0.41)

8.3.6.3 Parenteral nutrition versus standard enteral nutrition after surgery

Overall Survival

No evidence was identified to inform this outcome

Treatment related morbidity

Moderate quality evidence from 1 RCT (n=141) showed no clinically important difference between parenteral nutrition and standard enteral nutrition on the relative risk of postoperative adverse effects (including infectious complications, non-infectious complications, and total complications) in adults with pancreatic cancer after surgery: RR 1.46 (95% CI 0.72-2.96), RR 1.28 (95% CI 0.79-2.76), and RR 1.34 (95% CI 0.97-1.86), where RR higher than 1 favours SEN group

Low quality evidence from 2 RCTs (n=141) showed no clinically important difference between parenteral nutrition and standard enteral nutrition about the relative risk of postoperative mortality in adults with pancreatic cancer after surgery: RR 4.29 (95% CI 0.49-37.47), where RR higher than 1 favours SEN group

Health Related Quality of Life

No evidence was identified to inform this outcome

Symptom control

No evidence was identified to inform this outcome

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Nutritional status

No evidence was identified to inform this outcome

Adverse events

No evidence was identified to inform this outcome

Patient experience

No evidence was identified to inform this outcome

8.3.6.4 Parenteral nutrition versus enteral immunonutrition after surgery

Overall Survival

No evidence was identified to inform this outcome

Treatment related morbidity

Moderate quality evidence from 1 RCT (n=139) showed that there is a clinically important difference favouring enteral immunonutrition on post-operative infectious and non-infectious complications compared to parenteral nutrition in adults with pancreatic cancer after surgery: RR 1.74 (95% CI 1.19-2.55).

- Moderate quality evidence from 1 RCT showed there is a clinically important difference favouring enteral immunonutrition on post-operative infectious complications compared to parenteral nutrition in adults with pancreatic cancer after surgery: RR 2.61 (95% CI 1.08-6.33).
- Moderate quality evidence from 1 RCT (n=139) showed no clinically important difference between parenteral nutrition and enteral immunonutrition on post-operative non-infectious complications in adults with pancreatic cancer after surgery: RR 1.45 (95% CI 0.87-2.41).

Low quality evidence from 1 RCT (n=139) showed no clinically important difference between parenteral nutrition and enteral immunonutrition on post-operative mortality in adults with pancreatic cancer after surgery: RR 2.09 (95% CI 0.40-11.3).

Health Related Quality of Life

No evidence was identified to inform this outcome

Symptom control

No evidence was identified to inform this outcome

Nutritional status

No evidence was identified to inform this outcome

Adverse events

No evidence was identified to inform this outcome

Patient experience

No evidence was identified to inform this outcome

8.3.6.5 Parenteral nutrition versus no intervention after surgery

Overall Survival

Low quality evidence from 1 RCT (n=117) showed no clinically important difference between parenteral nutrition and no intervention on overall survival (actuarial median survival=24 months) at 18 months in adults with pancreatic cancer after surgery (data not reported).

Treatment related morbidity

Very low quality evidence from 1 RCT (n=117) showed there is a clinically important difference favouring no intervention on major treatment-related complications (excluding death) compared to parenteral nutrition in adults with pancreatic cancer after surgery: RR 1.82 (95% CI 1.0-3.31).

- Very low quality evidence from 1 RCT (n=117) showed no clinically important difference between parenteral nutrition and no intervention on the majority of treatment-related major complications including deep infection (RR 0.95 [95% CI 0.25-3.62]), fistula (RR 1.52 [95% CI 0.53-4.37]), peritonitis (RR 3.33 [95% CI 0.72-15.34]), haemorrhage (RR 0.47 [95% CI, 0.04-5.1]), intestinal obstruction (RR 8.56 [95% CI 0.47-155.45]), anastomotic breakdown (RR 2.22 [95% CI 0.6-8.16]), aspiration (RR 0.32 [95% CI 0.01-7.62]), pneumonia (RR 0.79 [95% CI 0.26-2.45]), pulmonary embolus (RR 0.32 [95% CI 0.01-7.62]), myocardial infarction (RR 1.9 [95% CI 0.18-20.38]), and reoperation rate (RR 1.9 [95% CI 0.5-7.24]) in adults with pancreatic cancer after surgery.
- Low quality evidence from 1 RCT (n=117) showed that there is a clinically important difference favouring no intervention on treatment-related abscesses compared to parenteral nutrition in adults with pancreatic cancer after surgery: RR 5.7 (95% CI 1.33-24.36).

Very low quality evidence from 1 RCT (n=117) showed no clinically important difference between parenteral nutrition and no intervention on minor treatment-related complications in adults with pancreatic cancer after surgery: RR 1.27 (95% CI 0.86-1.86).

- Very low quality evidence from 1 RCT (n=117) showed no clinically important difference between parenteral nutrition and no intervention on the majority of treatment-related minor complications including superficial wound infection (RR 4.75 [95% CI 0.57-39.42]), cellulitis (RR 2.85 [95% CI 0.12-68.62]), gastric atony (RR 1.9 [95% CI 0.18-20.38]), atelectasis (RR 1.19 [95% CI 0.61-2.31]), pleural effusion (RR 0.88 [95% CI 0.44-1.76]), catheter sepsis (RR 4.75 [95% CI 0.57-39.42]), urinary tract infection (RR 0.63 [95% CI 0.19-2.13]), complications related to parenteral nutrition (RR 4.75 [95% CI 0.23-96.93]), and liver function abnormality (RR 1.0), in adults with pancreatic cancer after surgery.
- Very low quality evidence from 1 RCT (n=117) showed there may be a clinically important difference favouring no intervention on prolonged ileus compared to parenteral nutrition in adults with pancreatic cancer after surgery, although there is some uncertainty: RR 2.47 (95% CI 0.94-6.49).

Very low quality evidence from 1 RCT (n=117) showed no clinically important difference between parenteral nutrition and no intervention on post-operative mortality in adults with pancreatic cancer after surgery: RR 3.8 (95% CI 0.44-32.99).

Health Related Quality of Life

No evidence was identified to inform this outcome

Symptom control

No evidence was identified to inform this outcome

Nutritional status

No evidence was identified to inform this outcome

Adverse events

No evidence was identified to inform this outcome

Patient experience

No evidence was identified to inform this outcome

8.3.6.6 Oral nutritional supplements (n-3 fatty acids) versus isocaloric-isonitrogenous supplement (without n-3 fatty acids)

Overall Survival

No evidence was identified to inform this outcome

Treatment related morbidity

No evidence was identified to inform this outcome

Health Related Quality of Life

No evidence was identified to inform this outcome

Symptom control

No evidence was identified to inform this outcome

Nutritional status

Low quality evidence from 1 RCT (n=110) showed no clinically important difference between n-3 fatty acids oral nutritional supplements and isocaloric-isonitrogenous supplements on absolute monthly change in weight (kg) at 8 weeks in weight-losing adults with unresectable pancreatic cancer: MD 0.12 (95% CI -0.09 to 1.72).

Low quality evidence from 1 RCT (n=97) showed that there is a clinically important difference favouring isocaloric-isonitrogenous supplements on change in lean body mass (kg) at 4 and 8 weeks compared to n-3 fatty acids oral nutritional supplements in weight-losing adults with unresectable pancreatic cancer: MD 0.15 (95% CI 0.02 to 0.28).

Low to moderate quality evidence from 1 RCT (n=24) showed no clinically important difference between n-3 fatty acids oral nutritional supplements and isocaloric-isonitrogenous supplements on change at 8 weeks in resting energy expenditure (MD 14.0 [95% CI, -81.8 to 109.8]), total energy expenditure (MD 187.0 [95% CI -114.4 to 488.4]) and physical activity level (MD 0.17 [95% CI -0.05 to 0.39]) in adults with advanced pancreatic cancer.

Adverse events

No evidence was identified to inform this outcome

Patient experience

No evidence was identified to inform this outcome

8.3.6.7 Oral nutritional supplements (oral L-Carnitine therapy) versus placebo

Overall Survival

Low quality evidence from 1 RCT (n=72) showed no clinically important difference between oral L-Carnitine-enriched nutritional supplements (median survival=519 days [SD=50]) and placebo (median survival=399 days [SD=43]) on overall survival at 1500 days in adults with unresectable pancreatic cancer.

Treatment related morbidity

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No evidence was identified to inform this outcome

Health Related Quality of Life

Low quality evidence from 1 RCT (n=72) showed that there is a clinically important difference favouring oral L-Carnitine-enriched nutritional supplements on the EORTC QLQ C30-Pan26 cognitive function subscale at 6 weeks (p=0.034) and global health status subscale at 12 weeks (p=0.041) compared to placebo in adults with unresectable pancreatic cancer.

Symptom control

No evidence was identified to inform this outcome

Nutritional status

Low quality evidence 1 RCT (n=72) showed that there is a clinically important difference at 12 weeks favouring oral L-Carnitine-enriched nutritional supplements on percentage change in BMI (MD 4.9 [95% CI 2.71-7.09]) and percentage change of body fat and body cell mass (MD 8.8 [95% CI 7.2 to 10.4) compared to placebo in adults with unresectable pancreatic cancer.

Adverse events

No evidence was identified to inform this outcome

Patient experience

No evidence was identified to inform this outcome

8.3.6.8 Pancreatic enzyme replacement therapy (PERT) versus placebo

Overall Survival

Low quality evidence from 1 RCT (n=67) showed no clinically important difference between pancreatic enzyme replacement therapy and placebo on overall survival (5.84 vs 8.13 months, p=0.77) in adults with unresectable cancer.

Treatment related morbidity

No evidence was identified to inform this outcome

Health Related Quality of Life

Low quality evidence from 1 RCT (n=62) showed no clinically important difference between pancreatic enzyme replacement therapy and placebo at 8 weeks on the EORTC QLQ-C30 global health status scale (MD 8.76 (95% CI, -2.63 to 20.15]), functional scale (MD 6.93 [95% CI, -5.36 to 19.22]) and symptom scale (MD -4.67 [95% CI -17.73 to 8.39]), and the majority of their subscales, in adults with unresectable cancer.

- Low quality evidence from 1 RCT (n=62) showed that there may be a clinically important difference at 8 weeks favouring pancreatic enzyme replacement therapy on the EORTC QLQ-C30 social functioning subscale compared to placebo in adults with unresectable cancer, although there is some uncertainty: MD 9.36 (95% CI -1.21 to 19.93).
- Low quality evidence from 1 RCT (n=62) showed that there is a clinically important difference at 8 weeks favouring pancreatic enzyme replacement therapy on the EORTC QLQ-C30 appetite loss subscale compared to placebo in adults with unresectable cancer: MD -8.8 (95% CI -36.51 to -1.09).

Symptom control

No evidence was identified to inform this outcome

Nutritional status

Moderate quality evidence from 2 RCTs (n=88) showed that there is a clinically important difference at 8 weeks favouring pancreatic enzyme replacement therapy on percentage change in body weight compared to placebo in adults with unresectable pancreatic cancer: MD 2.89 (95% CI 0.51 to 5.27).

Moderate quality evidence from 2 RCTs (n=88) showed no clinically important difference between pancreatic enzyme replacement therapy and placebo on absolute change in body weight (kg) in adults with unresectable pancreatic cancer: MD 1.64 (95% CI -0.7 to 3.98).

Low quality evidence from 1 RCT (n=21) that there is a clinically important difference at 8 weeks favouring pancreatic enzyme replacement therapy on daily dietary intake of total calories compared to placebo in adults with unresectable pancreatic cancer: MD 1.76 (95% CI 0.19 to 3.33).

Adverse events

No evidence was identified to inform this outcome

Patient experience

No evidence was identified to inform this outcome

8.3.6.9 Pancrelipase replacement therapy versus PERT

Overall Survival

No evidence was identified to inform this outcome

Treatment related morbidity

Low quality evidence from 1 RCT (n=57) showed no clinically important difference between pancreatic enzyme replacement therapy and pancrelipase replacement therapy on non-alcoholic fatty liver disease in adults with pancreatic cancer 12 months after surgery: RR 0.53 (95% CI 0.23-1.23).

Health Related Quality of Life

No evidence was identified to inform this outcome

Symptom control

No evidence was identified to inform this outcome

Nutritional status

Low quality evidence 1 RCT (n=57) showed no clinically important difference between pancreatic enzyme replacement therapy and pancrelipase replacement therapy on BMI in adults with pancreatic cancer 6 months (MD 0.95 [95% CI -0.68 to 2.58]) and 12 months (MD 0.51 [95% CI -1.11 to 2.13]) after surgery.

Adverse events

No evidence was identified to inform this outcome

Patient experience

No evidence was identified to inform this outcome

8.3.7 Recommendations

23. **Offer enteric-coated pancreatin for people with unresectable pancreatic cancer.**

24. **Consider enteric-coated pancreatin before and after pancreatic cancer resection.**

25. **Do not use fish oils as a nutritional intervention to manage weight loss in people with unresectable pancreatic cancer.**

26. **For people who have had pancreatoduodenectomy and who have a functioning gut, offer early enteral nutrition (including oral and tube feeding) rather than parenteral nutrition.**

For more guidance on nutrition support, see the NICE guideline on Nutritional support in adults.

8.3.8 Evidence to recommendations

8.3.8.1 Relative value placed on the outcomes considered

Overall survival, treatment related morbidity, health-related quality of life, symptom control, nutritional status, adverse events and patient experience were considered to be the critical outcomes for this question.

Nutritional status was reported for the majority of studies. Overall survival, treatment related morbidity and health-related quality of life were reported for approximately half of the studies. Patient experience was only reported by one study. The outcomes of symptom control and adverse events were not reported by any studies.

8.3.8.2 Quality of evidence

The quality of the outcomes for the comparisons identified by this review were as follows:

- Enteral immunonutrition versus standard enteral nutrition – ranged from very low to low
- Enteral immunonutrition versus standard nutrition (no intervention) – ranged from very low to low
- Parenteral nutrition versus no intervention after surgery – ranged from very low to low
- Pancreolipase replacement therapy versus pancreatic enzyme replacement therapy (PERT) - low
- Parenteral nutrition versus standard enteral nutrition after surgery - low
- Oral nutritional supplements versus placebo – low
- Parenteral nutrition versus enteral immunonutrition after surgery – ranged from low to moderate
- Oral nutritional supplements (n-3 fatty acids) versus isocaloric-isonitrogenous supplement (without n-3 fatty acids) – ranged from low to moderate
- PERT versus placebo – ranged from low to moderate

No evidence was found on the effectiveness of glycaemic control or the addition of proton pump inhibitors to pancreatic replacement enzyme therapy (PERT), so the committee did not make any recommendations for clinical practice. They agreed not to recommend further research in these areas as they considered other areas were a higher priority for research funding.

The committee noted that the post hoc analysis of an RCT by Davidson et al was examining whether weight stabilisation was associated with improved survival and quality of life. As

such, it was not comparing the effectiveness of different nutritional interventions for people with pancreatic cancer. They therefore agreed not to use the data from this study when making recommendations.

The committee noted that there were several studies investigating the effectiveness of enteral immunonutrition. However, this evidence was mostly of low quality and the studies had used different immunonutrition, which confounded interpretation of the results. The committee agreed that there was not enough evidence of benefit for immunonutrition compared to standard enteral nutrition and so did not make a recommendation for clinical practice. They also agreed that other topics were a higher priority for research funding and so did not recommend any further research in this area.

The committee noted that whilst the data on oral L-Carnitine therapy showed an improvement in nutritional status, the study had used bioelectrical impedance to measure nutritional status, which is not an accurate measure in this patient group. They also noted that the authors of the study had said this data was preliminary and needs further investigation. Given this, the committee agreed not to make any recommendations for clinical practice about L-Cartinine. They also agreed that the data on other nutritional supplements was not strong enough to support a recommendation for clinical practice.

The committee agreed that overall, the evidence base for nutritional interventions was quite poor, most of the evidence was either very low or low quality and the comparators used often made it difficult to determine if the intervention was better or worse than standard care. They therefore agreed to recommend further research comparing nutritional interventions against standard care. The committee also agreed to recommend further research to compare cachexia assessment methods and anti-cachexia interventions with standard care as no effective treatments for cachexia had been identified by the evidence.

The committee noted that of the two studies comparing pancreatic enzyme replacement therapy with placebo, one was conducted in Korea which decreased its relevance to the UK population (as different pancreatic enzymes were used to those used in the UK). They therefore applied less weight to the results of this study when making recommendations about pancreatic enzyme replacement therapy.

8.3.8.3 Consideration of clinical benefits and harms

The committee noted that the evidence on PERT came from people with unresectable pancreatic cancer and showed that nutritional status was improved with the use of PERT. They therefore agreed to recommend the use of PERT in this patient group - they recommended enteric coated pancreatin treatment as this was the type of PERT that was used in the trials.

Based on their clinical experience and knowledge, the committee also agreed that people with resectable pancreatic cancer were unlikely to produce sufficient pancreatic enzymes and would probably also benefit from taking PERT. They therefore also recommended PERT for people with resectable disease (both before and after resection), but this was a weaker recommendation due to the lack of evidence.

The committee noted that, based on the evidence, fish oils had not been shown to reduce weight loss in people with unresectable pancreatic cancer. Given that the evidence was moderate quality, they agreed to recommend that this intervention should not be used.

Based on the evidence, the committee noted that there were less post-operative complications with enteral nutrition compared with parenteral nutrition following pancreatoduodenectomy and no clinically important difference in overall survival. They therefore agreed to recommend enteral feeding as the preferred method for providing nutrition but were not able to specify a particular route (oral or tube feeding).

8.3.8.4 Consideration of economic benefits and harms

The committee noted that no relevant published economic evaluations had been identified and no additional economic analysis had been undertaken in this area.

The committee considered that the recommendations made were unlikely to result in a substantial increase in resource use. Pancreatic enzymes do not have a high unit cost. Any additional costs compared with current usage would likely to be offset by a reduction in the costs associated with dealing with malnutrition.

8.3.8.5 Other considerations

Given that a high proportion of people with pancreatic cancer have less than optimal nutrition, the committee considered that the recommendations in the NICE guideline on Nutrition support in adults would also apply to this patient group. They therefore agreed to cross-reference these recommendations.

8.3.9 Research recommendations

4. A randomised trial should be undertaken comparing nutritional interventions (including pancreatic enzyme replacement, types of feed, route of administration, timing) against standard of care or against each other for people with resected or unresectable pancreatic cancer

The nutritional status of patients with resectable and unresectable pancreatic cancer can be significantly impacted by their disease, which can impact on morbidity and quality of life (it is a key issue frequently raised by patients in helping them manage the disease). There is no good quality research into the use of pancreatic enzyme replacement therapy in people with resected or resectable pancreatic cancer, the use of proton pump inhibitors, the preferred composition of nutritional supplements or enteral feeds, glycaemic control or the preferred route of nutritional delivery following pancreatic resection. Further research into nutritional interventions should help to improve nutritional support to people with pancreatic cancer. It should also enable resources to be focused on effective interventions which would streamline service delivery and be cost saving to the NHS. Outcomes of interest are survival, nutritional status, quality of life and patient experience.

5. A cohort study followed by phase II and III studies should be undertaken in people with pancreatic cancer and cachexia or pre-cachexia, to compare cachexia assessment methods and anti-cachexia interventions with standard care.

Most people with advanced and metastatic pancreatic cancer also have cachexia. This causes severe reductions in their quality of life and is associated with reduced overall survival. Cachexia has three phases: pre-cachexia, cachexia, and refractory cachexia. The condition cannot be stopped by conventional nutritional support and leads to progressive functional impairment. Complete or partial reversal of cachexia would cause major improvements in quality of life, and potentially improve survival if people recover enough to have more effective cancer treatments. The outcomes of interest are:

- prevention or reversal of cachexia
- overall survival
- quality of life
- pain relief
- tolerance to treatment.

8.3.10 References

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9 Interventions to relieve biliary and duodenal obstruction

9.1 Biliary obstruction

Review question: What is the optimal treatment of biliary obstruction in adults with newly diagnosed or recurrent pancreatic cancer?

9.1.1 Introduction

Biliary obstruction causing obstructive jaundice is the most visible manifestation of pancreatic cancer in the head of pancreas. Although it is not present in all patients, the main symptom associated with obstructive jaundice is itching, which can be severe and debilitating. Other symptoms that may be caused or exacerbated by biliary obstruction include early satiety and nausea. The visible signs of biliary obstruction, which may most concern the individual, include yellow sclera and skin. Biliary obstruction leads to malabsorption of the fat soluble vitamins, resulting in a vitamin K deficiency if obstruction is prolonged, and consequent derangement of blood clotting.

In patients with resectable tumours, standard practice has been to relieve the obstruction via insertion of a stent, and normalise blood tests as far as possible prior to surgery; due to concern that operating on patients with significant biliary obstruction would increase operative morbidity and possibly mortality. As the jaundice worsens quickly, the delay between presentation and the date for surgery (which at best is only a few weeks but usually longer), can be associated with a significant worsening of jaundice.

In addition to whether or not jaundice needs to be relieved prior to surgery, another important issue is the timing of any drainage, relative to imaging for staging. This is because the process of placing a biliary stent (usually when endoscopic retrograde cholangiopancreatography [ERCP] is performed) has been associated with pancreatitis, which may make staging of the tumour more difficult. In addition, whilst plastic stents (which have a small diameter lumen) are cheap and have been used for drainage in the last few years, considerably more expensive self-expanding mesh metal stents (SEMS) (which have a larger diameter and therefore considerably better flow and longevity) have become widely available. Moreover, it is thought that SEMS cause less morbidity than plastic stents. Thus, in individuals with resectable tumours, it remains to be established whether or not drainage is required before surgery, whether SEMS are better than plastic stents, and - if it is indicated – when is the optimal time for drainage.

With regards to treatment of biliary obstruction in individuals with borderline resectable tumours, the issues are similar to those for individuals with resectable tumours (although they are perhaps clearer because the patient will not be considered for immediate surgery). The case for pre-operative drainage is stronger based on a patient's symptoms and any jaundice will need to be relieved prior to neoadjuvant chemotherapy. However, which stent should be used for drainage and when drainage should occur are still open questions.

With regards to biliary obstruction in individuals with unresectable tumours, it is still unclear whether a plastic or metal stent should be used. One important issue is endoscopic management (ERCP and stenting), which is the most commonly-performed intervention, as it is perceived to be less invasive than alternative methods.

Guidance is needed on the optimal treatment of biliary obstruction in people with pancreatic cancer.

9.1.1.1 Review protocol summary

The review protocol summary used for this question can be found in Table 97. Full details of the review protocol can be found in Appendix C.

Table 97: Clinical review protocol summary for the review of optimal treatment of biliary obstruction

Population	Patients with biliary obstruction: • Resectable pancreatic cancer • Borderline resectable pancreatic cancer • Unresectable or metastatic pancreatic cancer
Intervention	• Biliary stent placement • Plastic stents • Self-expandable metallic/metal stents (fully covered, partially covered, uncovered) • Preoperative biliary drainage followed by resection • Biliary bypass Surgery • Surgical resection without stenting
Comparison	Best supportive care Each Other
Outcomes	• Relief of obstruction • Relief of symptoms • Treatment-related mortality • Treatment related morbidity • Treatment-related complications • Overall Survival • Time to definitive treatment • Health Related Quality of Life • Patient experience • PROMS

9.1.2 Description of clinical evidence

Twenty-two RCTs were included in the review. Several of the studies included individuals that did not have pancreatic cancer. Generally, the Committee decided to only include studies that had at least 66% pancreatic cancer patients, though the quality of evidence for relevant outcomes was downgraded one level for indirectness.

Further information about the search strategy can be found in Appendix D. See study selection flow chart in Appendix E, forest plots in Appendix H, GRADE tables in Appendix I, study evidence tables in Appendix F and list of excluded studies in Appendix G.

9.1.2.1 Plastic stent versus self-expanding metal stents (SEMS) in adults with pancreatic cancer and biliary obstruction

Eight studies (n=815) compared the use of plastic stents with SEMS (Gardner et al., 2016; Isayama et al., 2011; Kaassis et al., 2003; Moses et al., 2013; Schmidt et al., 2015; Söderlund & Linder, 2006; Travis & Nicholson, 1997; Walter et al., 2015). Seven of these studies used ERCP to aid insertion of a stent, whilst only one used percutaneous transhepatic cholangiography (PTC) (Travis & Nicholson, 1997). Seven of the studies were in adults with either unresectable pancreatic cancer or unresectable malignant biliary obstruction (Isayama et al., 2011; Kaassis et al., 2003; Moses et al., 2013; Schmidt et al., 2015; Söderlund & Linder, 2006; Travis & Nicholson, 1997; Walter et al., 2015). One study

included resectable and borderline resectable adult pancreatic cancer patients in addition to those whose tumours were unresectable (Gardner et al., 2016). A variety of plastic stents (e.g. polyethylene or polyurethane) and SEMS (e.g. covered, partially covered, or uncovered) were used.

9.1.2.2 Covered self-expanding metal stent versus uncovered self-expanding metal stent in adults with pancreatic cancer and biliary obstruction

Five studies (n=708) compared a covered SEMS with an uncovered SEMS (Gardner et al., 2016; Kitano et al., 2013; Krokidis et al., 2011; Kullman et al., 2010; Ung et al., 2013). The majority of the studies were in adults with unresectable pancreatic cancer.

9.1.2.3 Partially-covered self-expanding metal stent versus uncovered self-expanding metal stent in adults with pancreatic cancer and biliary obstruction

Two studies (n=243) compared a partially-covered SEMS with an uncovered SEMS (Telford et al., 2010; Walter et al., 2015) in adults with unresectable tumours.

9.1.2.4 Paclitaxel-eluting self-expanding metal stent versus covered self-expanding metal stent in adults with an unresectable distal malignant biliary obstruction

One study (n=52) compared a paclitaxel-eluting SEMS with a covered SEMS in adults with unresectable distal malignant biliary obstruction (Song et al., 2011). Although this study only included 51% pancreatic cancer patients, it was decided to include it and downgrade the quality of evidence two levels for indirectness for the relevant outcomes.

9.1.2.5 Preoperative endoscopic biliary drainage (PEBD) then surgery versus surgery in adults with suspected pancreatic cancer

One study (n=196) compared endoscopic preoperative biliary drainage using a plastic stent followed by surgery with surgery only in adults with obstructive jaundice due to suspected pancreatic head cancer (Eshuis et al., 2010). The study included resectable and unresectable tumour patients.

9.1.2.6 Endoscopic sphincterotomy then stent versus stent in adults with unresectable pancreatic cancer

Three studies (n=446) compared endoscopic sphincterotomy (ES) followed by the insertion of a stent with a stent only (Artifon et al. 2008; Giorgio & Luca, 2004; Hayashi et al., 2015) in adults with unresectable tumours. The majority of these studies used a partially-covered or covered SEMS.

9.1.2.7 Endoscopic sphincterotomy then stent versus surgical bypass in adults with unresectable pancreatic cancer

One study (n=30) compared endoscopic sphincterotomy (ES) followed by the insertion of a covered SEMS with surgical bypass only (Artifon et al., 2006) in adults with unresectable pancreatic cancer.

9.1.2.8 Endoscopic ultrasound-guided choledochoduodenostomy (EUS-CD) and stent versus percutaneous transhepatic biliary drainage (PTBD) in adults with an unresectable malignant biliary obstruction where either ERCP or EUS-guided transpapillary rendezvous has failed

One study (n=25) compared endoscopic ultrasound-guided choledochoduodenostomy (EUS-CD) and insertion of a partially-covered SEMS with percutaneous transhepatic biliary drainage (PTBD) (Artifon et al., 2012) in adults with an unresectable tumour where either

ERCP or EUS-guided transpapillary rendezvous has failed. Although data regarding the number of individuals with pancreatic cancer in this study was not available, it was decided to include it but downgrade the relevant outcomes by two levels for indirectness.

9.1.2.9 Endoscopic ultrasound-guided choledochoduodenostomy (EUS-CD) and stent versus surgical bypass in adults with an unresectable malignant biliary obstruction where ERCP has failed

One study (n=32) compared endoscopic ultrasound-guided choledochoduodenostomy (EUS-CD) and insertion of a partially-covered SEMS with surgical bypass/drainage only (Artifon et al., 2015) in adults with unresectable tumour where ERCP has failed. Although data regarding the number of individuals with pancreatic cancer in this study was not available, it was decided to include it but downgrade the relevant outcomes by two levels for indirectness.

9.1.31 Summary of included studies

2 A summary of the studies that were included in this review are presented in Table 98.

3 **Table 98: Summary of included studies**

Study	Population	Intervention	Comparison	Outcomes
Artifon, Aparicio et al. 2012	Unresectable malignant biliary obstruction in which ERCP or EUS-guided transpapillary rendezvous has failed (n=25) [Number of PC patients unclear]	EUS-CD	PTBD	Relief of symptoms Treatment-related complications Quality of life
Artifon, Loureiro et al. 2015	Unresectable malignant biliary obstruction in which ERCP has failed (n=32) [Number of PC patients unclear]	EUS-CD	Surgical Bypass (HJT)	Relief of symptoms # >50% reduction in bilirubin Overall survival Treatment-related complications Quality of life
Artifon, Sakai et al. 2006	Unresectable metastatic PC with biliary obstruction	Endoscopic Sphincterotomy + Stent	Surgery	Relief of obstruction Relief of symptoms Treatment related-mortality Treatment-related morbidity Treatment-related complications Quality of life
Artifon, Sakai et al. 2008	Unresectable malignant distal bile duct obstruction (n=74) [81% PC patients]	Endoscopic Sphincterotomy + Stent	Stent	Treatment-related complications
Eshuis et al. 2010/van der Gaag et al. 2010	Obstructive jaundice with suspected PC of head (n=196) [92% PC patients; includes 45% resectable or borderline resectable patients]	Preoperative Biliary Drainage then Surgery	Surgery	Mortality/Overall Survival Time to surgery Time to complications Stent Dysfunction Treatment-related complications Treatment-related hospitalisation

Study	Population	Intervention	Comparison	Outcomes
Gardner et al. 2016	PC with malignant biliary obstruction receiving neoadjuvant CRT (n=63) [3-arm trial including covered (n=17) and uncovered (n=20) SEMS; includes resectable and unresectable patients]	Plastic Stent Covered SEMS	Uncovered SEMS	Stent Dysfunction Treatment-related complications
Giorgio et al. 2004	Unresectable malignant bile duct obstruction (n=172) [76% PC patients]	Endoscopic Sphincterotomy + Stent	Stent	Stent Dysfunction Treatment-related complications
Hayashi et al. 2015	Unresectable PC with malignant distal biliary stricture(n=200)	Endoscopic Sphincterotomy + Stent	Stent	Stent Dysfunction Treatment-related complications Deaths due to PC progression Serum amylase
Isayama et al. 2011	Unresectable PC of head with distal biliary obstruction (n=120)	Plastic Stent	SEMS	Overall Survival Stent Dysfunction Stent-related complications
Kaassis et al. 2003	Unresectable malignant common bile duct stricture (n=118) [75% PC patients]	Plastic Stent	SEMS	Stent Dysfunction Stent-related complications Hospitalisation
Kitano et al. 2013	Unresectable PC with malignant distal biliary obstruction (n=120)	Covered SEMS	Uncovered SEMS	Survival Stent patency Time to stent dysfunction Adverse events
Krokidis et al 2013	Unresectable PC with jaundice caused by occlusion of biliary tree (n=80)	Covered SEMS	Uncovered SEMS	Survival Stent patency Stent dysfunction Adverse events
Kullman et al 2010	Unresectable malignant bile duct obstruction (n=400)	Covered SEMS	Uncovered SEMS	Survival Stent dysfunction

Study	Population	Intervention	Comparison	Outcomes
	[77% PC patients]			Adverse events
Moses et al. 2013	Unresectable malignant biliary obstruction (n=85) [68% PC patients]	Plastic Stent	SEMS	Reduction in bilirubin Stent Dysfunction Stent-related complications
Schmidt et al. 2014	Unresectable malignant distal biliary obstruction (n=37) [67% PC patients]	Plastic Stent	SEMS	Overall Survival Stent Dysfunction Stent-related complications
Söderlund et al. 2006	Non-referred patients with unresectable malignant common bile duct stricture (n=100) [78% PC patients]	Plastic Stent	SEMS	Treatment-related mortality Overall Survival Stent-related complications Aspartate aminotransferase Serum bilirubin
Song et al. 2011	Unresectable malignant biliary obstruction (n=52) [51% PC patients]	Paclitaxel-eluting SEMS	Covered SEMS	Treatment-related mortality Overall Survival Stent Dysfunction Treatment-related complications
Telford 2010	Unresectable malignant distal biliary obstruction (n=129) [82% PC patients]	Partially covered SEMS	Uncovered SEMS	Survival Time to obstruction Adverse events
Travis et al. 1997	PC with unresectable malignant biliary obstruction (n=52) [All participants had PTC]	Plastic Stent	SEMS	Stent Dysfunction
Ung et al. 2013	Incurable malignant distal biliary obstruction (n=71) [84% PC patients]	Covered SEMS	Uncovered SEMS	Survival Stent patency Adverse events
Walter et al. 2015	Unresectable extrahepatic malignant bile duct obstruction (n=240) [75% PC patients; 3-arm trial including partially covered and uncovered SEMS; also	Plastic Stent Partially covered SEMS	SEMS Uncovered SEMS	Stent Dysfunction Treatment-related complications

Study	Population	Intervention	Comparison	Outcomes
	primary and secondary stent subgroups]			

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9.1.4 Clinical evidence profiles

The clinical evidence profiles for this review question are presented in Table 99 to Table 107.

Table 99: Summary clinical evidence profile for plastic stent versus self-expanding metal stent in adults with pancreatic cancer and biliary obstruction

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	SEMS	Plastic				
Treatment-related mortality	0 per 1000	0 per 1000 (0 to 0)	RR 2.88 (0.12 to 69.16)	100 (1 study)	⊕⊖⊖⊖ very low[1,2]	
Overall Survival	Study population		HR 1 (0.75 to 1.31)	247 (3 studies)	⊕⊖⊖⊖ very low[1,4,5,9,13,21,22]	
	See comment[3]	See comment[3]				
	Moderate					
	0 per 10003	-2147483648 per 1000 (-2147483648 to -2147483648)3				
Time to stent dysfunction for unresectable PC - primary and/or secondary stent	Study population		HR 2.59 (1.67 to 4)	229 (3 studies)	⊕⊖⊖⊖ very low[3,4,5,8,9,13,17,18]	
	See comment[3]	See comment[3]				
	Moderate					
	0 per 1000[3]	-2147483648 per 1000 (-2147483648 to -2147483648)[3]				
Time to stent dysfunction for unresectable PC - Covered or Partially Covered SEMS	257 per 1000	489 per 1000 (350 to 649)	HR 2.26 (1.45 to 3.53)	224 (2 studies)	⊕⊖⊖⊖ very low[4,5,6,7,8]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	SEMS	Plastic				
(Primary Stent only)						
Time to stent dysfunction for unresectable PC - Uncovered SEMS (Primary Stent only)	167 per 1000	421 per 1000 (232 to 677)	HR 3 (1.45 to 6.2)	117 (1 study)	⊕⊖⊖⊖ very low[4,6,7,8]	
Time to stent dysfunction for unresectable PC - Partially Covered SEMS (Secondary Stent only)	118 per 1000	567 per 1000 (160 to 982)	HR 6.69 (1.39 to 32.07)	33 (1 study)	⊕⊖⊖⊖ very low[4,6,7,8]	
Time to stent dysfunction for unresectable PC - Uncovered SEMS (Secondary Stent only)	67 per 1000	497 per 1000 (212 to 862)	HR 9.97 (3.46 to 28.74)	31 (1 study)	⊕⊖⊖⊖ very low[4,6,7,8]	
Stent Dysfunction - Stent Occlusion	191 per 1000	430 per 1000 (319 to 577)	RR 2.25 (1.67 to 3.02)	471 (6 studies)	⊕⊕⊖⊖ low[1,4,5,9,10,11,12,13,14,15]	
Stent Dysfunction - Stent Migration	91 per 1000	17 per 1000 (2 to 143)	RR 0.19 (0.02 to 1.57)	113 (1 study)	⊕⊖⊖⊖ very low[2,4,5]	
Stent Dysfunction - Stent Occlusion or Migration	167 per 1000	403 per 1000 (240 to 677)	RR 2.42 (1.44 to 4.06)	171 (1 study)	⊕⊖⊖⊖ very low[4,6,7,8]	
Stent Occlusion -	176 per 1000	387 per 1000	RR 2.2 (1.45	258 (4 studies)	⊕⊖⊖⊖ very low[4,8,9,10,11,12,13,14,15]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	SEMS	Plastic				
any type of SEMS		(255 to 590)	to 3.35)			
Stent Occlusion - Covered SEMS	212 per 1000	487 per 1000 (319 to 738)	RR 2.3 (1.51 to 3.49)	213 (2 studies)	⊕⊖⊖⊖ very low[1,4,5,8]	
Stent Occlusion - unresectable patients	174 per 1000	410 per 1000 (295 to 570)	RR 2.36 (1.7 to 3.28)	417 (5 studies)	⊕⊕⊖⊖ low[1,4,5,9,11,12,13,14]	
Stent Occlusion - resectable, borderline resectable or locally advanced	303 per 1000	524 per 1000 (270 to 1000)	RR 1.73 (0.89 to 3.34)	54 (1 study)	⊕⊕⊖⊖ low[4,10,15,16]	
Pancreatitis	22 per 1000	18 per 1000 (7 to 46)	RR 0.81 (0.32 to 2.04)	720 (7 studies)	⊕⊖⊖⊖ very low[1,2,4,5,6,9,10,11,13,14,15,17]	
Pancreatitis - any SEMS	25 per 1000	26 per 1000 (9 to 73)	RR 1.02 (0.36 to 2.92)	473 (4 studies)	⊕⊖⊖⊖ very low[2,4,6,7,10,11,14,15,17,18]	
Pancreatitis - covered SEMS	19 per 1000	6 per 1000 (1 to 58)	RR 0.32 (0.03 to 3.01)	213 (2 studies)	⊕⊖⊖⊖ very low[1,2,4,5]	
Pancreatitis - unresectable patients	1 per 100	1 per 100 (0 to 4)	RR 1.52 (0.51 to 4.59)	632 (5 studies)	⊕⊖⊖⊖ very low[1,2,4,5,6,7,9,11,14,17,18]	
Pancreatitis - resectable, borderline resectable or locally advanced patients	182 per 1000	22 per 1000 (2 to 365)	RR 0.12 (0.01 to 2.01)	54 (1 study)	⊕⊖⊖⊖ very low[2,4,10,15]	
Cholangitis - unresectable patients	30 per 1000	93 per 1000 (38 to 224)	RR 3.1 (1.28	334 (4 studies)	⊕⊕⊖⊖ low[1,4,9,11,13,17,18]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	SEMS	Plastic				
			to 7.48)			
Cholangitis - any SEMS	39 per 1000	67 per 1000 (19 to 229)	RR 1.71 (0.5 to 5.89)	152 (2 studies)	⊕⊖⊖⊖ very low[2,4,9,11,13,14]	
Cholangitis - covered SEMS	0 per 1000	0 per 1000 (0 to 0)	RR 4.81 (0.24 to 97.68)	100 (1 study)	⊕⊖⊖⊖ very low[1,2]	
Cholangitis - partially-covered SEMS	49 per 1000	244 per 1000 (57 to 1000)	RR 5 (1.17 to 21.43)	82 (1 study)	⊕⊖⊖⊖ very low[4,16,17,18]	
Cholecystitis - unresectable patients	27 per 1000	13 per 1000 (4 to 41)	RR 0.47 (0.15 to 1.53)	448 (4 studies)	⊕⊖⊖⊖ very low[2,4,5,6,7,9,13,17,18]	
Cholecystitis - any SEMS	6 per 1000	16 per 1000 (2 to 123)	RR 2.56 (0.33 to 20.1)	253 (2 studies)	⊕⊖⊖⊖ very low[2,4,6,7,9,13]	
Cholecystitis - partially-covered SEMS	49 per 1000	10 per 1000 (0 to 197)	RR 0.2 (0.01 to 4.04)	82 (1 study)	⊕⊖⊖⊖ very low[2,4,17,18]	
Cholecystitis - Covered SEMS	73 per 1000	8 per 1000 (1 to 139)	RR 0.11 (0.01 to 1.91)	113 (1 study)	⊕⊖⊖⊖ very low[2,4,5]	
# patients with cholestatic symptoms to 2-year FU Follow-up: 2 years	250 per 1000	360 per 1000 (183 to 710)	RR 1.44 (0.73 to 2.84)	79 (1 study)	⊕⊖⊖⊖ very low[2,4,17,18]	
Post-ES Haemorrhage	Study population		RR 3 (0.12 to	118 (1 study)	⊕⊖⊖⊖ very low[2,4,11,14]	
	0 per 1000	0 per 1000 (0 to 0)				
	Moderate					

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	SEMS	Plastic				
	0 per 1000	0 per 1000 (0 to 0)	72.18)			
Hospitalisation Days		The mean hospitalisation in the intervention groups was 0.49 standard deviations higher (0.21 to 0.77 higher)		197 (2 studies)	⊕⊖⊖⊖ very low[4,11,14,16,17,18]	
# >=30% decrease in serum bilirubin	1000 per 1000	940 per 1000 (790 to 1000)	RR 0.94 (0.79 to 1.1)	34 (1 study)	⊕⊕⊖⊖ low[9,16]	
% Reduction in total serum bilirubin levels	The mean % reduction in total serum bilirubin levels in the control groups was 74 percentage	The mean % reduction in total serum bilirubin levels in the intervention groups was 10.3 lower (32.51 lower to 11.91 higher)		79 (1 study)	⊕⊖⊖⊖ very low[4,17,18,19,20]	
Total Serum Bilirubin - rate of change		The mean total serum bilirubin - rate of change in the intervention groups was 0.23 standard deviations lower (0.62 lower to 0.17 higher)		98 (1 study)	⊕⊕⊖⊖ low[1,16]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	SEMS	Plastic				

1 Soderlund et al. 2006 sample included 78% pancreatic cancer patients.
2 Crosses 2 default MIDs for dichotomous outcomes (0.8 and 1.25).
3 Not all included studies provided data regarding number of patients who were still alive or experienced stent dysfunction.
4 Majority of studies are high/unclear risk of bias due to insufficient reporting regarding blinding and incomplete reporting of outcomes.
5 Isayama et al. 2001 (all patients received endoscopic sphincterotomy).
6 Walter et al. 2015 (unclear whether blinding would affect outcome; selective reporting of outcomes).
7 Walter et al. 2015 included 75% pancreatic cancer patients.
8 Small sample size for dichotomous outcomes (<300 events).
9 Schmidt et al. 2015 (selective reporting of outcomes; study terminated early due to high rate of stent failure in plastic [winged] stent group).
10 Gardner et al. 2016 (unclear allocation concealment and blinding of outcome assessment; selective reporting of outcomes; participants were receiving 1 of 3 neoadjuvant chemoradiotherapy regimens).
11 Kaassis et al. 2003 (unclear randomisation method and allocation concealment; selective reporting of outcomes; significant difference in % weight loss at baseline; some patients also received sphincterotomy).
12 Travis et al. 1997 (unclear randomisation method, allocation concealment, blinding of personnel/participants/outcome assessment; imbalance in group numbers and selective reporting of outcomes).
13 Schmidt et al 2015 sample included 67% pancreatic cancer patients.
14 Kaassis et al. 2003 sample included 75% pancreatic cancer patients.
15 Gardner et al. 2016 includes both resectable (19%), borderline resectable (26%), and unresectable (55%) pancreatic cancer patients.
16 Crosses 1 default MID for dichotomous (0.8 or 1.25) or continuous outcomes (0.5 or -0.5).
17 Moses et al. 2013 (unclear randomisation method; selective reporting of outcomes).
18 Moses et al. 2013 sample included 68% pancreatic cancer patients.
19 MID for this outcome assumed to be 21.81/-21.81 (0.5 SD of control group at follow up; data from Moses et al. 2013).
20 Crosses 1 MID for this outcome.
21 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant.
22 Not statistically significant.

Table 100: Summary clinical evidence profile for covered SEMS versus uncovered SEMS in adults with pancreatic cancer and biliary obstruction

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Uncovered	SEMS: Covered				
Relief of obstruction cumulative - stent patency, time to obstruction[a]	Mean time=74 (R: 45-90) days	Mean time=220 (R: 21-341) days	Not estimable	63 (1 study)	⊕⊕⊖⊖ low[19]	Log-rank p-value=n.r.
	Median time=314 (n.r.) days	Median time=583 (n.r.) days	Not estimable	120 (1 study)	⊕⊕⊖⊖ low[19]	Log-rank p-value=0.02
	Median time=166 (SE: 13.1; SD: 82.8) days	Median time=234 (SE: 20.8; SD: 132) days	Not estimable	80 (1 study)	⊕⊕⊖⊖ low[19]	Log-rank p-value=0.01

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Uncovered	SEMS: Covered				
	Median time[1st quartile]=199 (n.r) days	Median time[1st quartile]=154 (n.r.) days	Not estimable	400 (1 study)	⊕⊕⊖⊖ low[19]	Log-rank p-value=0.33 for pancreatic cancer patients only, log-rank p-value=0.349
	Median time= 127 (IQR: 70-196; R: 18-486) days	Median time=153 (IQR: 65-217; R: 20-609) days	Not estimable	71 (1 study)	⊕⊕⊖⊖ low[19]	Log-rank p-value=n.s.
Stent Dysfunction	259 per 1000	210 per 1000 (158 to 272)	RR 0.81 (0.61 to 1.05)	701 (5 studies)	⊕⊖⊖⊖ very low[1,2,3]	
Stent Dysfunction by cause - Sludge formation	33 per 1000	81 per 1000 (41 to 162)	RR 2.43 (1.22 to 4.85)	600 (3 studies)	⊕⊖⊖⊖ very low[4,5,6]	
Stent Dysfunction by cause - Stent migration	0 per 1000	0 per 1000 (0 to 0)	RR 13 (0.74 to 229.23)	520 (2 studies)	⊕⊖⊖⊖ very low[7,8,9]	
Stent Dysfunction by cause - Tumour ingrowth	133 per 1000	48 per 1000 (27 to 85)	RR 0.36 (0.2 to 0.64)	600 (3 studies)	⊕⊖⊖⊖ very low[3,8,10]	
Stent Dysfunction by cause - Tumour overgrowth	40 per 1000	75 per 1000 (39 to 146)	RR 1.88 (0.97 to 3.66)	600 (3 studies)	⊕⊖⊖⊖ very low[6,8,11]	
Adverse Events	78 per 1000	69 per 1000 (40 to 118)	RR 0.89 (0.52 to 1.51)	668 (4 studies)	⊕⊖⊖⊖ very low[2,9,12]	
Adverse Events by type - Cholangitis	60 per 1000	40 per 1000 (17 to 96)	RR 0.67 (0.28 to 1.6)	400 (1 study)	⊕⊖⊖⊖ very low[8,9,13]	
Adverse Events by type - Cholecystitis	15 per 1000	12 per 1000 (3 to 51)	RR 0.75 (0.17 to 3.31)	520 (2 studies)	⊕⊖⊖⊖ very low[9,14]	
Adverse Events by type - Haemorrhage	12 per 1000	9 per 1000 (2 to 44)	RR 0.71 (0.14 to 3.52)	480 (2 studies)	⊕⊖⊖⊖ very low[8,9,15]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Uncovered	SEMS: Covered				
Adverse Events by type - Pancreatitis	14 per 1000	16 per 1000 (5 to 53)	RR 1.2 (0.37 to 3.89)	588 (3 studies)	⊕⊖⊖⊖ very low[2,9,11]	
Adverse Events by type - Peritoneal irritation	50 per 1000	0 per 1000 (13 to 425)	RR 0 (0.26 to 8.5)	80 (1 study)	⊕⊖⊖⊖ very low[9,16]	
Adverse Events by type - Retroperitoneal perforation	5 per 1000	5 per 1000 (0 to 79)	RR 1 (0.06 to 15.88)	400 (1 study)	⊕⊖⊖⊖ very low[8,9,13]	
Adverse Events by type - Sepsis	0 per 1000	0 per 1000 (0 to 0)	RR 3 (0.13 to 71.15)	68 (1 study)	⊕⊖⊖⊖ very low[9,17,18]	
Overall survival - time to death[a]	Median time=242(R: 122-453) days	Median time=71(R: 7-196) days	Not estimable	63 (1 study)	⊕⊕⊖⊖ low[19]	Log-rank p-value=n.r.
	Median time=222 (n.r.) days	Median time=285(n.r.) days	Not estimable	120 (1 study)	⊕⊕⊖⊖ low[19]	Log-rank p-value=0.68
	Median time=203.2(SE: 11.8; SD: 74.8) days	Median time=247(SE: 20; SD: 126.7) days	Not estimable	80 (1 study)	⊕⊕⊖⊖ low[19]	Log-rank p-value=0.06
	Median time=174(IQR: 284) days	Median time=116(IQR: 242) days	Not estimable	400 (1 study)	⊕⊕⊖⊖ low[19]	Log-rank p-value=0.32
	Median time=157(IQR: 70-273; R: 20-690) days	Median time=154 (IQR: 65-217; R: 21-609) days	Not estimable	71 (1 study)	⊕⊕⊖⊖ low[19]	Log-rank p-value=n.s.

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes.*

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; IQR: interquartile range; R: range; n.s.: not significant; n.r.: not reported; SEMS: self-expanding metal stent.

a The five included RCTs did not report data for cumulative stent patency (time to obstruction) and overall survival in a way that allowed a meta-analysis (Gardner et al. 2016; Kitano et al. 2013; Krokidis et al. 2011; Kullman et al. 2010; and Ung et al. 2013).
1 Overall high risk of bias due to selective reporting and other source of bias. Kullman et al. 2010 contributed almost 50% to this outcome and had risk of bias due to significant difference in mean age of groups, number with hepatic or metastasis (at baseline) and number with unknown causes of stent failure.
2 Two of the studies (Kullman et al. 2010; Ung et al. 2013) used samples that had less than 85% pancreatic cancer patients.
3 Small sample size for dichotomous outcomes (<300 events).
4 Overall all 3 studies had high/unclear risk of bias mainly due to selective reporting. Two of these, which contributed approximately 57% and 38% to outcome, were at high risk due to other sources of bias: in Kitano et al. 2013, there was significant difference in the length of stents used in each group, whilst majority of sample had had prior biliary drainage; in Kullman et al 2010 there were significant differences in mean age of groups

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Uncovered	SEMS: Covered				

and number with hepatic or metastasis (at baseline) and number with unknown causes of stent failure).
5 Sample in Kullman et al. 2010, which contributed 38% to the outcome, had 77% pancreatic cancer patients.
6 Crosses 1 default MID for dichotomous outcomes (0.8 or 1.25).
7 Both studies had high risk of bias due to selective reporting and other sources of bias. Kullman et al. 2010 contributed 100% to this outcome and there were significant differences between the groups in mean age and hepatic or other metastasis at baseline and in number of patients with unknown causes of stent failure.
8 Sample in Kullman et al. 2010 had 77% pancreatic cancer patients.
9 Crosses 2 default MID for dichotomous outcomes (0.8 and 1.25).
10 Overall high risk of bias due to selective reporting and other source of bias. Kullman et al. 2010 contributed almost 52% to this outcome and had risk of bias due to significant difference in mean age of groups, number with hepatic or metastasis (at baseline) and number with unknown causes of stent failure. Kitano et al. 2013 contributed approximately 38% to this outcome and similar risk of bias due to significant differences in the length of stent used in each group and fact that majority of sample had had prior biliary drainage.
11 Overall high risk of bias due to selective reporting and other source of bias. Kullman et al. 2010 contributed 80% to this outcome and had risk of bias due to significant difference in mean age of groups, number with hepatic or metastasis (at baseline) and number with unknown causes of stent failure.
12 Overall high risk of bias due to selective reporting and other source of bias. Kullman et al. 2010 contributed almost 80% to this outcome and had risk of bias due to significant difference in mean age of groups, number with hepatic or metastasis (at baseline) and number with unknown causes of stent failure.
13 Kullman et al. 2010 is at high risk of bias due to selective reporting and other sources of bias. There were significant differences between the groups in mean age and hepatic or other metastasis at baseline and in number of patients with unknown causes of stent failure.
14 Both studies, each of which contributed 50% to this outcome, had high risk of bias due to selective reporting and other sources of bias (in Kullman et al. 2010, there were significant differences between the groups in mean age and hepatic or other metastasis at baseline and in number of patients with unknown causes of stent failure; in Kitano et al. 2013, there was significant difference in length of stents used in each group, and majority of sample had received prior biliary drainage).
15 Overall high or unclear risk of bias. Krokidis et al. 2011, which contributed approximately 57% to this outcome, at risk due to selective reporting, and unclear randomisation method/allocation concealment.
16 Krokidis et al. 2011 had overall high or unclear risk of bias due to selective reporting, and unclear randomisation method/allocation concealment.
17 Ung et al. 2013 had high risk of bias due to unclear randomisation method, selective reporting, and fact that more than 80% of the sample died with patent stents.
18 Sample in Ung et al. 2013 had 84% pancreatic cancer patients.
19 Overall the studies were at high risk of bias due to selective (e.g. incomplete) reporting of outcomes, other sources of bias (such as significant differences at baseline), and insufficient information about the randomisation method or allocation concealment (Gardner et al. 2016; Kitano et al. 2013; Krokidis et al. 2011; Kullman et al. 2010; and Ung et al. 2013).

Table 101: Summary clinical evidence profile for partially covered SEMS versus uncovered SEMS in adults with pancreatic cancer and biliary obstruction

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Uncovered	SEMS: Partially covered				
Relief of obstruction cumulative - stent patency,	Median time= 711 (IQR: 264-1302) days	Median time= 357 (IQR: 283-n.r.) days	Not estimable	129 (1 study)	⊕⊕⊖⊖ low[9]	Log-rank p-value=0.53

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Uncovered	SEMS: Partially covered				
time to obstruction[a]	Median time= 268 (219-317) days	Median time= 286 (240-332) days	Not estimable	240 (1 study)	⊕⊕⊖⊖ low[9]	Log-rank p-value=n.r.
Stent Dysfunction - Any cause	174 per 1000	234 per 1000 (141 to 387)	RR 1.35 (0.81 to 2.23)	243 (2 studies)	⊕⊖⊖⊖ very low[1,2,3]	
Stent Dysfunction - Stent migration	0 per 1000	0 per 1000 (0 to 0)	RR 15.28 (0.9 to 259.23)	129 (1 study)	⊕⊖⊖⊖ very low[3,4,5]	
Adverse events - Any cause	443 per 1000	620 per 1000 (443 to 868)	RR 1.4 (1 to 1.96)	129 (1 study)	⊕⊖⊖⊖ very low[3,4,5]	
Adverse events - Pancreatitis	7 per 1000	7 per 1000 (1 to 48)	RR 0.97 (0.14 to 6.58)	275 (2 studies)	⊕⊖⊖⊖ very low[2,6,7]	
Adverse events - Cholecystitis	25 per 1000	25 per 1000 (5 to 115)	RR 0.98 (0.21 to 4.59)	237 (2 studies)	⊕⊖⊖⊖ very low[4,5,7]	
Adverse events - Other	140 per 1000	159 per 1000 (92 to 278)	RR 1.14 (0.66 to 1.99)	275 (2 studies)	⊕⊖⊖⊖ very low[2,7,8]	
Overall survival[a]	Median time=239 (IQR: 84-401) days	Median time=227 (IQR: 99-365) days	Not estimable	129 (1 study)	⊕⊕⊖⊖ low[9]	Log-rank p-value=1.0
	Median time= n.r.	Median time= n.r.	Not estimable	240 (1 study)	⊕⊕⊖⊖ low[9]	Log-rank p-value=n.r.

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes.*

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; IQR: interquartile range; R: range; n.s.: not significant; n.r.: not reported; SEMS: self-expanding metal stent.

a The two included RCTs did not report data for cumulative stent patency (time to obstruction) and overall survival in a way that allowed a meta-analysis (Telford et al. 2010; and Walter et al. 2015a).
1 Telford et al. 2010, which contributed 55% to this outcome, had high/unclear risk of bias due to insufficient information about allocation concealment, imbalance in numbers due to failure to attain adequately powered groups, and selective reporting.
2 Both studies used samples comprised of less than 85% pancreatic cancer patients.
3 Crosses 1 default MID for dichotomous outcomes (0.8 or 1.25).
4 Telford et al. 2010 had high/unclear risk of bias due to insufficient information about allocation concealment, imbalance in numbers due to failure to attain adequately powered groups, and selective reporting.
5 Telford et al. 2010 had 82% pancreatic cancer patients.
6 Telford et al. 2010, which contributed approximately 77% to this outcome, had high/unclear risk of bias due to insufficient information about allocation concealment, imbalance in numbers due to failure to attain adequately powered groups, and selective reporting.

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Uncovered	SEMS: Partially covered				

7 Crosses 2 default MID for dichotomous outcomes (0.8 and 1.25).
8 Telford et al. 2010, which contributed 65% to this outcome, had high/unclear risk of bias due to insufficient information about allocation concealment, imbalance in numbers due to failure to attain adequately powered groups, and selective reporting.
9 Overall the studies were at high risk of bias due to selective (e.g. incomplete) reporting of outcomes, other sources of bias (such as significant differences at baseline), and insufficient information about the randomisation method or allocation concealment (Telford et al. 2010; and Walter et al. 2015a).

Table 102: Summary clinical evidence profile for paclitaxel-eluting SEMS versus covered SEMS in adults with an unresectable distal malignant biliary obstruction

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Covered SEMS for unresectable PC	Paclitaxel-eluting SEMS				
Time to stent dysfunction- All patients	Study population		HR 0.53 (0.16 to 1.78)	52 (1 study)	⊕⊖⊖⊖ very low[2,3,4]	
	See comment[1]	See comment[1]				
	Moderate					
	0 per 1000[1]	-2147483648 per 1000 (-2147483648 to -2147483648)[1]				
Time to stent dysfunction - Pancreatic cancer patients	Study population		HR 0.52 (0.1 to 3.09)	25 (1 study)	⊕⊖⊖⊖ very low[2,3,4]	
	See comment[1]	See comment1				
	Moderate					
	0 per 1000[1]	-2147483648 per 1000 (-2147483648 to -2147483648)[1]				
Overall Survival - All patients	Study population		HR 1.19 (0.65 to 2.18)	52 (1 study)	⊕⊖⊖⊖ very low[2,3,5,6]	
	See comment[1]	See comment[1]				
	Moderate					
	0 per 1000[1]	-2147483648 per 1000 (-2147483648 to -2147483648)[1]				

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Covered SEMS for unresectable PC	Paclitaxel-eluting SEMS				
Overall Survival - Pancreatic cancer patients	Study population		HR 0.85 (0.35 to 2.06)	25 (1 study)	⊕⊕⊖⊖ low[2,5,6]	
	See comment[1]	See comment[1]				
	Moderate					
	0 per 1000[1]	-2147483648 per 1000 (-2147483648 to -2147483648)[1]				
Stent Dysfunction - Stent Occlusion	320 per 1000	208 per 1000 (80 to 547)	RR 0.65 (0.25 to 1.71)	49 (1 study)	⊕⊖⊖⊖ very low[2,3,4]	
Cholangitis symptoms<30 days after surgery	0 per 1000	0 per 1000 (0 to 0)	RR 7.28 (0.4 to 133.89)	49 (1 study)	⊕⊖⊖⊖ very low[2,3,4]	
Pancreatitis<30 days after surgery	40 per 1000	42 per 1000 (3 to 629)	RR 1.04 (0.07 to 15.73)	49 (1 study)	⊕⊖⊖⊖ very low[2,3,4]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes.*

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;

1 Study did not report number of deaths nor number of stent failures.
2 Song et al. 2011: overall high risk of bias (unclear allocation concealment, blinding of outcome assessment and selective reporting; no power calculation; randomised participants were patients with unresectable distal malignant biliary obstruction who did not wish to undergo chemotherapy nor radiotherapy).
3 There were only 51% pancreatic cancer patients in this study. Since this was the only study that compared paclitaxel-eluting SEMS with another type of SEMS, it was decided to include this study though downgrade one level for indirectness.
4 Crosses 2 default MIDs for dichotomous outcomes (0.8 and 1.25).
5 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant.
6 Not statistically significant.

Table 103: Summary clinical evidence profile for preoperative endoscopic biliary drainage then surgery versus surgery in adults with suspected pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Surgery	Preoperative Endoscopic Biliary Drainage>Surgery				
Mortality at 120 days	128 per 1000	147 per 1000 (73 to 297)	RR 1.15 (0.57 to 2.33)	196 (1 study)	⊕⊖⊖⊖ very low[1,2,3]	
Mortality at 2 years	844 per 1000	811 per 1000 (709 to 920)	RR 0.96 (0.84 to 1.09)	185 (1 study)	⊕⊖⊖⊖ very low[1,2,4]	
Treatment-related mortality	43 per 1000	88 per 1000 (28 to 277)	RR 2.07 (0.66 to 6.51)	196 (1 study)	⊕⊖⊖⊖ very low[1,2,3]	
Overall Survival at 2 years	844 per 1000	839 per 1000 (738 to 917)	HR 0.98 (0.72 to 1.34)	185 (1 study)	⊕⊖⊖⊖ very low[1,2,5,6]	
Overall Survival at 2 years - resectable patients after resection	783 per 1000	701 per 1000 (562 to 835)	HR 0.79 (0.54 to 1.18)	113 (1 study)	⊕⊖⊖⊖ very low[1,2,5,6,7]	
Overall Survival at 2 years - unresectable patients after palliative surgery	966 per 1000	968 per 1000 (880 to 996)	HR 1.02 (0.63 to 1.67)	67 (1 study)	⊕⊖⊖⊖ very low[1,2,5,6,7]	
Time to surgery Weeks	The mean time to surgery in the control groups was 1.2 Weeks	The mean time to surgery in the intervention groups was 4 higher (3.58 to 4.42 higher)		196 (1 study)	⊕⊖⊖⊖ very low[1,2,4,8]	
Hospitalisation due to protocol-specific complication	117 per 1000	334 per 1000 (179 to 619)	RR 2.85 (1.53	196 (1 study)	⊕⊖⊖⊖ very low[1,2,4]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Surgery	Preoperative Endoscopic Biliary Drainage>Surgery				
			to 5.29)			
Rate of serious complications (<120 days after randomisation)	394 per 1000	606 per 1000 (506 to 706)	HR 1.86 (1.41 to 2.45)	196 (1 study)	⊕⊖⊖⊖ very low[1,2,4]	
Total protocol-specified complications	394 per 1000	736 per 1000 (559 to 968)	RR 1.87 (1.42 to 2.46)	196 (1 study)	⊕⊖⊖⊖ very low[1,2,4]	
Pre-surgery Pancreatitis	0 per 1000	0 per 1000 (0 to 0)	RR 13.83 (0.8 to 238.96)	196 (1 study)	⊕⊖⊖⊖ very low[1,2,9]	
Pre-surgery Cholangitis	21 per 1000	265 per 1000 (65 to 1000)	RR 12.44 (3.04 to 50.89)	196 (1 study)	⊕⊖⊖⊖ very low[1,2,4]	
Pre-surgery Post-ERCP Haemorrhage	0 per 1000	0 per 1000 (0 to 0)	RR 4.61 (0.22 to 94.83)	196 (1 study)	⊕⊖⊖⊖ very low[1,3]	
Pre-surgery Perforation	0 per 1000	0 per 1000 (0 to 0)	RR 4.61 (0.22 to 94.83)	196 (1 study)	⊕⊖⊖⊖ very low[1,2,3]	
Stent Malfunction - Stent Occlusion	11 per 1000	147 per 1000 (20 to 1000)	RR 13.82 (1.86 to 102.63)	196 (1 study)	⊕⊖⊖⊖ very low[1,2,4]	
Total Surgery-related Complications	372 per 1000	469 per 1000 (339 to 655)	RR 1.26 (0.91 to 1.76)	196 (1 study)	⊕⊖⊖⊖ very low[1,2,9]	
Total Surgery-related Complications for unresectable PC	179 per 1000	545 per 1000 (232 to 1000)	RR 3.05 (1.3 to 7.17)	61 (1 study)	⊕⊖⊖⊖ very low[1,2,4]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Surgery	**Preoperative Endoscopic Biliary Drainage>Surgery**				
Surgery-related Haemorrhage	43 per 1000	20 per 1000 (4 to 105)	RR 0.46 (0.09 to 2.46)	196 (1 study)	⊕⊖⊖⊖ very low[1,2,3]	
Surgery-related Cholangitis	32 per 1000	29 per 1000 (6 to 142)	RR 0.92 (0.19 to 4.45)	196 (1 study)	⊕⊖⊖⊖ very low[1,2,3]	
Surgery-related Pneumonia	53 per 1000	88 per 1000 (31 to 254)	RR 1.66 (0.58 to 4.77)	196 (1 study)	⊕⊖⊖⊖ very low[1,2,3]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes.*

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;

1 Eshuis et al. 2010/van der Gaag 2010: overall unclear risk of bias (unclear allocation concealment and selective reporting).
2 After surgical exploration, sample was found to include 92% pancreatic cancer patients; sample also includes participants with either resectable or unresectable tumours. Five patients in surgery only group also underwent preoperative biliary drainage due to unavailability of surgical facility (3 patients), intercurrent cholangitis after ERCP (1 patient) and hyperglycaemia (1 patient).
3 Crosses 2 default MIDs for dichotomous outcomes (0.8 and 1.25).
4 Small sample size for dichotomous (<300 events) or continuous (<400 participants) outcome.
5 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant.
6 Not statistically significant.
7 Randomisation of patients were not stratified by resectability status.
8 MID for this outcome assumed to be 0.61/-0.61 weeks (0.5 SD of control arm at follow up, calculated from data in van der Gaag et al. 2010).
9 Crosses 1 default MID for dichotomous outcomes (0.8 or 1.25).

Table 104: Summary clinical evidence profile for endoscopic sphincterotomy then stent versus stent in adults with unresectable pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Stent only for unresectable PC	**Endoscopic Sphincterotomy->Stent**				

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Deaths due to PC progression	780 per 1000	671 per 1000 (562 to 796)	RR 0.86 (0.72 to 1.02)	200 (1 study)	⊕⊕⊕⊖ moderate[1]	
Stent Dysfunction - Stent Occlusion	119 per 1000	108 per 1000 (65 to 181)	RR 0.91 (0.55 to 1.52)	456 (3 studies)	⊕⊖⊖⊖ very low[2,3]	
Stent Dysfunction - Stent Migration	31 per 1000	57 per 1000 (23 to 140)	RR 1.84 (0.75 to 4.54)	456 (3 studies)	⊕⊖⊖⊖ very low[2,3]	
Early Complications <=30 days	69 per 1000	86 per 1000 (42 to 173)	RR 1.24 (0.61 to 2.5)	376 (2 studies)	⊕⊖⊖⊖ very low[3,4]	
Total stent-related Early Complications (<=30 days)	150 per 1000	150 per 1000 (78 to 289)	RR 1 (0.52 to 1.93)	200 (1 study)	⊕⊕⊖⊖ low[3]	
Pancreatitis <=30 days	44 per 1000	49 per 1000 (22 to 113)	RR 1.11 (0.49 to 2.54)	450 (3 studies)	⊕⊖⊖⊖ very low[2,3]	
Pancreatitis <=30 days related to stent placement	53 per 1000	59 per 1000 (26 to 135)	RR 1.11 (0.49 to 2.54)	376 (2 studies)	⊕⊖⊖⊖ very low[3,4]	
Perforation <=30 days	10 per 1000	3 per 1000 (0 to 84)	RR 0.34 (0.01 to 8.25)	194 (1 study)	⊕⊕⊖⊖ low[3]	
Cholecystitis <=30 days	43 per 1000	11 per 1000 (1 to 96)	RR 0.26 (0.03 to 2.24)	184 (1 study)	⊕⊕⊖⊖ low[3]	
Total Late Complications related to stent placement (>30 days)	50 per 1000	60 per 1000 (19 to 190)	RR 1.2 (0.38 to 3.81)	200 (1 study)	⊕⊕⊖⊖ low[3]	
Cholangitis >30 days	167 per 1000	173 per 1000 (92 to 330)	RR 1.04 (0.55 to 1.98)	182 (1 study)	⊕⊖⊖⊖ very low[3,4]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Cholecystitis >30 days	43 per 1000	11 per 1000 (1 to 96)	RR 0.26 (0.03 to 2.24)	184 (1 study)	⊕⊕⊖⊖ low[3]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes.*

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

1 Crosses 1 default MID for dichotomous outcomes (0.8 or 1.25).
2 Majority of studies (2 of 3) are unclear or high risk of bias (Artifon et al. 2008; Giorgio et al. 2004): Artifon et al. 2008 (unclear allocation concealment, selective reporting of outcomes); Giorgio et al. 2004 (unclear randomisation method, allocation concealment).
3 Crosses 2 default MIDs for dichotomous outcomes (0.8 and 1.25).
4 Unclear risk of bias for Giorgio et al. 2004 (unclear randomisation method, allocation concealment).
5 Final value in controls at relevant time point (data from Hayashi et al. 2015).

Table 105: Summary clinical evidence profile for endoscopic sphincterotomy then stent versus surgical bypass in adults with unresectable pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Surgical bypass for unresectable PC	Endoscopic Sphincterotomy->Stent				
Relief of biliary obstruction	1000 per 1000	1000 per 1000 (880 to 1000)	RR 1 (0.88 to 1.13)	30 (1 study)	⊕⊕⊖⊖ low[1,2]	
Treatment-related morbidity	267 per 1000	200 per 1000 (53 to 744)	RR 0.75 (0.2 to 2.79)	30 (1 study)	⊕⊖⊖⊖ very low[1,3]	
Treatment-related hospital readmissions	400 per 1000	600 per 1000 (284 to 1000)	RR 1.5 (0.71 to 3.16)	30 (1 study)	⊕⊖⊖⊖ very low[1,3]	
Bilirubin level <2.5 mg/dL on day 30	533 per 1000	533 per 1000 (272 to 1000)	RR 1 (0.51 to 1.95)	30 (1 study)	⊕⊖⊖⊖ very low[1,3]	
Serum bilirubin level at 30 days	The mean serum bilirubin level at 30 days in the control groups was 2.2 mg/dL	The mean serum bilirubin level at 30 days in the intervention groups was 0.3 lower		30 (1 study)	⊕⊕⊖⊖ low[1,4,5]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Surgical bypass for unresectable PC	**Endoscopic Sphincterotomy->Stent**				
		(1.06 lower to 0.46 higher)				
Stent-related complications	0 per 1000	0 per 1000 (0 to 0)	RR 9 (0.53 to 153.79)	30 (1 study)	⊕⊖⊖⊖ very low[1,3]	
Treatment-related early onset complications Definition of 'early' not provided	333 per 1000	200 per 1000 (57 to 690)	RR 0.6 (0.17 to 2.07)	30 (1 study)	⊕⊖⊖⊖ very low[1,3]	
Treatment-related late onset complications Definition of 'late' not provided	267 per 1000	200 per 1000 (53 to 744)	RR 0.75 (0.2 to 2.79)	30 (1 study)	⊕⊖⊖⊖ very low[1,3]	
Post-operative complications	467 per 1000	331 per 1000 (135 to 817)	RR 0.71 (0.29 to 1.75)	30 (1 study)	⊕⊖⊖⊖ very low[1,3]	
Pneumonia	133 per 1000	27 per 1000 (1 to 513)	RR 0.2 (0.01 to 3.85)	30 (1 study)	⊕⊖⊖⊖ very low[1,3]	
Post-ERCP Pancreatitis	0 per 1000	0 per 1000 (0 to 0)	RR 3 (0.13 to 68.26)	30 (1 study)	⊕⊖⊖⊖ very low[1,3]	
Quality of Life - SF-36 at 30 days		The mean quality of life - sf-36 at 30 days in the intervention groups was 0.78 standard deviations higher (0.04 to 1.52 higher)		30 (1 study)	⊕⊕⊖⊖ low[1,6]	SMD - 0.78 (-1.52 to -0.04)
Quality of Life - SF-36 at 60 days		The mean quality of life - sf-36 at 60 days in the intervention groups was		30 (1 study)	⊕⊕⊖⊖ low[1,6]	SMD - 0.75 (-1.49 to -0.01)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Surgical bypass for unresectable PC	**Endoscopic Sphincterotomy->Stent**				
		0.75 standard deviations higher (0.01 to 1.49 higher)				

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes.*

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

1 Artifon et al. 2006: overall high/unclear risk of bias (unclear allocation concealment; selective reporting of survival and QoL outcomes; no power calculation/small sample size).
2 Small sample size (<300 events).
3 Crosses 2 default MIDs for dichotomous outcomes (0.8 and 1.25).
4 MIDs for this outcome assumed to be 0.5 SD or -0.5 SD of control arm at baseline calculated as 5.64/-5.64 (from data in Artifon et al. 2006).
5 Small sample size for continuous outcome (<400 participants).
6 Crosses 1 default MID for continuous outcomes (0.5 or -0.5).

Table 106: Summary clinical evidence profile for endoscopic ultrasound-guided choledochoduodenostomy and stent versus percutaneous transhepatic biliary drainage in adults with an unresectable malignant biliary obstruction where either ERCP or EUS-guided transpapillary rendezvous has failed

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Percutaneous transhepatic biliary drainage	**EUS-CD**				
Total serum bilirubin - at 7 days		The mean total serum bilirubin - at 7 days in the intervention groups was 0.53 standard deviations lower (1.33 lower to 0.27 higher)		25 (1 study)	⊕⊖⊖⊖ very low[1,2,3]	SMD -0.53 (-1.33 to 0.27)
Total serum bilirubin - at 30 days		The mean total serum bilirubin - at 30 days in the intervention groups was 0.42 standard		25 (1 study)	⊕⊖⊖⊖ very low[1,2,3]	SMD 0.42 (-0.37 to 1.22)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Percutaneous transhepatic biliary drainage	**EUS-CD**				
		deviations higher (0.37 lower to 1.22 higher)				
Treatment-related complications - Total	250 per 1000	155 per 1000 (30 to 767)	RR 0.62 (0.12 to 3.07)	25 (1 study)	⊕⊖⊖⊖ very low[1,2,4]	
SF-36 Overall - at 7 days		The mean sf-36 overall - at 7 days in the intervention groups was 0.29 standard deviations lower (1.08 lower to 0.5 higher)		25 (1 study)	⊕⊖⊖⊖ very low[1,2,3]	SMD -0.29 (-1.08 to 0.5)
SF-36 Overall - at 30 days		The mean sf-36 overall - at 30 days in the intervention groups was 0.31 standard deviations lower (1.1 lower to 0.48 higher)		25 (1 study)	⊕⊖⊖⊖ very low[1,2,3]	SMD -0.31 (-1.1 to 0.48)

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes.*

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

1 Artifon et al. 2012: overall high risk of bias (inadequate randomisation method, unclear allocation concealment, selective reporting of outcomes, no power calculation/small sample size; participants not blinded for QoL outcomes).
2 Sample has 64% pancreatic cancer patients.
3 Crosses 1 default MID for continuous outcomes (0.5 or -0.5).
4 Crosses 2 default MIDs for dichotomous outcomes (0.8 and 1.25).

Table 107: Summary clinical evidence profile for endoscopic ultrasound-guided choledochoduodenostomy and stent versus surgical bypass in adults with an unresectable malignant biliary obstruction where ERCP has failed

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Surgical bypass	EUS-CD				
Reduction>=50% from baseline in total serum bilirubin after 7 days	933 per 1000	719 per 1000 (504 to 1000)	RR 0.77 (0.54 to 1.09)	29 (1 study)	⊕⊖⊖⊖ very low[1,2,3]	
Total serum bilirubin - at 7 days	The mean total serum bilirubin - at 7 days in the control groups was 3.43 mg/dL[4]	The mean total serum bilirubin - at 7 days in the intervention groups was 1.71 higher (0.24 lower to 3.66 higher)		29 (1 study)	⊕⊖⊖⊖ very low[1,2,5,6]	
Total serum bilirubin - at 30 days	The mean total serum bilirubin - at 30 days in the control groups was 2.17 mg/dL	The mean total serum bilirubin - at 30 days in the intervention groups was 0.26 higher (0.37 lower to 0.89 higher)		29 (1 study)	⊕⊖⊖⊖ very low[1,2,5,7]	
Total serum bilirubin - at 60 days	The mean total serum bilirubin - at 60 days in the control groups was 1.8 mg/dL[4]	The mean total serum bilirubin - at 60 days in the intervention groups was 0.06 higher (0.31 lower to 0.43 higher)		25 (1 study)	⊕⊖⊖⊖ very low[1,2,5,7]	
Total serum bilirubin - at 90 days	The mean total serum bilirubin - at 90 days in the control groups was 1.83 mg/dL[4]	The mean total serum bilirubin - at 90 days in the intervention groups was 0.01 higher (0.58 lower to 0.6 higher)		13 (1 study)	⊕⊖⊖⊖ very low[1,2,5,7]	
Treatment-related complications	133 per 1000	215 per 1000 (41 to 1000)	RR 1.61 (0.31 to 8.24)	29 (1 study)	⊕⊖⊖⊖ very low[1,2,8]	
Overall Survival 90 days after surgery	600 per 1000	444 per 1000 (190 to 808)	HR 0.64 (0.23 to 1.8)	29 (1 study)	⊕⊖⊖⊖ very low[1,2,9,10]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Surgical bypass	EUS-CD				
SF-36 Functional Capacity - at 7 days Scale from: 0 to 100.	The mean sf-36 functional capacity - at 7 days in the control groups was 33.7 [4]	The mean sf-36 functional capacity - at 7 days in the intervention groups was 6.3 higher (5.12 lower to 17.72 higher)		29 (1 study)	⊕⊖⊖⊖ very low[1,2,5,11]	
SF-36 Functional Capacity - at 30 days Scale from: 0 to 100.	The mean sf-36 functional capacity - at 30 days in the control groups was 40.7 [4]	The mean sf-36 functional capacity - at 30 days in the intervention groups was 10.7 higher (0.93 to 20.47 higher)		29 (1 study)	⊕⊖⊖⊖ very low[1,2,5,12]	
SF-36 Functional Capacity - at 60 days Scale from: 0 to 100.	The mean sf-36 functional capacity - at 60 days in the control groups was 44.3 [4]	The mean sf-36 functional capacity - at 60 days in the intervention groups was 9.9 higher (1.04 to 18.76 higher)		26 (1 study)	⊕⊖⊖⊖ very low[1,2,5,12]	
SF-36 Functional Capacity - at 90 days Scale from: 0 to 100.	The mean sf-36 functional capacity - at 90 days in the control groups was 57.5 [4]	The mean sf-36 functional capacity - at 90 days in the intervention groups was 1.8 lower (9.86 lower to 6.26 higher)		13 (1 study)	⊕⊖⊖⊖ very low[1,2,5,11]	
SF-36 Physical Health - at 7 days Scale from: 0 to 100.	The mean sf-36 physical health - at 7 days in the control groups was 21.7 [4]	The mean sf-36 physical health - at 7 days in the intervention groups was 1.5 higher (11.76 lower to 14.76 higher)		29 (1 study)	⊕⊖⊖⊖ very low[1,2,5,11]	
SF-36 Physical Health - at 30 days Scale from: 0 to 100.	The mean sf-36 physical health - at 30 days in the control groups was 31.7 [4]	The mean sf-36 physical health - at 30 days in the intervention groups was 4.9 lower (18.55 lower to 8.75 higher)		29 (1 study)	⊕⊖⊖⊖ very low[1,2,5,11]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Surgical bypass	EUS-CD				
SF-36 Physical Health - at 60 days Scale from: 0 to 100.	The mean sf-36 physical health - at 60 days in the control groups was 28.6 [4]	The mean sf-36 physical health - at 60 days in the intervention groups was 6.8 higher (5.67 lower to 19.27 higher)		26 (1 study)	⊕⊖⊖⊖ very low[1,2,5,11]	
SF-36 Physical Health - at 90 days Scale from: 0 to 100.	The mean sf-36 physical health - at 90 days in the control groups was 45.8 [4]	The mean sf-36 physical health - at 90 days in the intervention groups was 10.1 lower (33.62 lower to 13.42 higher)		13 (1 study)	⊕⊖⊖⊖ very low[1,2,5,11]	
SF-36 Pain - at 7 days Scale from: 0 to 100.	The mean sf-36 pain - at 7 days in the control groups was 78 [4]	The mean sf-36 pain - at 7 days in the intervention groups was 3.7 lower (17.22 lower to 9.82 higher)		29 (1 study)	⊕⊖⊖⊖ very low[1,2,5,7]	
SF-36 Pain - at 30 days Scale from: 0 to 100.	The mean sf-36 pain - at 30 days in the control groups was 76.7 [4]	The mean sf-36 pain - at 30 days in the intervention groups was 2.7 higher (9.6 lower to 15 higher)		29 (1 study)	⊕⊖⊖⊖ very low[1,2,5,7]	
SF-36 Pain - at 60 days Scale from: 0 to 100.	The mean sf-36 pain - at 60 days in the control groups was 70.4 [4]	The mean sf-36 pain - at 60 days in the intervention groups was 4.4 lower (17.51 lower to 8.71 higher)		26 (1 study)	⊕⊖⊖⊖ very low[1,2,5,12]	
SF-36 Pain - at 90 days Scale from: 0 to 100.	The mean sf-36 pain - at 90 days in the control groups was 88.7 [4]	The mean sf-36 pain - at 90 days in the intervention groups was 15.3 lower (27.76 to 2.84 lower)		13 (1 study)	⊕⊖⊖⊖ very low[1,2,5,12]	
SF-36 General Health - at 7 days Scale from: 0 to 100.	The mean sf-36 general health - at	The mean sf-36 general health - at 7 days in the intervention		29 (1 study)	⊕⊖⊖⊖ very low[1,2,5,12]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Surgical bypass	EUS-CD				
	7 days in the control groups was 42.1 [4]	groups was 3.4 lower (10.15 lower to 3.35 higher)				
SF-36 General Health - at 30 days Scale from: 0 to 100.	The mean sf-36 general health - at 30 days in the control groups was 40.7 [4]	The mean sf-36 general health - at 30 days in the intervention groups was 4.1 lower (11.85 lower to 3.65 higher)		29 (1 study)	⊕⊖⊖⊖ very low[1,2,5,12]	
SF-36 General Health - at 60 days Scale from: 0 to 100.	The mean sf-36 general health - at 60 days in the control groups was 38.4 [4]	The mean sf-36 general health - at 60 days in the intervention groups was 3.3 lower (10.58 lower to 3.98 higher)		26 (1 study)	⊕⊖⊖⊖ very low[1,2,5,12]	
SF-36 General Health - at 90 days Scale from: 0 to 100.	The mean sf-36 general health - at 90 days in the control groups was 34.8 [4]	The mean sf-36 general health - at 90 days in the intervention groups was 4.5 higher (7.44 lower to 16.44 higher)		13 (1 study)	⊕⊖⊖⊖ very low[1,2,5,11]	
SF-36 Vitality - at 7 days Scale from: 0 to 100.	The mean sf-36 vitality - at 7 days in the control groups was 38 [4]	The mean sf-36 vitality - at 7 days in the intervention groups was 2.7 higher (5.64 lower to 11.04 higher)		29 (1 study)	⊕⊖⊖⊖ very low[1,2,5,11]	
SF-36 Vitality - at 30 days Scale from: 0 to 100.	The mean sf-36 vitality - at 30 days in the control groups was 40.3 [4]	The mean sf-36 vitality - at 30 days in the intervention groups was 7.6 higher (2.43 lower to 17.63 higher)		29 (1 study)	⊕⊖⊖⊖ very low[1,2,5,12]	
SF-36 Vitality - at 60 days Scale from: 0 to 100.	The mean sf-36 vitality - at 60 days in the control groups was 42.9 [4]	The mean sf-36 vitality - at 60 days in the intervention groups was 2.1 higher (8.61 lower to 12.81 higher)		26 (1 study)	⊕⊖⊖⊖ very low[1,2,5,11]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Surgical bypass	EUS-CD				
SF-36 Vitality - at 90 days Scale from: 0 to 100.	The mean sf-36 vitality - at 90 days in the control groups was 32.5 [4]	The mean sf-36 vitality - at 90 days in the intervention groups was 14.6 higher (3.2 lower to 32.4 higher)		13 (1 study)	⊕⊖⊖⊖ very low[1,2,5,12]	
SF-36 Social Role Functioning - at 7 days Scale from: 0 to 100.	The mean sf-36 social role functioning - at 7 days in the control groups was 45.8 [4]	The mean sf-36 social role functioning - at 7 days in the intervention groups was 0.3 lower (9.69 lower to 9.09 higher)		29 (1 study)	⊕⊖⊖⊖ very low[1,2,5,11]	
SF-36 Social Role Functioning - at 30 days Scale from: 0 to 100.	The mean sf-36 social role functioning - at 30 days in the control groups was 54.2 [4]	The mean sf-36 social role functioning - at 30 days in the intervention groups was 0.3 higher (7.56 lower to 8.16 higher)		29 (1 study)	⊕⊖⊖⊖ very low[1,2,5,12]	
SF-36 Social Role Functioning - at 60 days Scale from: 0 to 100.	The mean sf-36 social role functioning - at 60 days in the control groups was 43.8 [4]	The mean sf-36 social role functioning - at 60 days in the intervention groups was 1.1 lower (12.32 lower to 10.12 higher)		26 (1 study)	⊕⊖⊖⊖ very low[1,2,5,11]	
SF-36 Social Role Functioning - at 90 days Scale from: 0 to 100.	The mean sf-36 social role functioning - at 90 days in the control groups was 52.1 [4]	The mean sf-36 social role functioning - at 90 days in the intervention groups was 1.5 higher (9.73 lower to 12.73 higher)		14 (1 study)	⊕⊖⊖⊖ very low[1,2,5,11]	
SF-36 Emotional Role Functioning - at 7 days Scale from: 0 to 100.	The mean sf-36 emotional role functioning - at 7 days in the control	The mean sf-36 emotional role functioning - at 7 days in the intervention groups was 2.5 higher		29 (1 study)	⊕⊖⊖⊖ very low[1,2,5,11]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Surgical bypass	EUS-CD				
	groups was 35.6 [4]	(11.19 lower to 16.19 higher)				
SF-36 Emotional Role Functioning - at 30 days Scale from: 0 to 100.	The mean sf-36 emotional role functioning - at 30 days in the control groups was 46.7 [4]	The mean sf-36 emotional role functioning - at 30 days in the intervention groups was 0.9 higher (15.69 lower to 17.49 higher)		29 (1 study)	⊕⊖⊖⊖ very low[1,2,5,11]	
SF-36 Emotional Role Functioning - at 60 days Scale from: 0 to 100.	The mean sf-36 emotional role functioning - at 60 days in the control groups was 40.5 [4]	The mean sf-36 emotional role functioning - at 60 days in the intervention groups was 9.5 higher (11.05 lower to 30.05 higher)		26 (1 study)	⊕⊖⊖⊖ very low[1,2,5,11]	
SF-36 Emotional Role Functioning - at 90 days Scale from: 0 to 100.	The mean sf-36 emotional role functioning - at 90 days in the control groups was 38.9 [4]	The mean sf-36 emotional role functioning - at 90 days in the intervention groups was 8.7 higher (15.33 lower to 32.73 higher)		13 (1 study)	⊕⊖⊖⊖ very low[1,2,5,11]	
SF-36 Mental Health - at 7 days Scale from: 0 to 100.	The mean sf-36 mental health - at 7 days in the control groups was 44 [4]	The mean sf-36 mental health - at 7 days in the intervention groups was 9.1 higher (1.49 to 16.71 higher)		29 (1 study)	⊕⊖⊖⊖ very low[1,2,5,12]	
SF-36 Mental Health - at 30 days Scale from: 0 to 100.	The mean sf-36 mental health - at 30 days in the control groups was 39.7 [4]	The mean sf-36 mental health - at 30 days in the intervention groups was 12.9 higher (4.63 to 21.17 higher)		29 (1 study)	⊕⊖⊖⊖ very low[1,2,5,12]	
SF-36 Mental Health - at 60 days	The mean sf-36 mental health - at	The mean sf-36 mental health - at 60 days in the intervention		26 (1 study)	⊕⊖⊖⊖ very low[1,2,5,12]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Surgical bypass	EUS-CD				
Scale from: 0 to 100.	60 days in the control groups was 45.1 [4]	groups was 8.9 higher (0.92 lower to 18.72 higher)				
SF-36 Mental Health - at 90 days Scale from: 0 to 100.	The mean sf-36 mental health - at 90 days in the control groups was 42.7 [4]	The mean sf-36 mental health - at 90 days in the intervention groups was 1.9 higher (9.98 lower to 13.78 higher)		14 (1 study)	⨁⊖⊖⊖ very low[1,2,5,11]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes.*

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;

1 Artifon et al. 2015: Overall high risk of bias (no power calculation; no blinding for QoL outcomes).
2 Cause of biliary obstruction unclear/number of pancreatic cancer patients unclear
3 Crosses 1 default MID for dichotomous outcomes (0.8 or 1.25).
4 Final value in controls at relevant time point (data from Artifon et al. 2015).
5 MIDs for these outcomes assumed to be 0.5 SD or -0.5 SD of control arm at baseline (calculated from data in Artifon et al. 2015). The MIDs for total bilirubin levels were 2.81/-2.81, 217.68/-217.68 for gamma glutamyl transferase levels, and 127.95/-127.95 for alkaline phosphatase levels. For the SF-36 subscales, the MIDs were calculated to be 4.95/-4.95 for Functional Capacity, 5.5/-5.2 for Physical Health, 17.3/-17.3 for Pain, 5.35/-5.35 for General Health, 5.45/-5.45 for Vitality, 7.75/-7.75 for Social Role Functioning, 7.65/-7.65 for Emotional Role Functioning, and 6.6/-6.6 for Mental Health.
6 Crosses 1 MID for total bilirubin levels (2.81 or -2.81).
7 Small sample size for continuous outcome (<400 participants).
8 Crosses 2 default MIDs for dichotomous outcomes (0.8 and 1.25).
9 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant.
10 Not statistically significant.
11 Crosses 2 MIDs for relevant SF-36 subscale.
12 Crosses 1 MID for relevant SF-36 subscale.

9.1.5 Economic Evidence

9.1.5.1 Systematic literature review

References to all included studies and evidence tables for all economic evaluations included in the systematic literature review of the economic evidence are presented in Appendix L. Economic evidence profiles of these studies are presented in Appendix K.

Two studies (Arguedas et al. 2002; Morris et al. 2014) were included in the current review of published economic evidence for this topic. Both economic evaluations considered different interventions in different patient groups and therefore meaningful comparisons between the studies could not be drawn. A bespoke economic model was also built to help inform recommendations for part of this topic.

Morris et al. (2014) compared preoperative biliary drainage (PBD) to direct surgery in patients with potentially resectable pancreatic or periampullary cancer and obstructive jaundice from a UK NHS and PSS perspective. The study was deemed to only have minor methodological limitations.

The effectiveness side of the model is nearly entirely based on one Cochrane Review of six RCTs comparing PBD to direct surgery. The utility values for the model were taken from patient responses to the EQ-5D questionnaire, scored using the UK population weightings, completed by people with hepatic colorectal metastases. Although this was not the patient group considered by the economic evaluation the study did report that the trends closely matched those reported in disease specific quality of life measures for the relevant patient group. However, the results of the model were not sensitive to this input and it noted that alternative plausible values were unlikely to change the preferred option. Cost inputs for the model were all sourced from NHS reference costs.

The model concluded that sending patients directly to surgery led to a cost saving of £2,552 per patient. It also led to a small increase in health of 0.006 QALYS. This result was robust to all sensitivity analyses performed with probabilistic sensitivity analysis showing a strategy of PBD prior to surgery being the preferred option in less than 10% of iterations when a £20,000 willingness to pay per QALY is assumed.

The economic evaluation did not explicitly consider the issues of capacity (i.e. operating theatres and surgeons being available when needed) although it was unclear if there would be additional costs to having to reorganise services or not. However, unless the increases in cost per patient were significant it would be unlikely to change the conclusions.

Arguedas et al. (2002) compared plastic stenting to metal stenting in patients with pancreatic cancer and obstructive jaundice presenting for palliative biliary stenting. The study took a US Societal Perspective and was deemed to have very serious methodological limitations. The study estimated that initial stenting with metal stents would lead to a cost saving of US$433 and a health increase of 0.033 QALYs. This result was robust to all parameters apart from length of survival. Given the age of the study, the US societal perspective, methodological issues and that a contemporary bespoke economic model had been built to answer an almost identical decision problem from a UK NHS and PSS perspective, for the purposes of this guideline it was difficult to give much weight to the conclusions of this economic evaluation.

9.1.5.2 Economic modelling

As this topic was deemed a high economic priority and the previous economic evidence did not fully answer the decision problem, a bespoke economic model was developed. The rationale for economic modelling, methods, results and discussion are reported in full in Chapter 12. This section provides an overview of the methods and results for the bespoke economic model.

9.1.5.3 Overview of methods

A decision-analytical model in the form of a Markov model was developed to evaluate the relative cost effectiveness of different strategies for stenting in people with unresectable or metastatic pancreatic cancer and obstructive jaundice. Three different strategies were considered by the model: a strategy of initial stenting with a plastic stent followed by stenting with a self-expanding metal stent (SEMS) upon dysfunction and initial stenting with SEMS followed by replacement/repositioning upon dysfunction (SEMS/SEMS) compared to a base case strategy of initial plastic stenting replaced with plastic stents upon dysfunction. The model did not consider different types of SEMS (covered, uncovered, partially covered) because it was determined there would not be significant cost differences by type and that the decision of the best type to use would be made wholly on clinical and not economic

considerations if the strategies involving SEMS were cost effective. The main outcome of the economic model was incremental cost per QALY compared to the base case strategy. A NHS and PSS perspective was taken. The model had a time horizon of two years which was deemed sufficient to capture the lifetime of the vast majority of the cohort.

Clinical data were derived entirely from studies identified in the accompanying systematic review of clinical evidence. All costs were derived from NHS reference costs. The cost of initial stent insertion were taken from NHS reference costs. This figure would include all pre-operative imaging, the unit costs of the stents, the insertion of the stent and any peri-operative treatment and hospital stay.

NHS Reference costs gave a difference in total insertion costs between insertion of metal stents and plastic stents of £760, slightly less than the difference in unit cost of the different stents as reported in the NHS Supply Catalogues. Where the insertion of the stent is a secondary or later insertion the costs are assumed to be equal to those above apart from where a person is receiving a secondary SEMS stenting having previously received SEMS stenting (i.e. the SEMS/SEMS strategy). In this case the cost is assumed equal to that of receiving a plastic stent. This is because, unlike plastic stents, SEMS can be reused on migration or occlusion and thus the stent costs are not incurred again.

When occlusion or migration is suspected a patient would receive a diagnostic endoscopic procedure to investigate and confirm the suspicion and to rule out any other causes of the associated symptoms. Following this, patients would receive their secondary or later stenting.

During the base case analysis hospital days were not costed. Hospital days were not costed as the reference costs for stent placement allow for some days in hospital. It was likely that costing this difference could lead to double counting of this cost. Days in hospital above those in the perioperative period were costed in line with excess bed days for the procedure. In the base case analysis adverse events were not assigned a cost as it was assumed that these adverse events would often be treated as part of surgical treatment follow-up.

Quality of life weights were taken from one Dutch study (Walter et al. 2017), in an identical patient group, using the EQ-5D questionnaire, administered alongside an RCT. The EQ-5D questionnaire scored using Dutch population values showed no difference in quality of life between the SEMS and plastic stent groups. Therefore, the base case analysis was a de facto cost minimisation study. It was hypothesised that the EQ-5D questionnaire was not sensitive enough to pick up quality of life changes between the groups, therefore a secondary analysis was run using the values from the EQ-5D Visual Analogue Scale (VAS) to measure differences in quality of life between the different strategies.

All health and cost outcomes were discounted at a rate of 3.5% per annum.

9.1.5.4 Results of the economic model

In the base case analysis where overall survival and quality of life were assumed equal across the different strategies SEMS/SEMS was the least costly strategy with a cost saving, over the lifetime of one person of over £1500 when compared to the plastic/plastic strategy(Table 108). When scoring from the EQ-5D VAS was included in the secondary model the SEMS/SEMS strategy also lead to the largest amount of QALYs with an additional 0.024 QALYS compared to a plastic/plastic strategy. It was also cost saving and health improving compared to the plastic/SEMS strategy making it dominant compared to all other strategies considered in the base case analysis.

Table 108: Deterministic Base Case Results

	Total Costs	Total QALYs	Incremental Cost	Incremental QALY	ICER
Plastic/Plastic	£11,774	0.1608	Reference	Reference	
Plastic/SEMS	£11,371	0.1721	-£ 402	0.0113	Dominant†
SEMS/SEMS	£11,114	0.1852	-£ 659	0.0244	Dominant
	†Whilst Plastic/SEMS dominated Plastic/Plastic it was dominated by the SEMS/SEMS approach.				

This result was only sensitive to overall survival with plastic stenting followed by plastic stenting becoming the least costly for survival less than 24 days. The robustness of the result is supported by the probabilistic sensitivity analysis. The initial stenting with SEMS strategy is cost saving compared to plastic stenting followed by plastic stenting in 98% of iterations.

9.1.5.5 Conclusions

A strategy of SEMS replaced with SEMS upon dysfunction was the preferred option in the base case results for both deterministic and base case results - being cost saving compared to the other two strategies. When quality of life data from the EQ-5D VAS was used this strategy was also health improving.

These conclusions were robust to both one way deterministic sensitivity analyses and probabilistic sensitivity analysis. SEMS/SEMS was the preferred option in nearly all deterministic sensitivity analysis. The robustness of these results are further highlighted by the probabilistic sensitivity analysis where a SEMS/SEMS strategy is cost saving in greater than 98% of iterations.

The results of this economic model were based on evidence from the clinical evidence review which was derived entirely from RCT evidence. The costings for the model were taken from UK NHS sources and quality of life from a European EQ-5D questionnaire administered alongside an RCT. The results, conclusions and sensitivities are almost identical to the one economic evaluation identified by the review of the previous economic evidence review (Arguedas et al. 2002).

9.1.6 Evidence statements

9.1.6.1 Plastic stent versus self-expanding metal stent in adults with pancreatic cancer and biliary obstruction

Relief of obstruction

Very low quality evidence from 3 RCTS (n=229) showed that, when used as either a primary or secondary stent, there is a clinically important difference favouring SEMS on time to dysfunction in adults with unresectable pancreatic cancer compared to plastic stents: HR 2.59 (95% CI 1.67-4.0).

- Very low quality evidence from 2 RCTS (n=224) showed that when used as a primary stent, there is a clinically important difference favouring covered or partially-covered SEMS on time to dysfunction in adults with unresectable pancreatic cancer compared to plastic stents: HR 2.26 (95% CI 1.45-3.53).
- Very low quality evidence from 1 RCT (n=117) showed that when used as a primary stent, there is a clinically important difference favouring uncovered SEMS on time to dysfunction in adults with unresectable pancreatic cancer compared to plastic stents: HR 3.0 (95% CI 1.45-6.2).

- Very low quality evidence from 1 RCT (n=33) showed that when used as a secondary stent, there is a clinically important difference favouring partially-covered SEMS plastic stents on time to dysfunction in adults with unresectable pancreatic cancer compared to plastic stents: HR 6.69 (95% CI 1.39-32.07).
- Very low quality evidence from 1 RCT (n=31) showed that when used as a secondary stent, there is a clinically important difference favouring uncovered SEMS on time to dysfunction in adults with unresectable pancreatic cancer compared to plastic stents: HR 9.97 (95% CI 3.46-28.74).

Low quality evidence from 6 RCTs (n=471) showed that there is a clinically important difference favouring SEMS on the number of adults with pancreatic cancer who experience stent occlusion compared to plastic stents: RR 2.25 (95% CI 1.67-3.02).

- Very low quality evidence from 4 RCTs (n=258) showed that there is a clinically important difference favouring covered, partially-covered or uncovered SEMS on the number of adults with pancreatic cancer who experience stent occlusion compared to plastic stents: RR 2.2 (95% CI 1.45-3.35).
- Very low quality evidence from 2 RCTs (n=213) showed that there is a clinically important difference favouring covered SEMS on the number of adults with pancreatic cancer who experience stent occlusion compared to plastic stents: RR 2.3 (95% CI 1.51-3.49).
- Low quality evidence from 5 RCTs (n=417) showed that there is a clinically important difference favouring SEMS on the number of adults with unresectable pancreatic cancer who experience stent occlusion compared to plastic stents: RR 2.36 (95% CI 1.7-3.28).
- Low quality evidence from 1 RCT (n=54) showed that there is no clinically important difference between SEMS and plastic stents on the number of adults with resectable, borderline resectable, or locally advanced pancreatic cancer who experience stent occlusion: RR 1.73 (95% CI 0.89-3.34).

Very low quality evidence from 1 RCT (n=113) showed that there is no clinically important difference between plastic stents and SEMS on the number of adults with pancreatic cancer who experience stent migration: RR 0.19 (95% CI 0.02-1.57).

Very low quality evidence from 1 RCT (n=117) showed that there is a clinically important difference favouring partially-covered or uncovered SEMS on the number of adults with pancreatic cancer who experience either stent occlusion or stent migration compared to plastic stents: RR 2.42 (95% CI 1.44-4.06).

Relief of symptoms

No evidence was identified to inform this outcome.

Treatment-related mortality

Very low quality evidence from 1 RCT (n=100) showed no clinically important difference between plastic stents and SEMS on treatment-related mortality in adults with unresectable pancreatic cancer: RR 2.88 (95% CI 0.12-69.16).

Treatment-related morbidity

Low quality evidence from 1 RCT (n=34) showed that there is no clinically important difference between wing-shaped plastic stents and SEMS on the number of adults with unresectable biliary obstruction caused by pancreatic cancer whose serum bilirubin levels decrease by 30% or more after their insertion: RR 0.94 (95% CI 0.79-1.1).

Low quality evidence from 1 RCT (n=98) showed that there is no clinically important difference between plastic stents and SEMS on the rate of change in total serum bilirubin

(SMD 0.23 [95% CI -0.62-0.17]) after their insertion in adults with unresectable pancreatic cancer.

Treatment-related complications

Very low quality evidence from 7 RCTs (n=720) showed that there is no clinically important difference between plastic stents and SEMS on the number of adults with pancreatic cancer who experience pancreatitis after their insertion: RR 0.81 (95% CI 0.32-2.04).

- Very low quality evidence from 4 RCTs (n=473) showed that there is no clinically important difference between plastic stents and covered, partially covered or uncovered SEMS on the number of adults with pancreatic cancer who experience pancreatitis after their insertion: RR 1.02 (95% CI 0.36-2.92).
- Very low quality evidence from 2 RCTs (n=213) showed that there is no clinically important difference between plastic stents and covered, partially covered or uncovered SEMS on the number of adults with pancreatic cancer who experience pancreatitis after their insertion: RR 0.32 (95% CI 0.03-3.01).
- Very low quality evidence from 5 RCTs (n=632) showed that there is no clinically important difference between plastic stents and SEMS on the number of adults with unresectable pancreatic cancer who experience pancreatitis after their insertion: RR 1.52 (95% CI 0.51-4.59).
- Very low quality evidence from 1 RCT (n=54) showed that there is no clinically important difference between plastic stents and SEMS on the number of adults with resectable, borderline resectable or locally advanced pancreatic cancer who experience pancreatitis after their insertion: RR 0.12 (95% CI 0.01-2.01).

Low quality evidence from 4 RCTs (n=334) showed that there is a clinically important difference favouring SEMS on the number of adults with unresectable pancreatic cancer who experience cholangitis after their insertion compared to the insertion of plastic stents: RR 3.1 (95% CI 1.28-7.48).

- Very low quality evidence from 2 RCTs (n=152) showed that there is a clinically important difference favouring covered, partially-covered or uncovered SEMS on the number of adults with unresectable pancreatic cancer who experience cholangitis after their insertion compared to the insertion of plastic stents: RR 1.71 (95% CI 0.5-5.89).
- Very low quality evidence from 1 RCT (n=100) showed that there is no clinically important difference between plastic stents and covered SEMS on the number of adults with unresectable pancreatic cancer who experience cholangitis after their insertion: RR 4.81 (95% CI 0.24-97.68).
- Very low quality evidence from 1 RCT (n=82) showed that there is a clinically important difference favouring partially-covered SEMS on the number of adults with unresectable pancreatic cancer who experience cholangitis after their insertion compared to the insertion plastic stents: RR 5.0 (95% CI 1.17-21.43).

Very low quality evidence from 4 RCTs (n=448) showed that there is no clinically important difference between plastic stents and SEMS on the number of adults with unresectable pancreatic cancer who experience cholecystitis after their insertion: RR 0.47 (95% CI 0.15-1.53).

- Very low quality evidence from 2 RCTs (n=253) showed that there is no clinically important difference between plastic stents and covered, partially-covered or uncovered SEMS on the number of adults with unresectable pancreatic cancer who experience cholecystitis after their insertion: RR 2.56 (95% CI 0.33-20.1).
- Very low quality evidence from 1 RCT (n=82) showed that there is no clinically important difference between plastic stents and partially-covered SEMS on the number of adults with unresectable pancreatic cancer who experience cholecystitis after their insertion: RR 0.2 (95% CI 0.01-4.04).

- Very low quality evidence from 1 RCT (n=113) showed that there is no clinically important difference plastic stents and covered SEMS on the number of adults with unresectable pancreatic cancer who experience cholecystitis after their insertion: RR 0.11 (95% CI 0.01-1.91).

Very low quality evidence from 1 RCT (n=118) showed that there is no clinically important difference between plastic stents and covered SEMS on the number of adults with unresectable pancreatic cancer who experience post-endoscopic sphincterotomy haemorrhage after their insertion: RR 3.0 (95% CI 0.12-72.18).

Very low quality evidence from 2 RCTs (n=197) showed that there is no clinically important difference between plastic stents and SEMS on the number of days adults with unresectable pancreatic cancer are hospitalised after their insertion: SMD 0.49 (95% CI 0.21-0.77).

Overall survival

Very low quality evidence from 3 RCTS (n=247) showed no significant difference between plastic stents and SEMS on overall survival in adults with unresectable pancreatic cancer: HR 1 (95% CI 0.75-1.31).

Time to definitive treatment

No evidence was identified to inform this outcome.

Health-related quality of life

No evidence was identified to inform this outcome.

Patient experience

No evidence was identified to inform this outcome.

PROMS

No evidence was identified to inform this outcome.

9.1.6.2 Covered self-expanding metal stent versus uncovered self-expanding metal stent in adults with pancreatic cancer and biliary obstruction

Narrative summary for overall survival

The five included RCTs did not report data for overall survival in a way that allowed a meta-analysis. Overall the studies were at high risk of bias due to selective (e.g. incomplete) reporting of outcomes, other sources of bias (such as significant differences at baseline), and insufficient information about the randomisation method or allocation concealment. None of the studies reported the hazard ratios and associated 95% confidence intervals. Unlike the other studies – all of which used ‘standard’ covered SEMSs (e.g. with a silicone membrane) - Krokidis 2011 used an SEMS with an expanded polytetrafluoroethylene/fluorinated-ethylene-propylene covering. Median overall survival of a covered SEMS ranged from 116 days to 285 days (one study reported a mean of 71 days), whilst for an uncovered SEMS it ranged from 155 to 222 days. One study (Gardner et al., 2016) reported a mean overall survival of 71 (range 7-196) days for covered SEMS and 242 (range 122-453) days for an uncovered SEMS. One study (Krokidis et al., 2011) reported a near significant difference (p=0.06) on overall survival favouring a covered SEMS over an uncovered SEMS, three studies (Kitano et al., 2013, Kullman et al., 2010, Ung et al., 2013) reported no difference between them, and one study did not provide a p-value. However, all of the participants in this study were receiving neoadjuvant therapy.

Narrative summary for relief of obstruction (cumulative stent patency)

The five included RCTs did not report data for cumulative stent patency (time to obstruction) in a way that allowed a meta-analysis. Overall the studies were at high risk of bias due to selective (e.g. incomplete) reporting of outcomes, other sources of bias (such as significant differences at baseline), and insufficient information about the randomisation method or allocation concealment. None of the studies reported the hazard ratios and associated 95% confidence intervals. Unlike the other studies – all of which used 'standard' covered SEMSs (e.g. with a silicone membrane) - Krokidis 2011 used an SEMS with an expanded polytetrafluoroethylene/fluorinated-ethylene-propylene covering; all of the participants in this study were also receiving neoadjuvant therapy. Median stent patency for a covered SEMS ranged from 153 to 583 days, whilst for an uncovered SEMS it ranged from 127 to 314 days. One study (Gardner et al., 2016) reported a mean stent patency of 220 days (range 21-341) for a covered SEMS and 74 days (range 45-90) for an uncovered SEMS. Two studies (Kitano et al., 2013, Krokidis et al.,2011) reported a significant difference on stent patency favouring a covered SEMS over an uncovered SEMS, two studies (Kullman et al., 2010, Ung et al., 2013), reported no significant difference between them, whilst one study (Gardner et al., 2016) did not provide a p-value.

Relief of obstruction

Very low quality evidence from 5 RCTs (n=701) showed that there is no clinically important difference between covered and uncovered SEMS on the number of people experiencing stent dysfunction: RR 0.81 (95% CI 0.61-1.05).

- Very low quality evidence from 3 RCTs (n=600) showed that there is a clinically important difference favouring uncovered SEMS on the number of stent dysfunctions caused by sludge formation compared to covered SEMS in adults with pancreatic cancer and biliary obstruction: RR 2.43 (95% CI 1.22-4.85).
- Very low quality evidence from 2 RCTs (n=520) showed that there is no clinically important difference between covered and uncovered SEMS on the number of stent dysfunctions caused by stent migration in adults with pancreatic cancer and biliary obstruction: RR 13 (95% CI 0.74-229.23).
- Very low quality evidence from 3 RCTs (n=600) showed that there is a clinically important difference favouring covered SEMS on the number of stent dysfunctions caused by tumour ingrowth compared to uncovered SEMS in adults with pancreatic cancer and biliary obstruction: RR 0.36 (95% CI 0.2-0.64).
- Very low quality evidence from 3 RCTs (n=600) showed that there may be a clinically important difference favouring uncovered SEMS on the number of stent dysfunctions caused by tumour overgrowth compared to covered SEMS in adults with pancreatic cancer and biliary obstruction, although there is some uncertainty: RR 1.88 (95% CI 0.97-3.66).

Relief of symptoms

No evidence was identified to inform this outcome.

Treatment-related mortality

No evidence was identified to inform this outcome.

Treatment-related morbidity

No evidence was identified to inform this outcome.

Treatment-related complications

Very low quality evidence from 4 RCTs (n=668) showed that there is no clinically important difference between covered and uncovered SEMS on the number of adults with pancreatic cancer and biliary obstruction who experience adverse events: RR 0.89 (95% CI 0.52-1.51).

- Very low quality evidence from 1 RCT (n=400) showed that there is no clinically important difference between covered and uncovered SEMS on the number of adults with pancreatic cancer and biliary obstruction who experience cholangitis (RR 0.67 [95% CI 0.28-1.6]) and retroperitoneal perforation (RR 1.0 [95% CI 0.06-15.88]).
- Very low quality evidence from 2 RCTs (n=520) showed that there is no clinically important difference between covered and uncovered SEMS on the number of adults with pancreatic cancer and biliary obstruction who experience cholecystitis: RR 0.75 (95% CI 0.17-3.31).
- Very low quality evidence from 2 RCTs (n=480) showed that there is no clinically important difference between covered and uncovered SEMS on the number of adults with pancreatic cancer and biliary obstruction who experience haemorrhage: RR 0.71 (95% CI 0.14-3.52).
- Very low quality evidence from 3 RCTs (n=588) showed that there is no clinically important difference between covered and uncovered SEMS on the number of adults with pancreatic cancer and biliary obstruction who experience pancreatitis: RR 1.2 (95% CI 0.37-3.89).
- Very low quality evidence from 1 RCT (n=80) showed that there is no clinically important difference between covered and uncovered SEMS on the number of adults with pancreatic cancer and biliary obstruction who experience peritoneal irritation: RR 1.5 (95% CI 0.26-8.5).
- Very low quality evidence from 1 RCT (n=68) showed that there is no clinically important difference between covered and uncovered SEMS on the number of adults with pancreatic cancer and biliary obstruction who experience sepsis: RR 3.0 (95% CI 0.13-71.15).

Time to definitive treatment

No evidence was identified to inform this outcome.

Health-related quality of life

No evidence was identified to inform this outcome.

Patient experience

No evidence was identified to inform this outcome.

PROMS

No evidence was identified to inform this outcome.

9.1.6.3 Partially-covered self-expanding metal stent versus uncovered self-expanding metal stent in adults with pancreatic cancer and biliary obstruction

Narrative summary for overall survival and relief of obstruction (cumulative stent patency)

The two included RCTs did not report data for overall survival and cumulative stent patency (time to obstruction) in a way that allowed a meta-analysis. Overall the two studies were at high/unclear risk of bias due to selective reporting of outcomes. None of the studies reported

the hazard ratios and associated 95% confidence intervals. Only one study (Telford et al., 2010) reported median overall survival by group, which was not significant (227 days for a partially covered SEMS and 239 days for an uncovered SEMS). Median stent patency ranged from 285 to 357 days for a partially covered SEMS compared to268 to 711 days for an uncovered SEMS. One study (Telford et al., 2010) reported no significant difference between partially covered and uncovered SEMS, whilst one study (Walter et al, 2015) did not provide a p-value.

Relief of obstruction

Very low quality evidence from 2 RCTs (n=243) showed that there is no clinically important difference between partially-covered and uncovered SEMS on the number of adults with pancreatic cancer and biliary obstruction who experience stent dysfunction from any cause: RR 1.35 (95% CI 0.81-2.23)

Very low quality evidence from 1 RCT (n=129) showed that there may be a clinically important difference favouring uncovered SEMS on the number of stent dysfunctions caused by stent migration compared to a partially-covered SEMS in adults with pancreatic cancer and biliary obstruction: RR 15.28 (95% CI 0.9-259.23).

Relief of symptoms

No evidence was identified to inform this outcome.

Treatment-related mortality

No evidence was identified to inform this outcome.

Treatment-related morbidity

No evidence was identified to inform this outcome.

Treatment-related complications

Very low quality evidence from 1 RCT (n=129) showed that there may be a clinically important difference favouring uncovered SEMS on the number of adverse events compared to a partially-covered SEMS in adults with pancreatic cancer and biliary obstruction, although there is some uncertainty: RR 1.4 (95% CI 1.0-1.96).

- Very low quality evidence from 2 RCTs (n=-275) showed that there is no clinically important difference between partially-covered and uncovered SEMS on the number of adults with pancreatic cancer and biliary obstruction who experience pancreatitis (RR 0.97 [95% CI 0.14-6.58]) or other adverse events (RR 1.14 [95% CI 0.66-1.99]).
- Very low quality evidence from 2 RCTs (n=-237) showed that there is no clinically important difference between partially-covered and uncovered SEMS on the number of adults with pancreatic cancer and biliary obstruction who experience cholecystitis: RR 0.98 (95% CI 0.21-4.59).

Time to definitive treatment

No evidence was identified to inform this outcome.

Health-related quality of life

No evidence was identified to inform this outcome.

Patient experience

No evidence was identified to inform this outcome.

PROMS

No evidence was identified to inform this outcome.

9.1.6.4 Paclitaxel-eluting self-expanding metal stent versus covered self-expanding metal stent in adults with an unresectable distal malignant biliary obstruction

Relief of obstruction

Very low quality evidence from 1 RCT (n=52) showed that there is no clinically important difference between paclitaxel-eluting and covered SEMS on time to stent dysfunction in adults with an unresectable distal malignant biliary obstruction: HR 0.53 (95% CI 0.16-1.78).

- Very low quality evidence from 1 RCT (n=25) showed that there is no clinically important difference between paclitaxel-eluting and covered SEMS on increasing time to stent dysfunction in adults with an unresectable distal malignant biliary obstruction caused by pancreatic cancer: HR 0.52 (95% CI 0.1-3.09).

Relief of symptoms

No evidence was identified to inform this outcome.

Treatment-related mortality

No evidence was identified to inform this outcome.

Treatment-related morbidity

No evidence was identified to inform this outcome.

Treatment-related complications

Very low quality evidence from 1 RCT (n=52) showed that there is no clinically important difference between paclitaxel-eluting and covered SEMS on the number of adults with an unresectable distal malignant biliary obstruction who experience cholangitis symptoms (RR 7.28 [95% CI 0.4-133.89]) and pancreatitis (RR 1.04 [95% CI 0.07-15.73]) within 30 days of surgery.

Overall survival

Very low quality evidence from 1 RCT (n=52) showed that there is no clinically important difference between paclitaxel-eluting and covered SEMS on overall survival in adults with an unresectable distal malignant biliary obstruction: HR 1.19 (95% CI 0.65-2.18).

- Very low quality evidence from 1 RCT (n=25) showed that there is no clinically important difference between paclitaxel-eluting and covered SEMS on overall survival in adults with an unresectable distal malignant biliary obstruction caused by pancreatic cancer: HR 0.85 (95% CI 0.35-2.06).

Very low quality evidence from 1 RCT (n=52) showed that there is no clinically important difference between paclitaxel-eluting and covered SEMS on the number of adults with an unresectable distal malignant biliary obstruction who experience stent occlusion: RR 0.65 (95% CI 0.25-1.71).

Time to definitive treatment

No evidence was identified to inform this outcome.

Health-related quality of life

No evidence was identified to inform this outcome.

Patient experience

No evidence was identified to inform this outcome.

PROMS

No evidence was identified to inform this outcome.

9.1.6.5 Preoperative endoscopic biliary drainage (PEBD) then surgery versus surgery in adults with suspected pancreatic cancer

Relief of obstruction

No evidence was identified to inform this outcome.

Relief of symptoms

No evidence was identified to inform this outcome.

Treatment-related mortality

Very low quality evidence from 1 RCT (n=196) showed that there is no clinically important difference between PEBD followed by surgery and surgery only in adults with pancreatic cancer on mortality at 120 days (RR 1.15 [95% CI 0.57-2.33]) nor on treatment-related mortality (RR 2.07 [95% CI 0.66-6.51]).

Very low quality evidence from 1 RCT (n=185) showed that there is no clinically important difference between PEBD followed by surgery and surgery only in adults with pancreatic cancer on mortality at 2 years: RR 0.96 (95% CI 0.84-1.09).

Treatment-related morbidity

No evidence was identified to inform this outcome.

Treatment-related complications

Very low quality evidence from 1 RCT (n=196) showed that there is a clinically important difference favouring surgery on the total number of adults with pancreatic cancer who experience protocol-specific complications (RR 1.87 [95% CI 1.42-2.46]), surgery-related complications (RR 1.26 [95% CI 0.91 to 1.76]), pre-surgery cholangitis (RR 12.44 [95% CI 3.04 to 50.89]), and the number that are hospitalised due to protocol-specific complications (RR 2.85 [95% CI 1.53-5.2]) compared to PEBD followed by surgery.

Very low quality evidence from 1 RCT (n=196) showed that there is a clinically important difference favouring surgery only on the rate of serious complications within 120 days of randomisation compared to PEBD followed by surgery: HR 1.86 (95% CI 1.41-2.45).

Very low quality evidence from 1 RCT (n=196) showed that there may be a clinically important difference favouring surgery only on the number of adults with pancreatic cancer

who experience pre-surgery pancreatitis compared to PEBD followed by surgery, although there may be some uncertainty: RR 13.83 [95% CI 0.8 to 238.96].

Very low quality evidence from 1 RCT (n=196) showed that there is no clinically important difference between PEBD followed by surgery and surgery only on the number of adults with pancreatic cancer who experience pre-surgery post-ERCP haemorrhage (RR 4.61 [95% CI 0.22-94.83]), pre-surgery perforation (RR 4.61 [95% CI 0.22 to 94.83]), surgery-related haemorrhage (RR 0.46 [95% CI 0.09-2.46]), surgery-related cholangitis (RR 0.92 (95% CI 0.19 to 4.45) and surgery-related pneumonia (RR 1.66 [95% CI 0.58 to 4.77]).

Overall survival

Very low quality evidence from 1 RCT (n=185) showed that there is no clinically important difference between PEBD followed by surgery and surgery only in adults with pancreatic cancer on overall survival at 2 years: HR 0.98 (95% CI 0.72-1.34).

- Very low quality evidence from 1 RCT (n=113) showed that there is no clinically important difference between PEBD followed by curative surgery and curative surgery only in adults with resectable or borderline resectable pancreatic cancer after undergoing resection on overall survival at 2 years: HR 0.98 (95% CI 0.72-1.34).
- Very low quality evidence from 1 RCT (n=67) showed that there is no clinically important difference between PEBD followed by palliative surgery and palliative surgery only in adults with unresectable pancreatic cancer on overall survival at 2 years: HR 1.02 (95% CI 0.63-1.67).

Time to definitive treatment

Very low quality evidence from 1 RCT (n=196) showed that there is a clinically important difference favouring surgery only on the delay to surgery in adults with pancreatic cancer compared to PEBD followed by surgery: MD 4.0 (95% CI 3.58-4.42).

Health-related quality of life

No evidence was identified to inform this outcome.

Patient experience

No evidence was identified to inform this outcome.

PROMS

No evidence was identified to inform this outcome.

9.1.6.6 Endoscopic sphincterotomy then stent versus stent in adults with unresectable pancreatic cancer

Relief of obstruction

Very low quality evidence from 3 RCTs (n=454) showed that there is no clinically important difference between endoscopic sphincterotomy followed by a stent and stent only on decreasing the number of adults with unresectable pancreatic cancer who experience stent occlusion (RR 0.91 [95% CI 0.55-1.52]), stent migration (RR 1.84 [95% CI 0.75 to 4.54]).

Relief of symptoms

No evidence was identified to inform this outcome

Treatment-related mortality

No evidence was identified to inform this outcome.

Treatment-related morbidity

Moderate quality evidence from 1 RCT (n=200) showed that there is no clinically important difference between endoscopic sphincterotomy followed by a stent and stent only on the number of adults with unresectable pancreatic cancer that die due to disease progression: RR 0.86 (95% CI 0.72-1.02).

Treatment-related complications

Very low quality evidence from 2 RCTs (n=376) showed that there is no clinically important difference between endoscopic sphincterotomy followed by a stent and stent only on the number of adults with unresectable pancreatic cancer who experience early complications within 30 days (RR 1.24 [95% CI 0.61 to 2.5]) and early stent-related pancreatitis (95% CI RR 1.11 [0.49 to 2.54]).

Low quality evidence from 1 RCT (n=200) showed that there is no clinically important difference between endoscopic sphincterotomy followed by a stent and stent only on the number of adults with unresectable pancreatic cancer who experience early stent-related complications within 30 days (RR 1.0 [95% CI 0.52 to 1.93]) and late stent-related complications after 30 days (RR 1.2 [95% CI 0.38 to 3.81]).

Very low quality evidence from 3 RCTs (n=450) showed that there is no clinically important difference between endoscopic sphincterotomy followed by a stent and stent only on the number of adults with unresectable pancreatic cancer who experience pancreatitis within 30 days: RR 1.11 (95% CI 0.49 to 2.54).

Low quality evidence from 1 RCT (n=194) showed that there is no clinically important difference between endoscopic sphincterotomy followed by a stent and stent only on the number of adults with unresectable pancreatic cancer who experience perforation within 30 days: RR 0.34 (95% CI 0.01-8.25).

Low quality evidence from 1 RCT (n=184) showed that there is no clinically important difference between endoscopic sphincterotomy followed by a stent and stent only on the number of adults with unresectable pancreatic cancer who experience cholecystitis within 30 days and after 30 days: RR 0.26 (95% CI 0.03-2.24) for both outcomes.

Very low quality evidence from 1 RCT (n=182) showed that there is no clinically important difference between endoscopic sphincterotomy followed by a stent and stent only on the number of adults with unresectable pancreatic cancer who experience cholangitis after 30 days: RR 1.04 (95% CI 0.55 to 1.98).

Overall survival

No evidence was identified to inform this outcome.

Time to definitive treatment

No evidence was identified to inform this outcome

Health-related quality of life

No evidence was identified to inform this outcome

Patient experience

No evidence was identified to inform this outcome

PROMS

No evidence was identified to inform this outcome

9.1.6.7 Endoscopic sphincterotomy then stent versus surgical bypass in adults with unresectable pancreatic cancer

Relief of obstruction

Low to very low quality evidence from 1 RCT (n=30) showed that there is no clinically important difference between endoscopic sphincterotomy followed by a covered stent and surgical bypass on relief of biliary obstruction in adults with unresectable pancreatic cancer: RR 1.0 (95% CI 0.88-1.13).

Relief of symptoms

No evidence was identified to inform this outcome.

Treatment-related mortality

No evidence was identified to inform this outcome.

Treatment-related morbidity

Low to very low quality evidence from 1 RCT (n=30) showed there is no clinically important difference between endoscopic sphincterotomy followed by a covered stent and surgical bypass on the number of people whose bilirubin level is less than 2.5 mg/dL on day 30 (RR 1 [95% CI 0.51 to 1.95]) nor on serum bilirubin levels at day 30 (MD -0.3 [95% CI -1.06-0.46]) in adults with unresectable pancreatic cancer.

Very low quality evidence from 1 RCT (n=30) showed that there is no clinically important difference between endoscopic sphincterotomy followed by a covered stent and surgical bypass on treatment-related morbidity in adults with unresectable pancreatic cancer: RR 0.75 (95% CI 0.2-2.79).

Treatment-related complications

Very low quality evidence from 1 RCT (n=30) showed that there is no clinically important difference between endoscopic sphincterotomy followed by a covered stent and surgical bypass on treatment-related hospitalisation (RR 1.5 [95% CI 0.71-3.16]), stent-related complications (RR 9 [95% CI 0.53-153.79]), treatment-related early complications (RR 0.6 [95% CI 0.17-2.07]), treatment-related late complications (RR 0.75 [95% CI 0.2- 2.79]), post-operative complications (RR 0.71 [95% CI 0.29-1.75]), pneumonia (RR 0.2 [95% CI 0.01-3.85]), post-ERCP pancreatitis (RR 3 [95% CI 0.13-68.26]) in adults with unresectable pancreatic cancer.

Overall survival

No evidence was identified to inform this outcome.

Time to definitive treatment

No evidence was identified to inform this outcome.

Health-related quality of life

Low quality evidence from 1 RCT (n=30) showed that there is a clinically important difference favouring endoscopic sphincterotomy followed by a covered stent on SF-36 overall quality of life scores at 30 days (SMD 0.78 [0.04-1.52]) and 60 days (SMD 0.75 [0.01-1.49]) in adults with unresectable pancreatic cancer, compared to surgical bypass.

Patient experience

No evidence was identified to inform this outcome.

PROMS

No evidence was identified to inform this outcome.

9.1.6.8 Endoscopic ultrasound-guided choledochoduodenostomy (EUS-CD) and stent versus percutaneous transhepatic biliary drainage (PTBD) in adults with an unresectable malignant biliary obstruction where either ERCP or EUS-guided transpapillary rendezvous has failed

Relief of obstruction

No evidence was identified to inform this outcome.

Relief of symptoms

No evidence was identified to inform this outcome.

Treatment-related mortality

No evidence was identified to inform this outcome.

Treatment-related morbidity

Very low quality evidence from 1 RCT (n=25) showed that there is no clinically important difference in the effect of EUS-CD compared to PTBD on total serum bilirubin at 7 days (SMD -0.53 [95% CI -1.33-0.27]) and 30 days (SMD 0.42 [95% CI -0.37-1.22]) in adults with unresectable malignant biliary obstruction where ERCP has failed.

Very low quality evidence from 1 RCT (n=25) showed that EUS-CD has a clinically significant benefit of lowering gamma glutamyl transferase levels at 7 days in adults with unresectable malignant biliary obstruction where ERCP has failed compared to PTBD: SMD -0.87 (95% CI -1.69- -0.05).

Very low quality evidence from 1 RCT (n=25) showed that EUS-CD may have a clinically significant benefit in lowering alkaline phosphatase levels at 7 days in adults with unresectable malignant biliary obstruction where ERCP has failed compared to PTBD, although there is some uncertainty: SMD -0.73 (95% CI -1.54-0.08).

Treatment-related complications

Very low quality evidence from 1 RCT (n=25) showed that there is no clinically important difference in the effect of EUS-CD compared to PTBD on the number of adults with unresectable malignant biliary obstruction where ERCP has failed who experience treatment-related complications: RR 0.62 (95% CI 0.12-3.07).

Overall survival

No evidence was identified to inform this outcome.

Time to definitive treatment

No evidence was identified to inform this outcome.

Health-related quality of life

Very low quality evidence from 1 RCT (n=25) showed that there is no clinically important difference in the effect of EUS-CD compared to PTBD on SF-36 quality of life scores at 7 days (SMD -0.29 [95% CI -1.08-0.5]) and 30 days (SMD -0.31 [95% CI -1.1-0.48]) in adults with unresectable malignant biliary obstruction where ERCP has failed.

Patient experience

No evidence was identified to inform this outcome.

PROMS

No evidence was identified to inform this outcome.

9.1.6.9 Endoscopic ultrasound-guided choledochoduodenostomy (EUS-CD) and stent versus surgical bypass in adults with an unresectable malignant biliary obstruction where ERCP has failed

Relief of obstruction

No evidence was identified to inform this outcome.

Relief of symptoms

No evidence was identified to inform this outcome.

Treatment-related mortality

No evidence was identified to inform this outcome.

Treatment-related morbidity

Very low quality evidence from 1 RCT (n=29) showed that there is no clinically important difference in the effect of EUS-CD after 7 days on the number of adults with unresectable malignant biliary obstruction (and where ERCP has failed) whose total serum bilirubin levels are reduced 50% or more compared to those who have surgical bypass: RR 0.77 (95% CI 0.54-1.09).

Very low quality evidence from 1 RCT (n=29) showed that EUS-CD may have a clinically significant effect on decreasing total serum bilirubin at 7 days compared to surgical bypass in adults with unresectable malignant biliary obstruction where ERCP has failed compared to those who have surgical bypass, although there is some uncertainty: MD 1.71 (95% CI -0.24-3.66).

Very low quality evidence from 1 RCT (n=29) showed that there is no clinically important difference in the effect of EUS-CD at 7 days on decreasing gamma glutamyl transferase (MD 116.46 [95% CI 34.63 to 198.29]) nor alkaline phosphatase (MD 64.54 [95% CI 16.34 to

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112.74]), compared to surgical bypass in adults with unresectable malignant biliary obstruction where ERCP has failed.

Very low quality evidence from 1 RCT (n=29) showed that there is no clinically important difference in the effect of EUS-CD at 30 days on decreasing total serum bilirubin (MD 0.26 [95% CI -0.37-0.89]), gamma glutamyl transferase (MD 53.83 [95% CI -20.42-128.08], nor alkaline phosphatase (MD 11.39 [95% CI -22.16-44.94]), compared to surgical bypass in adults with unresectable malignant biliary obstruction where ERCP has failed.

Very low quality evidence from 1 RCT (n=25) showed that there is no clinically important difference in the effect of EUS-CD at 60 days on decreasing total serum bilirubin (MD 0.06 [95% CI -0.31-0.43]), gamma glutamyl transferase (MD 0.22 [95% CI -16.88-17.32]), nor alkaline phosphatase (MD 4.79 [95% CI -7.11-16.69]) compared to surgical bypass in adults with unresectable malignant biliary obstruction where ERCP has failed.

Very low quality evidence from 1 RCT (n=13) showed that there is no clinically important difference in the effect of EUS-CD at 90 days on decreasing total serum bilirubin (MD 0.01 [95% CI -0.58-0.6]), gamma glutamyl transferase (MD 14.43 [95% CI -2.3-31.16]) nor alkaline phosphatase (MD 5.4 [95% CI -4.87-15.67]), compared to surgical bypass in adults with unresectable malignant biliary obstruction where ERCP has failed.

Treatment-related complications

Very low quality evidence from 1 RCT (n=29) showed that there is no clinically important difference in the effect of EUS-CD on the number of treatment-related complications compared to surgical bypass, in adults with unresectable malignant biliary obstruction where ERCP has failed: RR 1.61 (95% CI 0.31-8.24).

Overall survival

Very low quality evidence from 1 RCT (n=29) showed that there is no clinically important difference in the effect of EUS-CD on overall survival, compared to surgical bypass, in adults with unresectable malignant biliary obstruction where ERCP has failed: HR 0.64 (95% CI 0.23-1.8).

Time to definitive treatment

No evidence was identified to inform this outcome.

Health-related quality of life

Very low quality evidence from 1 RCT (n=29) showed that there is no clinically important difference in the effect of EUS-CD on improving SF-36 functional capacity at 7 days (MD 6.3 [95% CI -5.12-17.72]) and 30 days (MD 10.7 [95% CI 0.93-20.47]), compared to surgical bypass in adults with unresectable malignant biliary obstruction where ERCP has failed.

Very low quality evidence from 1 RCT (n=29) showed that there is no clinically important difference in the effect of EUS-CD on SF-36 physical health scores at 7 days (MD 1.5 [95% CI -11.76-14.76]) and 30 days (MD -4.9 [95% CI -18.55-8.75]) compared to surgical bypass, in adults with unresectable malignant biliary obstruction where ERCP has failed.

Very low quality evidence from 1 RCT (n=29) showed that there is no clinically important difference in the effect of EUS-CD on improving SF-36 pain scores at 7 days (MD -3.7 [95% CI -17.22-9.82]) and 30 days (MD 2.7 [95% CI -9.6-15.0]) compared to surgical bypass, in adults with unresectable malignant biliary obstruction where ERCP has failed.

Very low quality evidence from 1 RCT (n=29) showed that there is no clinically important difference in the effect of EUS-CD on improving SF-36 general health scores at 7 days (MD -

3.4 [95% CI -10.15-3.35]) and 30 days (MD -4.1 [95% CI -11.85-3.65]) compared to surgical bypass, in adults with unresectable malignant biliary obstruction where ERCP has failed.

Very low quality evidence from 1 RCT (n=29) showed that there is no clinically important difference in the effect of EUS-CD on improving SF-36 vitality scores at 7 days (MD 2.7 [95% CI -5.64-11.04]) and 30 days (MD 7.6 [95% CI -2.43-17.63]) compared to surgical bypass, in adults with unresectable malignant biliary obstruction where ERCP has failed.

Very low quality evidence from 1 RCT (n=29) showed that there is no clinically important difference in the effect of EUS-CD on improving SF-36 social role functioning scores at 7 days (MD -0.3 [95% CI -9.69-9.09]) and 30 days (MD 0.3 [95% CI -7.56-8.16]) compared to surgical bypass, in adults with unresectable malignant biliary obstruction where ERCP has failed.

Very low quality evidence from 1 RCT (n=29) showed that there is no clinically important difference in the effect of EUS-CD on improving SF-36 emotional role functioning scores at 7 days (MD 2.5 [95% CI -11.19-16.19]) and 30 days (MD 0.9 [95% CI -15.69-17.49]) compared to surgical bypass, in adults with unresectable malignant biliary obstruction where ERCP has failed.

Very low quality evidence from 1 RCT (n=29) showed that there is a clinically important difference in the effect of EUS-CD on improving SF-36 mental health scores at 7 days (MD 9.1 [95% CI 1.49-16.71]) and 30 days (MD 12.9 [95% CI 4.63-21.17]) compared to surgical bypass, in adults with unresectable malignant biliary obstruction where ERCP has failed.

Very low quality evidence from 1 RCT (n=26) showed that there is no clinically important difference in the effect of EUS-CD on improving SF-36 functional capacity scores at 60 days compared to surgical bypass, in adults with unresectable malignant biliary obstruction where ERCP has failed: MD 9.9 (95% CI 1.04-18.76).

Very low quality evidence from 1 RCT (n=13) showed that there is no clinically important difference in the effect of EUS-CD on improving SF-36 functional capacity scores at 90 days compared to surgical bypass, in adults with unresectable malignant biliary obstruction where ERCP has failed: MD -1.8 (95% CI -9.86-6.26).

Very low quality evidence from 1 RCT (n=26) showed that there is no clinically important difference in the effect of EUS-CD on improving SF-36 physical health scores at 60 days compared to surgical bypass, in adults with unresectable malignant biliary obstruction where ERCP has failed: MD 6.8 (95% CI -5.67-19.27).

Very low quality evidence from 1 RCT (n=13) showed that there is no clinically important difference in the effect of EUS-CD on improving SF-36 physical health scores at 90 days compared to surgical bypass, in adults with unresectable malignant biliary obstruction where ERCP has failed: MD -10.1 (95% CI -33.62-13.42).

Very low quality evidence from 1 RCT (n=26) showed that there is no clinically important difference in the effect of EUS-CD on improving SF-36 pain scores at 60 days compared to surgical bypass, in adults with unresectable malignant biliary obstruction where ERCP has failed: MD -4.4 (95% CI -17.51-8.71).

Very low quality evidence from 1 RCT (n=13) showed that there is no clinically important difference in the effect of EUS-CD on improving SF-36 functional capacity scores at 90 days compared to surgical bypass, in adults with unresectable malignant biliary obstruction where ERCP has failed: MD -15.3 (95% CI -27.76- -2.84).

Very low quality evidence from 1 RCT (n=26) showed that there is no clinically important difference in the effect of EUS-CD on improving SF-36 general health scores at 60 days compared to surgical bypass, in adults with unresectable malignant biliary obstruction where ERCP has failed: MD -3.3 (95% CI -10.58-3.98).

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Very low quality evidence from 1 RCT (n=13) showed that there is no clinically important difference in the effect of EUS-CD on improving SF-36 general health scores at 90 days compared to surgical bypass, in adults with unresectable malignant biliary obstruction where ERCP has failed: MD 4.5 (95% CI -7.44-16.44).

Very low quality evidence from 1 RCT (n=26) showed that there is no clinically important difference in the effect of EUS-CD on improving SF-36 vitality scores at 60 days compared to surgical bypass in adults with unresectable malignant biliary obstruction where ERCP has failed: MD 2.14 (95% CI -8.61-12.81).

Very low quality evidence from 1 RCT (n=13) showed that there is no clinically important difference in the effect of EUS-CD on improving SF-36 vitality scores at 90 days compared to surgical bypass, in adults with unresectable malignant biliary obstruction where ERCP has failed: MD 14.6 (95% CI -3.2-32.4).

Very low quality evidence from 1 RCT (n=26) showed that there is no clinically important difference in the effect of EUS-CD on improving SF-36 social role functioning scores at 60 days compared to surgical bypass, in adults with unresectable malignant biliary obstruction where ERCP has failed: MD -1.1 (95% CI -12.32-10.12).

Very low quality evidence from 1 RCT (n=13) showed that there is no clinically important difference in the effect of EUS-CD on improving SF-36 social role functioning scores at 90 days compared to surgical bypass in adults with unresectable malignant biliary obstruction where ERCP has failed: MD 1.5 (95% CI -9.73-12.73).

Very low quality evidence from 1 RCT (n=26) showed that there is no clinically important difference in the effect of EUS-CD on improving SF-36 emotional role functioning scores at 60 days compared to surgical bypass, in adults with unresectable malignant biliary obstruction where ERCP has failed: MD 9.5 (95% CI -11.05-30.05).

Very low quality evidence from 1 RCT (n=13) showed that there is no clinically important difference in the effect of EUS-CD on improving SF-36 emotional role functioning scores at 90 days compared to surgical bypass, in adults with unresectable malignant biliary obstruction where ERCP has failed: MD 8.7 (95% CI -15.33-32.73).

Very low quality evidence from 1 RCT (n=26) showed that there may be a clinically important difference in the effect of EUS-CD on improving SF-36 mental health scores at 60 days compared to surgical bypass, in adults with unresectable malignant biliary obstruction where ERCP has failed, although there is some uncertainty: MD 8.9 (95% CI 0.92-18.72).

Very low quality evidence from 1 RCT (n=14) showed that there is no clinically important difference in the effect of EUS-CD on improving SF-36 mental health scores at 90 days compared to surgical bypass, in adults with unresectable malignant biliary obstruction where ERCP has failed: MD 1.9 (95% CI -9.98-13.78).

Patient experience

No evidence was identified to inform this outcome

PROMS

No evidence was identified to inform this outcome

9.1.7 Recommendations

27. Offer resectional surgery rather than preoperative biliary drainage to people who:

- have resectable pancreatic cancer and obstructive jaundice and

- are well enough for the procedure and
- are not enrolled in a clinical trial that requires preoperative biliary drainage.

28. During attempted resection for pancreatic cancer, consider surgical biliary bypass if the cancer is found to be unresectable.

29. If biliary drainage is needed in a person with resectable pancreatic cancer and obstructive jaundice who is not yet fit enough for resectional surgery on the basis of the biliary obstruction, offer endoscopically placed self-expanding metal stents.

30. For people with suspected pancreatic cancer who may need their stent removed later on, consider endoscopically placed self-expanding fully covered metal stents.

31. Offer endoscopically placed self-expanding metal stents rather than surgical biliary bypass to people with unresectable pancreatic cancer.

9.1.8 Evidence to recommendations

9.1.8.1 Relative value placed on the outcomes considered

The committee considered relief of obstruction, relief of symptoms, treatment-related mortality, treatment related morbidity, treatment-related complications, overall survival, time to definitive treatment, health-related quality of life, patient experience and PROMS to be the critical outcomes for this question.

Patient experience and PROMS were not reported for any comparisons of interest. Relief of obstruction, relief of symptoms, treatment-related mortality and morbidity, time to definitive treatment and quality of life were only reported by a few studies. Treatment related complications and overall survival were reported by the majority of studies. The majority of studies also reported the outcome of stent dysfunction which the committee agreed was a useful outcome to consider.

9.1.8.2 Quality of evidence

The quality of the outcomes for the comparisons identified by this review were as follows:

- Plastic stent versus self-expanding metal stent (SEMS) – ranged from very low to low
- Covered SEMS versus uncovered SEMS – very low
- Partially-covered SEMS versus uncovered SEMS - very low
- Paclitaxel-eluting SEMS versus covered SEMS - very low
- Preoperative endoscopic biliary drainage then surgery versus surgery – very low
- Endoscopic sphincterotomy then stent versus stent – ranged from very low to moderate
- Endoscopic sphincterotomy then stent versus surgical bypass – ranged from very low to low
- Endoscopic ultrasound-guided choledochoduodenostomy (EUS-CD) versus percutaneous transhepatic biliary drainage – very low
- Endoscopic ultrasound-guided choledochoduodenostomy (EUS-CD) versus surgical bypass – very low

The committee noted that several of the studies included people who did not have pancreatic cancer. They agreed to focus on those studies which included at least 66% pancreatic

cancer as they considered this proportion would be high enough for the data to be representative of the population under consideration by this guideline.

The committee decided to include three studies that either had less than 66% pancreatic cancer patients or did not report the composition of the samples because the studied interventions were deemed to be sufficiently novel to merit consideration. Each of these studies was the only study that contributed data to the relevant three comparisons: paclitaxel-eluting SEMS versus covered SEMS; EUS-CD versus percutaneous transhepatic biliary drainage; and EUS-CD versus surgical bypass. In relation to the two studies on EUS-guided biliary drainage, it was unclear how many patients had pancreatic cancer and the sample sizes were very small so it was difficult to draw conclusions from these data. Given this, and the fact that this is a relatively new technique, the committee agreed not to make any recommendations about this intervention.

9.1.8.3 Consideration of clinical benefits and harms

The committee noted, based on the evidence, that preoperative biliary drainage was associated with an increased delay to surgery, more complications, more serious complications within 120 days, more hospitalisations and more people experiencing pre-surgery pancreatitis compared to surgery alone. Given this evidence, and the results of the published economic analysis showing that going straight to surgery was both cost saving and health improving, the committee made a strong recommendation to offer surgery to people with resectable pancreatic cancer. Based on their clinical knowledge, the committee also noted that there are ongoing clinical trials which require the insertion of a biliary stent to meet the inclusion criteria of the trial protocol. They were conscious that they did not want these recommendations to restrict entry into such clinical trials and therefore agreed to add a caveat that surgery should be offered, when outside of a clinical trial of preoperative biliary drainage.

The committee noted, based on the evidence, that the time to dysfunction was shorter with plastic stents compared with SEMS and that there was a decrease in stent occlusion and stent migration with SEMS. Moreover, whilst there was no difference in the number of people experiencing pancreatitis or cholecystitis with the different types of stent, the number of people experiencing cholangitis was lower after the insertion of an SEMS. Given this evidence, and the results of the bespoke economic model showing that SEMS was the most cost effective intervention, the committee made a strong recommendation for the use of SEMS, rather than plastic stents, in people with pancreatic cancer and biliary obstruction. They agreed, based on their knowledge and experience, that stent placement should be done endoscopically as this is safer than percutaneous insertion.

The committee noted, based on their experience, that sometimes a stent has to be inserted to relieve the biliary obstruction before it is known whether pancreatic cancer is the cause of this obstruction. In those people where pancreatic cancer does not turn out to be the cause of the obstruction, the stent is likely to need removal. The committee noted that the evidence comparing covered and partially covered SEMS with uncovered SEMS had not identified any clinically significant differences in effects between the two. However, they agreed based on their knowledge, that fully covered metal stents should be considered where it is possible that stent removal may be required, because it can be very difficult to remove uncovered or partially covered metal stents.

The committee noted that there would be a group of people who had biliary obstruction but whose pancreatic cancer was unresectable and recommendations were needed for this group too. Based on the evidence, the committee agreed that endoscopic stenting was associated with improvements in quality of life compared to surgical bypass. They, therefore, made a strong recommendation for endoscopic stenting in people with unresectable pancreatic cancer as stent placement would avoid a major operation in someone who was likely to be quite poorly. Based on their knowledge and experience the committee also

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agreed to recommend that surgical biliary bypass should be considered for people whose pancreatic cancer was deemed unresectable during an attempted resection. This would mean the person would not need to have a potential additional procedure in future to insert a stent.

Given that the data for the other comparisons of interest had not demonstrated any difference between interventions, the committee agreed not to make any further recommendations.

The committee considered that the potential benefits of the recommendations made would be earlier treatment of biliary obstruction, improved symptom control, a reduction in the complications associated with stent insertion (as metal stents are less likely to occlude or migrate than plastic stents) and avoidance of unnecessary repeat stenting procedures (as metal stents are less likely to become dysfunctional). The committee noted that the potential harms could be duodenal perforation, bleeding and post procedure pancreatitis from stenting or biliary leaking and anastomotic leakage from surgical bypass. However, without these interventions the person would die so they considered that the harms were balanced by the potential benefits.

9.1.8.4 Consideration of economic benefits and harms

The literature search for previous economic evaluations identified 2 relevant economic evaluations (Morris [2015] and Arguedas [2002]). Both economic evaluations considered different interventions in different patient groups and therefore meaningful comparisons between the studies could not be drawn. A bespoke economic model was also built to help inform recommendations.

Morris (2015) compared preoperative biliary drainage (PBD) to direct surgery in patients with potentially resectable pancreatic or periampullary cancer and obstructive jaundice from a UK NHS and PSS perspective. The study was deemed to only have minor methodological limitations.

The effectiveness side of the model was nearly entirely based on one Cochrane Review of six RCTs comparing PBD to direct surgery. The utility values for the model were taken from patient responses to the EQ-5D questionnaire, scored using the UK population weightings and completed by people with hepatic colorectal metastases. As this was not the patient group considered by the model the committee found it difficult to say whether quality of life would be similar between these groups. The study did report that the trends closely matched those reported in disease specific quality of life measures for pancreatic cancer. However, the results of the model were not sensitive to this input and it was unlikely to change the preferred option. Costs inputs for the model were all sourced from NHS reference costs.

The model concluded that sending patients directly to surgery led to a cost saving of £2,552 per patient. It led to a small increase in health of 0.006 QALYS. This result was robust to all sensitivity analyses performed. Probabilistic sensitivity analysis showing a strategy of PBD prior to surgery being the preferred option in less than 10% of iterations when a £20,000 per QALY willingness to pay is assumed.

The committee were broadly in agreement with the inputs and findings of the economic analysis although raised concerns that issues of capacity (for example, operating theatres and surgeons being available when needed) had not been considered by the model. The committee agreed that this could be dealt with through reorganisation of surgical set-ups with no, or very limited, additional costs as there would be no increase in total number of operations. Whilst this reorganisation could be done in multiple ways, where costs were incurred they were likely to be in employing a coordinator for facilitating immediate access. Even with this wage cost, including on-costs, the conclusions of the economic evaluation were unlikely to be changed. The committee were, therefore, able to make a strong

recommendation for sending patients with resectable pancreatic cancer and obstructive jaundice directly to surgery.

Arguedas (2002) compared plastic stenting to metal stenting in patients with pancreatic cancer and obstructive jaundice presenting for palliative biliary stenting. The study took a US Societal Perspective and was deemed to have very serious methodological limitations. The study estimated that initial stenting with metal stents would lead to a cost saving of US$433 and a health increase of 0.033 QALYs. This result was robust to all parameters apart from length of survival. Given the age of the study, the US societal perspective, methodological issues, and that a contemporary bespoke economic model had been built to answer an almost identical decision problem from a UK NHS and PSS perspective, the committee did not use this study in informing their recommendations.

The bespoke economic model considered three possible strategies for biliary stenting in patients with unresectable or metastatic pancreatic cancer and obstructive jaundice. The model compared a strategy of initial stenting with a plastic stent followed by stenting with a self-expanding metal stent (SEMS) upon dysfunction and initial stenting with SEMS replaced/repositioned upon dysfunction with a base case strategy of initial plastic stenting replaced with plastic stents upon dysfunction. The study took a UK NHS and PSS perspective and considered a 2 year time horizon which was adequate to represent the lifetime of over 99% of the patient group.

Clinical inputs and baseline values were largely taken from the accompanying clinical evidence review and cost inputs were exclusively taken from NHS reference costs. The utility values in the base-case were taken from a patient group, identical to that considered in the economic model, using the EQ-5D questionnaire and scored using Dutch population values. The questionnaire was completed alongside an RCT identified in the clinical evidence review. The hazard ratio for overall survival between plastic and metal stents in the clinical evidence review was equal to 1 (no difference) and there was no difference in deterioration in EQ-5D reported in the identified study. Therefore, the base case for the model assumed no difference on these parameters between the three strategies and the base case analysis became a de-facto cost minimisation. The committee, however, considered, based on their clinical experience, that quality of life, through reduced adverse events and lower need for repeat surgery would improve and therefore a secondary analysis was performed using the values reported in the same study but using the visual analogue scale. This measure reported that quality of life deteriorated at a lower rate with SEMS compared to plastic stents although this was not statistically significant.

In the base case a strategy of initial metal stenting followed by subsequent metal stenting was the least costly with a saving of over £1,500 per patient. When QoL was also considered it led to a small increase in QoL of 0.024 QALYs per patient. This result was only sensitive to overall survival with plastic stenting followed by plastic stenting becoming the least costly when survival was less than 24 days. The robustness of the result is supported by the probabilistic sensitivity analysis. The initial stenting with SEMS strategy is cost saving compared to plastic stenting followed by plastic stenting in 98% of iterations. The conclusions were broadly identical to that of Arguedas (2002), with metal stents being cost saving and results only being sensitive to survival. Although, given the differences between the studies described above, there is little validity to any comparison.

The committee, therefore, made a strong recommendation supporting the use of SEMS in this patient group. The economic model attempted to look at the type of SEMS used (covered, partially covered, uncovered) but results disaggregated by SEMS type were reported inconsistently and it was difficult to consider them as separate analyses. The 3 types of stents though have almost identical costs and the decision of which type to use was based on clinical and not economic considerations.

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9.1.9 References

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9.2 Duodenal obstruction

Review question: What is the optimal treatment of duodenal obstruction?

9.2.1 Introduction

Tumour invasion into the duodenum can result in obstruction to the flow of ingested food and secretions from the stomach into the duodenum. Gastric outflow obstruction results in recurrent large volume vomiting, fullness, dehydration and malnutrition. Duodenal obstruction is usually associated with advanced and unresectable pancreatic tumours and occurs in up to 20% of patients with pancreatic cancer.

When duodenal obstruction occurs in association with an operable tumour the definitive management of the obstruction will occur with resection of the tumour. For the majority of patients with duodenal obstruction who have inoperable disease, the options are between palliative surgery (gastrojejunostomy) to bypass the obstruction or the endoscopic placement of a self-expanding metal stent (SEMS). Placement of a SEMS may be tolerated better by frail individuals and are thought to be associated with faster recovery and symptom improvement, however the improvement may not be as marked or as durable as that achieved with surgery.

A proportion of individuals who undergo surgery with curative intent will be found to have inoperable disease at the time of surgery and will therefore not have a resection. Some of these individuals will subsequently develop duodenal obstruction due to disease progression. Prophylactic gastrojejunostomy performed during the operation when curative surgery is deemed not to be feasible may prevent the later development of duodenal obstruction.

Guidance is needed on the optimal treatment of duodenal obstruction in people with pancreatic cancer.

9.2.1.1 Review protocol summary

The review protocol summary used for this question can be found in Table 109. Full details of the review protocol can be found in Appendix C.

Table 109: Clinical review protocol summary for the review of optimal treatment of duodenal obstruction

Population	• Patients with duodenal obstruction • Resectable pancreatic cancer • Borderline resectable pancreatic cancer • Unresectable or metastatic pancreatic cancer
Intervention	• Duodenal stent placement • Gastric/duodenal bypass surgery (gastrojejunostomy [GJJ]) • Venting gastrostomy • Resectional surgery
Comparison	• Each Other • Pharmacological management • Best supportive care
Outcome	• Relief of obstruction • Change in symptoms • Nutritional status • Adverse events • Overall Survival • Health-related Quality of Life • Patient experience • PROMS

9.2.2 Description of Clinical Evidence

Six studies –2 RCTs (Lillemoe et al. 1999; Van Heek et al. 2004) from a recent Cochrane review (Gurusamy et al. 2013), and an additional 4 RCTs (Okuwaki et al. 2016; Jeurnink et al. 2010; Mehta et al. 2006; Shyr et al. 1997) were included in the evidence review. All the studies were in adults. A summary of the included studies is presented in Table 110.

Two RCTs (n=157) from a Cochrane review (Gurusamy et al. 2013) that compared prophylactic gastrojejunostomy (GJJ) combined with hepaticojejunostomy with hepaticojejunostomy only in patients with unresectable pancreatic cancer were included (Lillemoe et al. 1999; Van Heek et al. 2004).

Two RCTs (n=66) were found that compared laparoscopic GJJ with duodenal stenting as a means of palliating malignant gastric outflow obstruction in patients with pancreatic cancer (Jeurnink et al. 2010; Mehta et al. 2006). The sample in Metha et al. (2006) had only 56% pancreatic cancer patients and was thus downgraded for indirectness.

One RCT (n=45) was found that compared three types of GJJ for duodenal obstruction in patients with unresectable periampullary cancer (Shyr et al, 1997). Although the sample had only 51% pancreatic cancer patients, the study was included and downgraded for indirectness. The three types of GJJ differed according to the site of jejunum for the GJJ and the partition of duodenum: Type 1 (GJJ proximal to the Jejunal limb: Ligament of Treitz), Type 2 (Pylorus) and Type 3 (GJJ proximal to Roux-limb Jejunum).

One RCT (n=34) was found that compared two types of duodenal stents (WallFlex™ duodenal stent [W-group] and Niti-S™ pyloric/duodenal D-type stent) with different axial

forces for alleviating duodenal obstruction in patients with pancreatobiliary cancer (Okuwaki et al. 2016). The sample in this study was 74% pancreatic cancer patients.

Further information about the search strategy can be found in Appendix D. See study selection flow chart in Appendix E, forest plots in Appendix H, GRADE tables in Appendix I, study evidence tables in Appendix F and list of excluded studies in Appendix G.

9.2.3 Summary of included studies

A summary of the studies that were included in this review are presented in Table 110.

Table 110: Summary of included studies

Study	Design	Population	Intervention	Comparison	Outcomes
Gurusamy et al. 2013	Systematic review with meta-analysis (Cochrane review) Searches up to August 2012	Two RCTs from this review were included: Lillemoe et al, 1999 N=87 unresectable pancreatic cancer patients + gastric outlet obstruction Van Heek 2003 N=70 unresectable pancreatic cancer patients + gastric outlet obstruction	Routine prophylactic gastrojejunostomy (open or laparoscopic)	No prophylactic gastrojejunostomy	Relief of obstruction (gastric outlet obstruction) Adverse effects (Peri-operative morbidity) Overall Survival Health-related Quality of Life
Jeurnink et al. 2010	Multicentre non-blinded RCT	N=39 pancreatic cancer patients + gastric outlet obstruction	Gastrojejunostomy (open or laparoscopic and either antecolic or retrocolic)	Duodenal stent placement (Enteral Wallstent)	Relief of obstruction Change in symptoms Nutritional status Adverse events
Metha et al. 2006	Single centre non-blinded RCT	N=27 patients with malignant gastric outflow obstruction (56% pancreatic cancer)	Laparoscopic gastrojejunostomy	Duodenal stent placement (Enteral Wallstent)	Overall Survival Health-related Quality of Life PROMS
Okuwaki et al. 2016	Single centre non-blinded RCT	N=34 patients with pancreatobiliary cancer (74% pancreatic cancer) + duodenal obstruction	WallFlex™ duodenal uncovered SEMS	Niti-S™ pyloric/duodenal D-type uncovered SEMS	Relief of obstruction Change in symptoms Nutritional status Adverse events Overall Survival

Study	Design	Population	Intervention	Comparison	Outcomes
Shyr et al. 1997	Single centre non-blinded RCT	N=45 with unresectable periampullary cancer (51% pancreatic cancer) + gastric outlet obstruction	Type I Gastrojejunostomy proximal to the Jejunal limb: Ligament of Treitz	Type II Gastrojejunostomy beyond pylorus Type III Gastrojejunostomy proximal to Roux-limb Jejunum	Change in symptoms Nutritional status

Source/Note: *SEMS, self-expanding metal stent*

9.2.4 Clinical evidence profile

The clinical evidence profiles for this review question are presented in Table 111 to Table 116.

Table 111: Summary clinical evidence profile for prophylactic gastrojejunostomy (GJJ) and hepaticojejunostomy versus hepaticojejunostomy only in adults with unresectable pancreatic cancer and gastric outlet obstruction

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	HJJ only	Prophylactic GJJ + HJJ				
Relief of obstruction (Gastric outlet obstruction) Follow-up: 1 months	278 per 1000	31 per 1000 (8 to 111)	RR 0.11 (0.03 to 0.4)	152 (2 studies[1])	⊕⊕⊖⊖ low[2]	
Adverse events (Perioperative morbidity) - Peri-operative mortality Follow-up: 1 months	0 per 1000	0 per 1000 (0 to 0)	RR 2.43 (0.1 to 57.57)	152 (2 studies[1])	⊕⊖⊖⊖ very low[2,3]	
Adverse events (Perioperative morbidity) - Cholangitis Follow-up: 1 months	47 per 1000	91 per 1000 (18 to 471)	RR 1.95 (0.38 to 10.12)	87 (1 study[1])	⊕⊖⊖⊖ very low[2,3,4]	
Adverse events (Perioperative morbidity) - Bile leak Follow-up: 1 months	42 per 1000	51 per 1000 (12 to 222)	RR 1.23 (0.28 to 5.34)	152 (2 studies[1])	⊕⊖⊖⊖ very low[2,3]	
Adverse events (Perioperative morbidity) - Gastroenteral leak Follow-up: 1 months	14 per 1000	11 per 1000 (1 to 171)	RR 0.81 (0.05 to 12.33)	152 (2 studies[1])	⊕⊖⊖⊖ very low[2,3]	
Adverse events (Perioperative morbidity) - Delayed gastric emptying Follow-up: 1 months	28 per 1000	75 per 1000 (14 to 391)	RR 2.71 (0.52 to 14.08)	152 (2 studies[1])	⊕⊖⊖⊖ very low[2,3]	
Adverse events (Perioperative morbidity) - Wound infection	14 per 1000	43 per 1000 (7 to 255)	RR 3.09 (0.52 to 18.36)	152 (2 studies[1])	⊕⊖⊖⊖ very low[2,3]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	HJJ only	Prophylactic GJJ + HJJ				
Follow-up: 1 months						
Adverse events (Perioperative morbidity) - Chest complications Follow-up: 1 months	56 per 1000	24 per 1000 (4 to 131)	RR 0.44 (0.08 to 2.35)	152 (2 studies[2])	⊕⊖⊖⊖ very low[2,3]	
Adverse events (Perioperative morbidity) - Cardiac complications Follow-up: 1 months	69 per 1000	111 per 1000 (22 to 565)	RR 1.61 (0.32 to 8.19)	65 (1 study[1])	⊕⊖⊖⊖ very low[2,3,4]	
Overall survival	403 per 1000	409 per 1000 (351 to 475)	HR 1.02 (0.84 to 1.25)	152 (2 studies)	⊕⊕⊖⊖ low[2,5]	
Health Related Quality of Life (EORTC QoL) EORTC	See comment	See comment	No data reported	65 (1 study[4])	⊕⊕⊖⊖ low[4]	No sig. diff. in QoL at any time point

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes.*

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio; QoL: Quality of Life

1 Lillemoe et al. 1999, Van Heek et al. 2003
2 Potential risk of performance bias (no blinding of outcome assessors) in both RCTs. Van Heek et al. 2003 also had incomplete data (3 patients lost to follow up) and potential selective reporting of outcomes (no data provided for quality of life outcomes).
3 95% CI crosses 2 default MIDs (0.8 and 1.25).
4 van Heek et al. 2003
5 The committee decided to downgrade survival outcomes by one level if the difference in survival was not statistically significant.

Table 112: Summary clinical evidence profile for GJJ versus duodenal stent placement in adults with pancreatic cancer and gastric outlet obstruction

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Duodenal stent placement	GJJ				
Relief of obstruction (Days with GOOSS score >= 2 after	See comment	See comment	Not estimable	39 (1 study[1])	⊕⊕⊖⊖ low[2]	Food intake improved in a long term period after GJJ (median

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Duodenal stent placement	GJJ				
intervention - median)						72[GJJ] vs. 50[Stent] days, P = 0.05).
Change in symptoms - Persistent obstructive symptoms - Persistent obstructive symptoms	143 per 1000	167 per 1000 (39 to 726)	RR 1.17 (0.27 to 5.08)	39 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Change in symptoms - Persistent obstructive symptoms - Recurrent obstructive symptoms	238 per 1000	55 per 1000 (7 to 433)	RR 0.23 (0.03 to 1.82)	39 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Nutritional status - Days to restore ability to eat (median)	See comment	See comment	Not estimable	39 (1 study[1])	⊕⊕⊖⊖ low[2]	Food intake improved more rapidly after stent placement (median 8[GJJ] vs. 5[Stent] days, P < 0.01).
Adverse events - Minor complications	190 per 1000	278 per 1000 (88 to 882)	RR 1.46 (0.46 to 4.63)	39 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Adverse events - Major complications	190 per 1000	25 per 1000 (2 to 427)	RR 0.13 (0.01 to 2.24)	39 (1 study[1,4])	⊕⊖⊖⊖ very low[2,3]	
Overall survival	400 per 1000	340 per 1000 (130 to 711)	HR 0.81 (0.27 to 2.44)	27 (1 study[5])	⊕⊖⊖⊖ very low[2,6,7]	
Health Related Quality of Life: SF-36 - Physical Health score Follow-up: 1 months	The mean health related quality of life: sf-36 - physical health score in the control groups	The mean health related quality of life: sf-36 - physical health score in the intervention groups was 7.9 lower (22.74 lower to 6.94 higher)		25 (1 study[5])	⊕⊖⊖⊖ very low[2,6,8,9]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Duodenal stent placement	**GJJ**				
	was 41.2					
Health Related Quality of Life: SF-36 - Mental Health score Follow-up: 1 months	The mean health related quality of life: sf-36 - mental health score in the control groups was 45	The mean health related quality of life: sf-36 - mental health score in the intervention groups was 0.7 higher (18.29 lower to 19.69 higher)		25 (1 study[5])	⊕⊖⊖⊖ very low[2,6,8,9]	
PROMS - Self-report Pain (Visual Analog Scale) Follow-up: 1 months	The mean proms - self-report pain (visual analogue scale) in the control groups was 2.4	The mean proms - self-report pain (visual analogue scale) in the intervention groups was 2 higher (0.36 lower to 4.36 higher)		25 (1 study[5])	⊕⊖⊖⊖ very low[2,6,8,10]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes.*

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;

1 Jeurnink et al. 2010
2 The quality of the evidence was downgraded because of the unclear risk of selection bias and the potential risk of performance bias (no blinding of outcome assessors).
3 95% CI crosses 2 default MID (0.8 and 1.25).
4 Follow-up not clear.
5 Metha et al. 2006
6 Metha et al. 2006 sample had less than 66% pancreatic cancer patients.
7 The committee decided to downgrade survival outcomes by one level for imprecision only if the difference in survival was statistically significant.
8 MIDs for SF-36 subscales and pain score were calculated as +/- 0.5 SD of control arm at baseline and were as follows: +/- 6.41 for physical health subscale; +/- 11.78 for mental health subscale; +/- 1,39 for pain score.
9 95% CI crosses 2 MIDs for this outcome.
10 95% CI crosses 1 MID for this outcome.

Table 113: Summary clinical evidence profile for Type I GJJ (proximal to the Jejunal limb: Ligament of Treitz) versus Type II GJJ (Pylorus) in adults with pancreatic cancer and gastric outlet obstruction

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Type II GJJ Pylorus	Type I GJJ proximal to the Jejunal limb: Ligament of Treitz				
Change in symptoms - GOO overall GOO Follow-up: 1 months	133 per 1000	467 per 1000 (115 to 1000)	RR 3.5 (0.86 to 14.18)	30 (1 study)	⊕⊖⊖⊖ very low[1,2,3]	
Change in symptoms (GOO) - Anorexia GOO Follow-up: 1 months	0 per 1000	0 per 1000 (0 to 0)	RR 3 (0.13 to 68.26)	30 (1 study[4])	⊕⊖⊖⊖ very low[1,2,5]	
Change in symptoms (GOO) - Epigastric fullness GOO Follow-up: 1 months	67 per 1000	133 per 1000 (13 to 1000)	RR 2 (0.2 to 19.78)	30 (1 study[4])	⊕⊖⊖⊖ very low[1,2,5]	
Change in symptoms (GOO) - Nausea GOO Follow-up: 1 months	0 per 1000	0 per 1000 (0 to 0)	RR 3 (0.13 to 68.26)	30 (1 study[4])	⊕⊖⊖⊖ very low[1,2,5]	
Change in symptoms (GOO) - Vomiting GOO Follow-up: 1 months	0 per 1000	0 per 1000 (0 to 0)	RR 7 (0.39 to 124.83)	30 (1 study[4])	⊕⊖⊖⊖ very low[1,2,5]	
Nutritional status - Gastric emptying time Follow-up: 1 months	The mean nutritional status - gastric emptying time in the control groups was 118.1 min	The mean nutritional status - gastric emptying time in the intervention groups was 40.8 higher (67.85 lower to 149.45 higher)		30 (1 study[4])	⊕⊖⊖⊖ very low[1,2,6,7]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Type II GJJ Pylorus	Type I GJJ proximal to the Jejunal limb: Ligament of Treitz				
Nutritional status - Patients with delayed gastric emptying Follow-up: 10 days	67 per 1000	200 per 1000 (23 to 1000)	RR 3 (0.35 to 25.68)	30 (1 study[4])	⊕⊖⊖⊖ very low[1,2]	
The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. *The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).* *CI: Confidence interval; RR: Risk ratio;*						
1 Quality of evidence was downgraded by 1 point owing to unclear risk of performance bias and unclear selective reporting *2 Sample had <66% pancreatic cancer patients.* *3 95% CI crosses 1 default MID (0.8 or 1.25).* *4 Shyr et al. 1997* *5 95% CI crosses 2 default MIDs (0.8 and 1.25).* *6 MIDs for nutritional status (gastric emptying time) were calculated as +/- SD of control group immediately after resumption of oral diet and was +/- 75.91 min.* *7 95% CI crosses 1 MID for this outcome.*						

Table 114: Summary clinical evidence profile for Type I GJJ (proximal to the Jejunal limb: Ligament of Treitz) versus Type III GJJ (proximal to Roux-limb Jejunum) in adults with pancreatic cancer and gastric outlet obstruction

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Type III GJJ proximal to Roux-limb Jejunum	Type I GJJ proximal to the Jejunal limb: Ligament of Treitz				
Change in symptoms - GOO overall Follow-up: 1 months	133 per 1000	467 per 1000 (115 to 1000)	RR 3.5 (0.86 to 14.18)	30 (1 study)	⊕⊖⊖⊖ very low[1,2,3]	
Change in symptoms (GOO) - Anorexia GOO	67 per 1000	67 per 1000 (5 to 970)	RR 1 (0.07 to 14.55)	30 (1 study[4])	⊕⊖⊖⊖ very low[1,2,5]	
Change in symptoms (GOO) - Epigastric	67 per 1000	133 per 1000 (13 to 1000)	RR 2 (0.2 to 19.78)	30 (1 study[4])	⊕⊖⊖⊖ very low[1,2,5]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
fullness GOO Follow-up: 1 months						
Change in symptoms (GOO) - Nausea GOO Follow-up: 1 months	0 per 1000	0 per 1000 (0 to 0)	RR 3 (0.13 to 68.26)	30 (1 study[4])	⊕⊖⊖⊖ very low[1,2,5]	
Change in symptoms (GOO) - Vomiting GOO Follow-up: 1 months	0 per 1000	0 per 1000 (0 to 0)	RR 7 (0.39 to 124.83)	30 (1 study[4])	⊕⊖⊖⊖ very low[1,2,5]	
Nutritional status - Gastric emptying time Follow-up: 1 months	The mean nutritional status - gastric emptying time in the control groups was 245.3 min	The mean nutritional status - gastric emptying time in the intervention groups was 86.4 lower (192.05 lower to 19.25 higher)		30 (1 study[4])	⊕⊖⊖⊖ very low[1,2,6,7]	
Nutritional status - Patients with delayed gastric emptying Follow-up: 10 days	67 per 1000	200 per 1000 (23 to 1000)	RR 3 (0.35 to 25.68)	30 (1 study)	⊕⊖⊖⊖ very low[1,2,5]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes.*

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

1 Quality of evidence was downgraded by 1 point owing to unclear risk of performance bias and unclear selective reporting
2 Sample had <66% pancreatic cancer patients.
3 95% CI crosses 1 default MID (0.8 or 1.25).
4 Shyr et al. 1997
5 95% CI crosses 2 default MIDs (0.8 and 1.25).
6 MIDs for nutritional status (gastric emptying time) were calculated as +/- SD of control group immediately after resumption of oral diet and was +/- 71.65 min.
7 95% CI crosses 1 MID for this outcome.

Table 115: Summary clinical evidence profile for Type II GJJ (Pylorus) versus Type III GJJ (proximal to Roux-limb Jejunum) in adults with pancreatic cancer and gastric outlet obstruction

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Type III GJJ proximal to Roux-limb Jejunum	Type II GJJ Pylorus				
Change in symptoms - GOO overall GOO Follow-up: 1 months	133 per 1000	67 per 1000 (7 to 659)	RR 0.5 (0.05 to 4.94)	30 (1 study[1])	⊕⊖⊖⊖ very low[2,3,4]	
Change in symptoms (GOO) - Anorexia Follow-up: 1 months	See comment	See comment	Not estimable	30 (1 study[1])	⊕⊕⊖⊖ low[2,3]	There were no events in either group
Change in symptoms (GOO) - Epigastric fullness GOO Follow-up: 1 months	67 per 1000	67 per 1000 (5 to 970)	RR 1 (0.07 to 14.55)	30 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Change in symptoms (GOO) - Nausea GOO Follow-up: 1 months	67 per 1000	22 per 1000 (1 to 505)	RR 0.33 (0.01 to 7.58)	30 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Change in symptoms (GOO) - Vomiting GOO Follow-up: 1 months	See comment	See comment	Not estimable	30 (1 study[1])	⊕⊕⊖⊖ low[2,3]	There were no events in either group
Nutritional status - Gastric emptying time Follow-up: 1 months	The mean nutritional status - gastric emptying time in the control groups was 245.3 min	The mean nutritional status - gastric emptying time in the intervention groups was 127.2 lower (232.85 to 21.55 lower)		30 (1 study[1])	⊕⊖⊖⊖ very low[2,3,5,6]	
Nutritional status - Patients	67 per 1000	67 per 1000 (5 to 970)	RR 1 (0.07 to 14.55)	30 (1 study[1])	⊕⊖⊖⊖ very low[2,3,4]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Type III GJJ proximal to Roux-limb Jejunum	Type II GJJ Pylorus				
with delayed gastric emptying Follow-up: 10 days						
The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. *The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).* *CI: Confidence interval; RR: Risk ratio;*						
1 Shyr et al. 1997 *2 Quality of evidence was downgraded by 1 point owing to unclear risk of performance bias and unclear selective reporting* *3 Sample had <66% pancreatic cancer patients.* *4 95% CI crosses 2 default MIDs (0.8 and 1.25).* *5 MIDs for nutritional status (gastric emptying time) were calculated as +/- SD of control group immediately after resumption of oral diet and was +/- 71.65 min.* *6 95% CI crosses 1 MID for this outcome.*						

Table 116: Summary clinical evidence profile for duodenal stent-1 versus duodenal stent-2 in adults with pancreatic cancer and duodenal obstruction

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Duodenal stent-2 (Niti-S)	Duodenal stent-1 (WallFlex)				
Relief of obstruction - Mean change in GOO score at 2 weeks	The mean relief of obstruction - mean change in goo score at 2 weeks in the control groups was 1.5 GOO score	The mean relief of obstruction - mean change in goo score at 2 weeks in the intervention groups was 0.37 standard deviations higher (0.34 lower to 1.09 higher)		31 (1 study[1])	⊕⊕⊖⊖ low[2,3,4]	
Relief of obstruction - GOO recurrence Follow-up: 2 weeks	235 per 1000	285 per 1000 (87 to 941)	RR 1.21 (0.37 to 4)	31 (1 study[1])	⊕⊖⊖⊖ very low[2,5]	
Change in symptoms - Mean change	The mean change in symptoms -	The mean change in symptoms -		31 (1 study[1])	⊕⊕⊖⊖ low[2,3,4]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Duodenal stent-2 (Niti-S)	Duodenal stent-1 (WallFlex)				
in NVSS score	mean change in NVSS score in the control groups was -1.9 NVSS score	mean change in NVSS score in the intervention groups was 0.28 standard deviations higher (0.43 lower to 0.99 higher)				
Nutritional status- Mean change in BMI at 4 weeks	The mean nutritional status- mean change in BMI at 4 weeks in the control groups was 0.1 kg/m2	The mean nutritional status- mean change in BMI at 4 weeks in the intervention groups was 0.3 lower (1.22 lower to 0.62 higher)		30 (1 study[1])	⊕⊕⊕⊖ moderate [2]	
Adverse events (procedure-related) Follow-up: 30 days	235 per 1000	285 per 1000 (87 to 941)	RR 1.21 (0.37 to 4)	31 (1 study[1])	⊕⊖⊖⊖ very low[1,5]	
HRQL - Mean change in Karnofsky performance score at 2 weeks	The mean HRQL - mean change in Karnofsky performance score at 2 weeks in the control groups was 9 KPS score	The mean HRQL - mean change in Karnofsky performance score at 2 weeks in the intervention groups was 5.2 higher (5.47 lower to 15.87 higher)		27 (1 study[1])	⊕⊕⊖⊖ low[2,3,6]	
HRQL - Mean change in Performance score at 2 weeks	The mean HRQL - mean change in performance score at 2 weeks in the control groups was -0.5	The mean HRQL - mean change in performance score at 2 weeks in the intervention groups was 0.1 lower (0.69 lower to 0.49 higher)		31 (1 study[1])	⊕⊕⊖⊖ low[2,3,6]	
Overall survival	-	-	HR 0.53 (0.26 to 1.08)	31 (1 study[1])	⊕⊕⊖⊖ low[2,7]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Duodenal stent-2 (Niti-S)	Duodenal stent-1 (WallFlex)				
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;						
1 Okuwaki et al. 2016 2 Unclear randomisation method and whether blinded. 3 MIDs for change in BMI, change in Karnofsky Performance Score and change in Performance Score were calculated as +/- 0.5 SD of control arm at baseline and were as follows: +/- 1.4 kg/m2 for change in BMI, +/- 9.5 for Karnofsky Performance Score, and +/- 0.55 for Performance Score. MIDs for change in GOO score and change in NVSS score were assumed to be the default MIDs for continuous outcomes expressed as an SMD (i.e. +/- 0.5) due to insufficient baseline data. 4 95% CI crosses 1 default MID for SMDs (0.5 or -0.5). 5 95% CI crosses 2 default MIDs (0.8 and 1.25). 6 95% CI crosses 1 MID for this outcome. 7 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant.						

9.2.5 Economic evidence

A literature review of published cost effectiveness analyses did not identify any relevant studies for this topic. Although there were potential implications for resource use associated with making recommendations in this area, other topics in the guideline were agreed as a higher economic priority. Consequently, bespoke economic modelling was not done for this topic.

9.2.6 Evidence Statements

9.2.6.1 Prophylactic GJJ and hepaticojejunostomy versus hepaticojejunostomy only

Relief of obstruction

Low quality evidence from 2 RCTs (n=152) showed that there is a clinically important difference favouring prophylactic gastrojejunostomy combined with hepaticojejunostomy on relief of obstruction compared to hepaticojejunostomy only in adults with unresectable pancreatic cancer and gastric outlet obstruction: RR 0.11 (95% CI 0.03-0.4).

Change in symptoms

No evidence was identified to inform this outcome.

Nutritional status

No evidence was identified to inform this outcome.

Adverse events

Low quality evidence from 2 RCTs (n=152) showed no clinically important difference between prophylactic gastrojejunostomy combined with hepaticojejunostomy and hepaticojejunostomy only on peri-operative mortality (RR 2.43 [95% CI 0.1-57.57]), bile leak (RR 1.23 [95% CI 0.28-5.34]), gastroenteral leak (RR 0.81 [95% CI 0.05-12.33]), delayed

gastric emptying (RR 2.71 [95% CI 0.52-14.08]), wound infection (RR 3.09 [95% CI 0.52-18.36]), and chest complications (RR 0.44 [95% CI 0.08-2.35]) in adults with unresectable pancreatic cancer and gastric outlet obstruction.

Very low quality evidence from 1 RCT (n=87) showed no clinically important difference between prophylactic gastrojejunostomy combined with hepaticojejunostomy and hepaticojejunostomy only on cholangitis in adults with unresectable pancreatic cancer and gastric outlet obstruction: RR 1.95 (95% CI 0.38-10.12).

Very low quality evidence from 1 RCT (n=65) showed no clinically important difference between prophylactic gastrojejunostomy combined with hepaticojejunostomy and hepaticojejunostomy only on cardiac complications in adults with unresectable pancreatic cancer and gastric outlet obstruction: RR 1.61 (95% CI 0.32-8.19).

Overall survival

Low quality evidence from 2 RCTs (n=152) showed no clinically important difference between prophylactic gastrojejunostomy combined with hepaticojejunostomy and hepaticojejunostomy only on overall survival in adults with unresectable pancreatic cancer and gastric outlet obstruction: HR 1.02 (95% CI 0.84-1.25).

Health-related quality of life

Low quality evidence from 1 RCT (n=65) reported no statistically significant difference between prophylactic gastrojejunostomy combined with hepaticojejunostomy and hepaticojejunostomy only on EORTC quality of life at any time point in adults with unresectable pancreatic cancer and gastric outlet obstruction (no data reported).

Patient experience

No evidence was identified to inform this outcome.

PROMS

No evidence was identified to inform this outcome.

9.2.6.2 GJJ versus duodenal stent placement

Relief of obstruction

Low quality evidence from 1 RCT (n=39) reported a statistically significant difference favouring duodenal stent placement on the number of days with a Gastric Outlet Obstruction Scoring System score of 2 or more compared to gastrojejunostomy (median 72 days vs 50 days, p=0.05) in adults with pancreatic cancer and gastric outlet obstruction.

Very low quality evidence from 1 RCT (n=39) showed no clinically important difference between gastrojejunostomy and duodenal stent placement on either persistent obstructive symptoms (RR 1.17 [95% CI 0.27-1.72]) or recurrent obstructive symptoms (RR 0.23 [95% CI 0.03-1.82]) in adults with pancreatic cancer and gastric outlet obstruction.

Change in symptoms

No evidence was identified to inform this outcome.

Nutritional status

Low quality evidence from 1 RCT (n=39) reported a statistically significant difference favouring duodenal stent placement on the number of days to restore the ability to eat compared to gastrojejunostomy (median 8 days vs 5 days, p<0.01) in adults with pancreatic cancer and gastric outlet obstruction.

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Adverse events

Very low quality evidence from 1 RCT (n=39) showed no clinically important difference between gastrojejunostomy and duodenal stent placement on either major complications (RR 0.13 [95% CI 0.01-2.24]) or minor complications (RR 1.46 [95% CI 0.46-4.63]) in adults with pancreatic cancer and gastric outlet obstruction.

Overall survival

Very low quality evidence from 1 RCT (n=27) showed no clinically important difference between gastrojejunostomy and duodenal stent placement on overall survival in adults with pancreatic cancer and gastric outlet obstruction: HR 0.81 (95% CI 0.27-2.44).

Health-related quality of life

Very low quality evidence from 1 RCT (n=25) showed no clinically important difference between gastrojejunostomy and duodenal stent placement on either the SF-36 physical health (MD -7.9 [95% CI -22.74 to 6.94]) or mental health (MD 0.7 [95% CI -18.29 to 19.69]) subscales in adults with pancreatic cancer and gastric outlet obstruction.

Patient experience

No evidence was identified to inform this outcome.

PROMS

Very low quality evidence from 1 RCT (n=25) showed no clinically important difference between gastrojejunostomy and duodenal stent placement on self-reported pain visual analogue scale in adults with pancreatic cancer and gastric outlet obstruction: MD 2.0 (95% CI -0.36 to 4.36).

9.2.6.3 Types of gastrojejunostomy

9.2.6.3.1 Type I GJJ (proximal to the Jejunal limb: Ligament of Treitz) versus Type II GJJ (Pylorus)

Relief of obstruction

No evidence was identified to inform this outcome.

Change in symptoms

Very low quality evidence from 1 RCT (n=30) showed that there may be a clinically important difference favouring Type I gastrojejunostomy (proximal to the Jejunal limb: Ligament of Treitz) on change in clinical symptoms as assessed by the Gastric Outlet Obstruction Scoring System compared to Type II gastrojejunostomy (Pylorus) in adults with pancreatic cancer and gastric outlet obstruction, although there is some uncertainty: RR 3.5 (95% CI 0.86-14.18).

Very low quality evidence showed no clinically important difference between Type I gastrojejunostomy (proximal to the Jejunal limb: Ligament of Treitz) and Type II gastrojejunostomy (Pylorus) on change in symptoms of anorexia (RR 3.0 [95% CI 0.13-68.26]), epigastric fullness (RR 2.0 [95% CI 0.2-19.78]), nausea (RR 3.0 [95% CI 0.13-68.26]) and vomiting (RR 7.0 [95% CI 0.39-124.83]) as assessed by the Gastric Outlet Obstruction Scoring System in adults with pancreatic cancer and gastric outlet obstruction.

Nutritional status

Very low quality evidence from 1 RCT (n=30) showed no clinically important difference between Type I gastrojejunostomy (proximal to the Jejunal limb: Ligament of Treitz) and Type II gastrojejunostomy (Pylorus) on either minutes to gastric emptying (MD 40.8 [95% CI -

67.85 to 149.45]) or the number of patients with delayed gastric emptying (RR 3.0 [95% CI 0.35-25.68]) in adults with pancreatic cancer and gastric outlet obstruction.

Adverse events

No evidence was identified to inform this outcome.

Overall survival

No evidence was identified to inform this outcome.

Health-related quality of life

No evidence was identified to inform this outcome.

Patient experience

No evidence was identified to inform this outcome.

PROMS

No evidence was identified to inform this outcome.

9.2.6.3.2 Type I GJJ (proximal to the Jejunal limb: Ligament of Treitz) versus Type III GJJ (proximal to Roux-limb Jejunum)

Relief of obstruction

No evidence was identified to inform this outcome.

Change in symptoms

Very low quality evidence from 1 RCT (n=30) showed that there may be a clinically important difference favouring Type I gastrojejunostomy (proximal to the Jejunal limb: Ligament of Treitz) on change in clinical symptoms as assessed by the Gastric Outlet Obstruction Scoring System compared to Type III gastrojejunostomy (proximal to Roux-limb Jejunum) in adults with pancreatic cancer and gastric outlet obstruction, although there is some uncertainty: RR 3.5 (95% CI 0.86-14.18).

Very low quality evidence showed no clinically important difference between Type I gastrojejunostomy (proximal to the Jejunal limb: Ligament of Treitz) and Type III gastrojejunostomy (proximal to Roux-limb Jejunum) on change in symptoms of anorexia (RR 1.0 [95% CI 0.07-14.55]), epigastric fullness (RR 2.0 [95% CI 0.2-19.78]), nausea (RR 3.0 [95% CI 0.13-68.26]) and vomiting (RR 7.0 [95% CI 0.39-124.83]) as assessed by the Gastric Outlet Obstruction Scoring System in adults with pancreatic cancer and gastric outlet obstruction.

Nutritional status

Very low quality evidence from 1 RCT (n=30) showed no clinically important difference between Type I gastrojejunostomy (proximal to the Jejunal limb: Ligament of Treitz) and Type III gastrojejunostomy (proximal to Roux-limb Jejunum) on either minutes to gastric emptying (MD -86.4 [95% CI -192.05 to 19.25]) or the number of patients with delayed gastric emptying (RR 3.0 [95% CI 0.35-25.68]) in adults with pancreatic cancer and gastric outlet obstruction.

Adverse events

No evidence was identified to inform this outcome.

Overall survival

No evidence was identified to inform this outcome.

Health-related quality of life

No evidence was identified to inform this outcome.

Patient experience

No evidence was identified to inform this outcome.

PROMS

No evidence was identified to inform this outcome.

9.2.6.3.3 Type II GJJ (Pylorus) versus Type III GJJ (proximal to Roux-limb Jejunum)

Relief of obstruction

No evidence was identified to inform this outcome.

Change in symptoms

Very low quality evidence from 1 RCT (n=30) showed no clinically important difference between Type II gastrojejunostomy (Pylorus) and Type III gastrojejunostomy (proximal to Roux-limb Jejunum) on change in clinical symptoms as assessed by the Gastric Outlet Obstruction Scoring System in adults with pancreatic cancer and gastric outlet obstruction: RR 0.5 (95% CI 0.05-4.94).

Very low quality evidence showed no clinically important difference between Type II gastrojejunostomy (Pylorus) and Type III gastrojejunostomy (proximal to Roux-limb Jejunum) on change in symptoms of epigastric fullness (RR 1.0 [95% CI 0.07-14.55]), and nausea (RR 0.33 [95% CI 0.01-7.58]) as assessed by the Gastric Outlet Obstruction Scoring System in adults with pancreatic cancer and gastric outlet obstruction. (There were also no events on symptoms of anorexia and vomiting.)

Nutritional status

Very low quality evidence from 1 RCT (n=30) showed that there is a clinically important difference favouring Type II gastrojejunostomy (Pylorus) on minutes to gastric emptying compared to Type III gastrojejunostomy (proximal to Roux-limb Jejunum) in adults with pancreatic cancer and gastric outlet obstruction: MD -127.2 (95% CI -232.85 to -21.55).

Very low quality evidence showed no clinically important difference between Type II gastrojejunostomy (Pylorus) and Type III gastrojejunostomy (proximal to Roux-limb Jejunum) on the number of patients with delayed gastric emptying in adults with pancreatic cancer and gastric outlet obstruction: RR 1.0 (95% CI 0.07-14.55).

Adverse events

No evidence was identified to inform this outcome.

Overall survival

No evidence was identified to inform this outcome.

Health-related quality of life

No evidence was identified to inform this outcome.

Patient experience

No evidence was identified to inform this outcome.

PROMS

No evidence was identified to inform this outcome.

9.2.6.4 Duodenal stent-1 versus duodenal stent-2

Relief of obstruction

Very low quality evidence from 1 RCT (n=31) showed no clinically important difference between WallFlex™ duodenal stents and Niti-S™ pyloric/duodenal D-type stents on the number of people who had recurrence of obstruction as assessed by the Gastric Outlet Obstruction Scoring System at 2 weeks in adults with pancreatic cancer and duodenal obstruction: RR 1.21 (95% CI 0.37-4.0).

Change in symptoms

Low quality evidence from 1 RCT (n=31) showed no clinically important difference between WallFlex™ duodenal stents and Niti-S™ pyloric/duodenal D-type stents on mean change on the Gastric Outlet Obstruction Scoring System at 2 weeks in adults with pancreatic cancer and duodenal obstruction: SMD 0.37 (95% CI -0.34 to 1.09).

Nutritional status

Moderate quality evidence from 1 RCT (n=31) showed no clinically important difference between WallFlex™ duodenal stents and Niti-S™ pyloric/duodenal D-type stents on mean change on BMI at 4 weeks, in adults with pancreatic cancer and duodenal obstruction: MD -0.3 (95% CI -1.22 to 0.62).

Adverse events

Low to very low quality evidence from 1 RCT (n=31) showed no clinically important difference between WallFlex™ duodenal stents and Niti-S™ pyloric/duodenal D-type stents on either mean change in Nausea and Vomiting Scoring System score (SMD 0.28 [95% CI -0.43 to 0.99]) or the number of procedure-related adverse events (RR 1.21 [95% CI 0.37-4.0]) in adults with pancreatic cancer and duodenal obstruction.

Overall survival

Low quality evidence from 1 RCT (n=31) showed no clinically important difference between WallFlex™ duodenal stents and Niti-S™ pyloric/duodenal D-type stents on overall survival in adults with pancreatic cancer and duodenal obstruction: HR 0.52 (95% CI 0.26-1.08).

Health-related quality of life

Low quality evidence from 1 RCT (n=31) showed no clinically important difference at 2 weeks between WallFlex™ duodenal stents and Niti-S™ pyloric/duodenal D-type stents on either mean change in Karnofsky Performance Score (MD 5.2 [95% Ci -5.47 to 15.87]) or mean change in Performance Score (MD -0.1 [95% CI -0.69 to 0.49]) in adults with pancreatic cancer and duodenal obstruction

Patient experience

No evidence was identified to inform this outcome.

PROMS

No evidence was identified to inform this outcome.

9.2.7 Recommendations

32. During attempted resection for head of pancreas cancer, consider prophylactic gastrojejunostomy if the cancer is found to be unresectable.

33. If possible, relieve symptomatic duodenal obstruction caused by unresectable pancreatic cancer.

34. When deciding between gastrojejunostomy and duodenal stent placement, consider gastrojejunostomy for people with a more favourable prognosis.

9.2.8 Evidence to recommendations

9.2.8.1 Relative value placed on the outcomes considered

Relief of obstruction, change in symptoms, nutritional status, adverse events, overall survival, health-related quality of life, patient reported outcome measures and patient experience were considered to be the critical outcomes for this question.

Adverse events, overall survival and health-related quality of life were reported for all comparisons of interest except for gastrojejunostomy with duodenal partition versus other gastrojejunostomy types. Change in symptoms and nutritional status were reported for all comparisons of interest except prophylactic gastrojejunostomy versus no prophylactic gastrojejunostomy.

Relief of obstruction was only reported for duodenal stent placement and the comparison of prophylactic gastrojejunostomy with no prophylactic gastrojejunostomy. Patient reported outcome measures was only reported for the comparison of gastrojejunostomy with duodenal stent placement. Patient experience was not reported for any of the comparisons of interest.

The committee noted that the data on patient reported outcome measures looked at a self-reported pain score. They agreed that it was not possible to determine whether the pain was generated by the procedure or by the tumour itself, and consequently did not use this outcome when making recommendations.

9.2.8.2 Quality of evidence

The quality of the evidence was assessed by GRADE and the Cochrane risk of bias checklist. The evidence was either very low or low quality for all outcomes across all comparisons of interest.

The committee noted that the study looking at gastrojejunostomy with duodenal partition versus other gastrojejunostomy types was conducted in China. They considered that it had limited relevance to the UK setting, particularly because it used a type of gastrojejunostomy which is not done in the UK. The committee, therefore, agreed not to use the results of this study when making their recommendations.

The committee agreed that the study comparing different types of stent for relieving duodenal obstruction was not useful when making recommendations. This study was conducted in Japan and so had limited relevance to the UK healthcare setting. In addition, the aim of the study was to compare the effectiveness of two different types of stent. Given that there are several other types of stent available, which the study did not investigate, the committee agreed it would be difficult to draw robust conclusions as to which specific stent should be used.

The committee noted that the studies comparing gastrojejunostomy with duodenal stent placement had excluded people who were unfit for surgery. This is not representative of the group of people who get duodenal obstruction.

No evidence was found on the effectiveness of venting gastrostomy or resectional surgery for treating duodenal obstruction. Consequently, the committee did not make any recommendations for clinical practice for these interventions. The committee agreed that conducting further research in this area would not be practical because it would not be feasible to randomise people to these interventions and, therefore, did not make any research recommendations either.

The committee were not able to make any recommendations for people with resectable pancreatic cancer who have duodenal obstruction as there was no evidence available on this population.

9.2.8.3 Consideration of clinical benefits and harms

Due to the low quality evidence the committee was not able to make any strong recommendations.

The committee agreed, based on their knowledge and experience, that it is very important to relieve duodenal obstruction in people with unresectable pancreatic cancer. However they also recognised that people with unresectable pancreatic cancer may have more extensive disease, or may be too unwell for intervention, and this may make it difficult to relieve the obstruction. They, therefore, agreed to recommend that the obstruction should be relieved if possible.

The committee noted that the available evidence was of low quality and only covered some of the interventions of interest which made it difficult to specify the most effective method to relieve the obstruction. The evidence indicated a trend that stent placement was more effective in the short term whilst gastrojejunostomy was more effective in the longer term. This accorded with the committee's knowledge and experience that gastrojejunostomy is normally done only in people likely to have longer overall survival because of the morbidity associated with surgery. They, therefore, agreed to recommend both duodenal stents and gastrojejunostomy as options for people with duodenal obstruction with gastrojejunostomy being considered for people with a more favourable prognosis.

Based on the evidence, the committee noted that prophylactic gastrojejunostomy was associated with less gastric outlet obstruction and no difference in the proportion of people developing adverse events. The committee noted, based on their knowledge and experience, that duodenal obstruction is a recognised complication of pancreatic cancer. It is associated with significant co-morbidities and is known to have a detrimental effect on quality of life. They, therefore, agreed that, in people with large tumours who were felt to be at risk of duodenal obstruction who were otherwise fit and had a relatively good prognosis, the prophylactic use of gastrojejunostomy could be considered.

The committee agreed that the potential benefits of the recommendations made would be symptom relief by an appropriate technique and improved quality of life. The potential harms of the recommendations made would be potential complications of surgery or stent insertion. The committee agreed that the potential benefits for the person would outweigh the risk of harm.

9.2.8.4 Consideration of economic benefits and harms

The committee noted that no relevant published economic evaluations had been identified and no additional economic analysis had been undertaken in this area.

The committee noted that current practice is for people with duodenal obstruction to receive a stent or a gastrojejunostomy. Both of these interventions are still options in the recommendations. The committee considered that the costs of stent placement and gastrojejunostomy are broadly similar. The stent insertion procedure is more expensive than a gastrojejunostomy but the length of hospital stay is normally shorter for stent placement and, therefore, associated with less cost than the hospital stay for a gastrojejunostomy. Therefore, whilst it is possible that the balance between stent placement and gastrojejunostomy may alter, the committee agreed this was unlikely to have a significant resource impact. The committee also noted that the recommendation for prophylactic gastrojejunostomy was unlikely to cause significant resource impact because the procedure will be done at the same time as the resectional surgery.

9.2.9 References

Gurusamy KS, Kumar S, Davidson BR (2013) Prophylactic gastrojejunostomy for unresectable periampullary carcinoma. The Cochrane Library

Jeurnink SM, Polinder S, Steyerberg EW et al. (2010) Cost comparison of gastrojejunostomy versus duodenal stent placement for malignant gastric outlet obstruction. Journal of Gastroenterology 45(5): 537-43

Mehta S, Hindmarsh A, Cheong E, et al. (2006) Prospective randomized trial of laparoscopic gastrojejunostomy versus duodenal stenting for malignant gastric outflow obstruction. Surgical Endoscopy and Other Interventional Techniques 20(2): 239-42

Okuwaki K, Kida M, Yamauchi H, Imaizumi H, Miyawaza S, Iwai T, Masutani H, Matsumoto T, Hasegawa R, Koizumi W (2016) 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 Sciences 23(5): 289-97

Shyr YM, Su CH, King KL et al. (1997) Randomized trial of three types of gastrojejunostomy in unresectable periampullary cancer. Surgery 121(5): 506-12

9.2.9.1 Studies included from Gurusamy et al. (2013)

Lillemoe KD, Cameron JL, Hardacre JM et al. (1999) Is prophylactic gastrojejunostomy indicated for unresectable periampullary cancer?: a prospective randomized trial. Annals of Surgery 230(3): 322

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10 Management of resectable and borderline resectable pancreatic cancer

10.1 Neo-adjuvant treatment

Review question: Is neoadjuvant therapy for people with resectable and borderline resectable pancreatic adenocarcinoma an effective treatment?

10.1.1 Introduction

At best, only around 10% of people with pancreatic cancer are diagnosed early enough to undergo surgical resection of their cancer. However, the outcomes after surgery performed with curative intent are poor. Most people die from metastatic pancreatic cancer, which suggests that most people have disseminated disease before their primary surgery which is not identified by current staging investigations. An additional concern is that, while adjuvant therapy has been shown to improve survival rates, some people are unable to benefit from this treatment because of complications associated with the complex, major surgery involved in removing pancreatic cancer. There is therefore a theoretical justification for offering people non-surgical treatments in advance of primary surgery.

Neoadjuvant therapy aims to improve the success of surgery, increase the proportion of people able to access perioperative treatment, and ultimately improve overall survival from pancreatic cancer. Currently, there is uncertainty about the effectiveness of neoadjuvant therapy for pancreatic cancer, yet some centres offer such treatments routinely. The modalities being used as neoadjuvant treatment for resectable or borderline resectable disease include chemotherapy, radiotherapy, or combinations of these approaches.

Guidance is needed on whether there is a role for neoadjuvant therapy and if so, which type of neoadjuvant therapy is the most effective, compared with standard surgery for resectable and borderline resectable pancreatic cancer.

10.1.1.1 Review protocol summary

The review protocol summary used for this question can be found in Table 117. Full details of the review protocol can be found in Appendix C.

Table 117: Clinical review protocol summary for the review of effectiveness of neoadjuvant therapy

Population	Adults with • Resectable pancreatic cancer • Borderline resectable pancreatic cancer
Intervention	• Chemotherapy + resectional Surgery • Radiotherapy (stereotactic) + resectional Surgery • Chemoradiotherapy + resectional Surgery • Sequential chemotherapy + chemoradiotherapy + resectional Surgery
Comparison	Resectional surgery
Outcomes	• Response to neoadjuvant treatment pre-surgery • Disease-free interval • Relapse-free survival

	• Overall Survival • Resection rate • Time from initiating treatment to Surgery • Adverse Events • Health Related Quality of Life • Patient experience

10.1.2 Description of Clinical Evidence

Five studies have been included in the evidence review: 2 systematic reviews (Festa et al. 2013, Liu et al. 2016), (including a total of 18 studies: Festa et al. (2013) included 10 studies (Le Scodan et al. 2009; Lee et al. 2012; Leone et al. 2013; Magnin et al. 2003; Massucco et al. 2006; Mehta et al. 2001; Pipas et al. 2005; Sahora et al. 2011a- 2011b; and Small et al. 2011); Liu et al. (2016) included 8 studies (Casadei et al. 2015; Golcher et al. 2008; Golcher et al. 2015; Papalezova et al. 2012; Satoi et al. 2009; Sho et al. 2013; Tzeng et al. 2014; Vento et al. 2007) and 3 prospective single-arm phase II clinical trials (Evans et al. 2008; Taksahaki et al. 2013; Varadhachary et al. 2008). A summary of the included studies is presented in Table 118.

One systematic review (Liu et al. 2016) compared neoadjuvant chemoradiotherapy then surgery with surgery only in patients with resectable pancreatic cancer (n=833). This review included 3 randomised phase II/III trials (Casadei et al. 2015; Golcher et al. 2008, 2015) and 5 retrospective comparative studies (Papalezova et al. 2012; Satoi et al. 2009; Sho et al. 2013; Tzeng et al. 2014; Vento et al. 2007).

Two prospective single-arm phase II trials (Evans et al. 2008; Takahashi et al. 2013) evaluated neoadjuvant chemoradiotherapy then surgery in adults with resectable pancreatic adenocarcinoma (n=274).

One systematic review (Festa et al. 2013) and one prospective single-arm phase II trial (Takahashi et al. 2013) evaluated chemoradiotherapy delivered pre-operatively in downstaging adults with borderline resectable pancreatic cancer (n=217). Festa et al. (2013) included 7 studies involving this population subgroup: 3 phase II trials (Le Scodan et al. 2009; Pipas et al. 2005; Small Jr et al. 2011) and 4 prospective studies (Leone et al. 2012; Magnin et al. 2003; Massucco et al. 2006; Mehta et al. 2001).

One prospective single-arm phase II trial (Takahashi et al. 2013) evaluated the safety of neoadjuvant chemoradiotherapy then surgery in adults with resectable or borderline resectable pancreatic cancer (n=268).

One systematic review (n=45) evaluated chemotherapy delivered pre-operatively in downstaging adults with borderline resectable pancreatic cancer (Festa et al. 2013). This review included 3 prospective trials involving this population subgroup: 2 phase II trials (Sahora et al. 2011a; Sahora et al. 2011b) and 1 prospective cohort study (Lee et al. 2012).

One prospective single-arm phase II trial (n=79) was found that evaluated pre-operative gemcitabine and cisplatin then gemcitabine-based chemoradiotherapy followed by surgery in patients with resectable pancreatic cancer (Varadhachary et al. 2008).

Where possible data were extracted from the included systematic reviews (Liu et al. 2016; Festa et al. 2013). When there was not enough detail included in the review, the full copy of the original studies (in the reviews) were checked for accuracy and completeness.

The AMSTAR (A Measurement Tool to Assess Systematic Reviews) Checklist was used to assess the methodological quality of systematic reviews; the Cochrane Collaboration's 'Risk of bias' tool was used to assess the risk of bias of randomised phase II/III clinical trials; and the Newcastle-Ottawa Scale (NOS) for assessing the risk of bias of non-randomised studies

(i.e. prospective single-arm phase II studies and retrospective comparative studies). Where possible, the risk of bias information was taken from the systematic reviews, though in some cases when there was insufficient detail included in the review, the original study was used to determine risk of bias.

Further information about the search strategy can be found in Appendix D. See study selection flow chart in Appendix E, forest plots in Appendix H, GRADE tables in Appendix I, study evidence tables in Appendix F and list of excluded studies in Appendix G.

10.1.3 Summary of included studies

A summary of the studies that were included in this review is presented in Table 118.

Table 118: Summary of included studies

Study	Study type	Participants	Interventions	Comparison	Outcomes
Evans et al. 2008	Design: single-arm phase II clinical trial Duration: 1998-2001 Country: USA	N=86 patients with resectable PC	CRT before surgery (GEM and 30 Gy in 10 fractions over 2 weeks)	Not applicable	Overall Survival Resection rate Time from initiating treatment to Surgery Adverse Events
Festa et al. 2013	Design: Systematic review with meta-analysis Searches up to September 2012	This review includes 5 phase II trials Pipas et al. 2005 (n=6*) Le Scodan et al. 2009 (n=41) Small et al. 2011 (n=10*) Sahora et al. 2011a (n=12*) Sahora et al. 2011b (n=15*) and 5 prospective observational studies Mehta et al. 2001 (n=15*) Magnin et al. 2003 (n=32) Massucco et al. 2006 (n=18*) Leone et al. 2012 (n=15*) Lee et al. 2012 (n=18*)	Pre-operative administration of chemotherapy, alone or in combination with radiotherapy then surgery^	Not applicable	SR: Response to neoadjuvant treatment pre- surgery Overall Survival Resection rate Adverse Events Included studies: No additional outcomes

Study	Study type	Participants	Interventions	Comparison	Outcomes
Liu et al. 2016	Design: Systematic review with meta-analysis Searches up to November 2014	This review includes 3 RCTs Casadei et al. 2015 (n=38) Golcher et al. 2015 (n=66) Golcher et al. 2008 (n=79) and 5 retrospective cohort studies: Papalezova et al. 2012 (n=236) Satoi et al. 2009 (n=68) Sho et al. 2013 (n=132) Tzeng 2014 (n=167) Vento et al. 2007 (n=47)	Neoadjuvant CRT then surgery	Surgery (PD) alone	SR: Overall Survival Resection rate Included studies: Response to neoadjuvant treatment pre- surgery (Casadei et al. 2015, Golcher et al. 2015) Adverse Events (Casadei et al. 2015, Golcher et al. 2015, Sho et al. 2013, Tzeng 2014, Vento et al. 2007)
Takahashi et al. 2013	Design: single-arm phase II clinical trial Duration: 2002-2011 Country: Japan	n= 268 patients with resectable (n=188) and BR resectable (n=80) PC	CRT then surgery^ Further details: GEM and 50 Gy (with a daily fraction of 2 Gy 5 times per week)	Not applicable	Overall Survival Resection rate Adverse Events
Varadhachary et al. 2008	Design: single-arm phase II clinical trial Duration: 2002-2006 Country: USA	N=90 patients with resectable PC	Chemotherapy then CRT before surgery Further details: GEM + cisplatin then GEM and 30 Gy	Not applicable	Overall Survival Time from initiating treatment to Surgery Adverse Events
* Patients were stratified as (1) unresectable or (2) borderline resectable. The number of patients refers to those participants with borderline resectable disease (those patients included in the meta-analysis) ^ only for patients presenting with resectable disease at restaging					

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10.1.4 Clinical evidence profile

The clinical evidence profiles for this review question are presented in Table 119 to Table 124.

Table 119: Summary clinical evidence profile for neoadjuvant chemoradiotherapy followed by surgery versus surgery alone in patients with resectable pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Surgery alone in patients with resectable PC	CRT followed by surgery				
Response to neoadjuvant treatment pre-surgery - radiological response RECIST criteria[1]	See comment		Not estimable	47 (2 studies[2])	⊕⊕⊖⊖ low[3,11]	Radiological response to CRT was rarely seen, whereas most patients had no change or progression
Response to neoadjuvant treatment pre-surgery - pathological response Rebekah criteria	See comment		Not estimable	18 (1 study[8])	⊕⊕⊖⊖ low[3,4]	Pathological response to CRT was slightly higher than the radiological (n=0 none; n=2 minimal; n=3 small; n=5 moderate and 1 large response)
Complete resection rate	595 per 1000	690 per 1000 (577 to 826)	RR 1.16 (0.97 to 1.39)	183 (3 studies[9])	⊕⊕⊖⊖ low[3,5]	
Overall survival	-	-	HR 0.85 (0.58 to 1.25)	104 (2 studies[2])	⊕⊖⊖⊖ very low[3,6,11]	
Adverse events - Postoperative complications	774 per 1000	665 per 1000 (364 to 1000)	RR 0.86 (0.47 to 1.57)	104 (2 studies[2])	⊕⊖⊖⊖ very low[3,7,11]	
Adverse events - Pancreatic fistula	324 per 1000	181 per 1000 (97 to 340)	RR 0.56 (0.3 to 1.05)	132 (1 study[9])	⊕⊖⊖⊖ very low[3,7,11]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Surgery alone in patients with resectable PC	CRT followed by surgery				
Adverse events - Postoperative bleeding	41 per 1000	23 per 1000 (5 to 107)	RR 0.56 (0.12 to 2.65)	346 (3 studies[15])	⊕⊖⊖⊖ very low[3,7,11]	
Adverse events - Acute toxicity of chemoradiotherapy NCI common toxicity criteria v2.0 and RTOG/EORTC recommendations	See comment		Not estimable	18 (1 study[12])	⊕⊕⊖⊖ low[3,4]	All patients experienced toxicities. 16 patients experienced hematologic toxicities, whereas 15 patients experienced non-hematologic toxicities

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio;

1 Therasse P, Arbuck SG, Eisenhauer EA et al (2000) New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205–216
2 Casadei et al. 2015, Golcher et al. 2015
3 Quality of evidence was downgraded by 1 point owing to unclear risk of performance bias.
4 Numbers are too small for precise results to be obtained
5 95% CI crosses 1 default MID (0.8 and 1.25)
6 The committee decided to downgrade survival outcomes by one level if the difference in survival was not statistically significant.
7 95% CI crosses 2 default MIDs (0.8 and 1.25).
8 Casadei et al. 2015
9 Casadei et al. 2015, Golcher et al. 2015, Golcher et al. 2008
10 Golcher et al. 2008, Golcher et al. 2015
11 Quality of evidence was downgraded by 1 point owing to some inconsistency across studies
12 Sho et al. 2013
13 Retrospective
14 The quality of the evidence was downgraded of one point because of the potential risk of performance bias due to some issues of comparability between comparison groups
15 Sho et al. 2013, Tzeng et al. 2014, Vento et al. 2007

Table 120 Summary clinical evidence profile for neoadjuvant chemoradiotherapy then surgery in only adults with resectable pancreatic cancer

Outcomes	Effect	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
5 years survival rate- Resectable PC (follow-up 5 years)	The 5-year survival was 57%	Not estimable	188 (1 study[1])	⊕⊕⊖⊖ low[5]	

Outcomes	Effect	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Overall Survival - Resectable PC Follow-up: unclear	Median survival was 34 months for the 64 patients who underwent PD and 7 months for the 22 un-resected patients (P < .001). The 5-year survival for those who did and did not undergo PD was 36% and 0%, respectively.	Not estimable	86 (1 study[2])	⨁⨁⊖⊖ low[5]	
Resection rate - Resectable PC Follow-up: mean 8 weeks3	R0 resection rate was relatively high (99% and 89%, respectively) in those patients who underwent surgery and received the intervention.	Not estimable	250 (2 studies[1, 2])	⨁⨁⊖⊖ low[5]	
Time from initiating treatment to Surgery	The median time from completion of preoperative therapy to surgery in the 73 patients who went to surgery was 5.6 weeks.	Not estimable	73 (1 study[2])	⨁⨁⊖⊖ low[5]	
Adverse effects: Hematologic toxicities (Grade3 to 4) (Anaemia; Leukopenia; Granulocytopenia; Thrombocytopenia; Neutropenic fever) No of events Follow-up: - unclear	37 patients experienced hematologic toxicities	Not estimable	86 (1 study[2])	⨁⨁⊖⊖ low[5]	
Adverse effects: Constitutional toxicities(Grade3 to 4) (Fatigue; Anorexia; Pain; Failure to thrive) No of events Follow-up: - unclear	32 patients experienced constitutional toxicities	Not estimable	86 (1 study[2])	⨁⨁⊖⊖ low[5]	
Adverse effects: Gastrointestinal toxicities(Grade3 to 4) (Nausea; Emesis; Diarrhoea/enteritis; Dehydration; Constipation; Abdominal pain) No of events Follow-up: - unclear	30 patients experienced gastrointestinal toxicities	Not estimable	86 (1 study[2])	⨁⨁⊖⊖ low[5]	

Outcomes	Effect	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Adverse effects: Liver and biliary toxicities (Grade3 to 4) No of events Follow-up: - unclear	24 patients experienced liver and biliary toxicities	Not estimable	86 (1 study[2])	⨁⨁⊖⊖ low[5]	
Adverse effects: Cardiovascular toxicities (Grade3 to 4) (Deep venous thrombosis) No of events Follow-up: - unclear	4 patients experienced cardiovascular toxicities	Not estimable	86 (1 study[2])	⨁⨁⊖⊖ low[5]	
Adverse effects: Pulmonary embolism toxicities (Grade 3-4) No of events Follow-up: - unclear	No patient experienced pulmonary embolism toxicities (p=no reported)	Not estimable	86 (1 study[2])	⨁⨁⊖⊖ low[5]	
Adverse effects: Other toxicities (Grade 3-4) No of events Follow-up: - unclear	18 patients experienced other toxicities	Not estimable	86 (1 study[2])	⨁⨁⊖⊖ low[5]	
The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). *CI: Confidence interval; RR: Risk ratio;*					
1 Takashaki et al. 2013 *2 Evans et al. 2008* *3 From the initial staging* *4 NCI Common Terminology Criteria for Adverse Events (CTCAE) v.4. NCI Common Terminology Criteria for Adverse Events (CTCAE) v.4 data files. Available at: http://evs.nci.nih.gov/ftp1/CTCAE/About.html.* *5 Non-randomised study with no comparator*					

Table 121: Summary clinical evidence profile for neoadjuvant chemoradiotherapy followed by surgery in only adults with borderline resectable pancreatic cancer

Outcomes	Effect	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Response to neoadjuvant treatment pre-surgery Percent frequency of complete/partial response following neoadjuvant	The fraction of patients with complete/partial response at restaging was 13.5% (95% CI: 7-24.6%)	Not estimable	137 (7 studies[1])	⨁⨁⊖⊖ low[4]	

Outcomes	Effect	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
therapy –RECIST criteria					
5 years survival rate- Resectable PC	The 5-year survival was 34%	Not estimable	43 (1 study[2])	⊕⊕⊖⊖ low[4]	
Resection rate Percent frequency of pancreatic resection rates following neoadjuvant therapy	R0 resection rate was 78.5 % in those patients who underwent surgery and received the neoadjuvant CRT intervention (95% CI: 62.2-89.1%)	Not estimable	137 (7 studies[1])	⊕⊕⊖⊖ low[4]	
Adverse events: toxicity rates (grade 3-4)	28.8% of patients had grade 3-4 toxicities as consequence of the neoadjuvant intervention	Not estimable	137 (7 studies[1])	⊕⊕⊖⊖ low[4]	

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio

1 Festa et al. 2013 (included studies: Le Scodan et al. 2009; Leone et al. 2012; Magnin et al. 2003; Massucco et al. 2006; Mehta et al. 2001; Pipas et al. 2005; Small et al. 2011)
2 Takashaki et al. 2013
3 Non-randomised study with no comparator
4 Single-arm prospective clinical trials (non-comparative)

Table 122: Summary clinical evidence profile for neoadjuvant chemoradiotherapy followed by surgery in either adults with borderline resectable or resectable pancreatic cancer

Outcomes	Effect	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Adverse events: Leukopenia (Grade 3) - Borderline Resectable and Resectable PC National Cancer Institute Common Toxicity Criteria version 44	Following preoperative CRT there were 132 patients reported associated leukopenia toxicities (grade 3-4)	Not estimable	268 (1 study[1])	⊕⊕⊖⊖ low[5]	
Adverse events: Thrombocytopenia (Grade 3) - Borderline Resectable and Resectable PC National Cancer Institute Common	Following preoperative CRT there were 14 patients reported associated thrombocytopenia toxicities (grade 3-4)	Not estimable	268 (1 study[1])	⊕⊕⊖⊖ low[5]	

Outcomes	Effect	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Toxicity Criteria version 44					
Adverse events: Gastrointestinal toxicity (Grade 3) - Borderline Resectable and Resectable PC National Cancer Institute Common Toxicity Criteria version 44	Following preoperative CRT there were 4 patients reported associated gastrointestinal toxicities (grade 3-4)	Not estimable	268 (1 study[4])	⊕⊕⊖⊖ low[5]	
Adverse events: Delayed gastric emptying (Grade B/C) - Borderline Resectable and Resectable PC International study group of pancreatic surgery criteria[6]	Following preoperative CRT there were 23 patients reported associated delayed gastric emptying complications	Not estimable	268 (1 studies[1])	⊕⊕⊖⊖ low[5]	
Adverse events: Delayed gastric emptying (Operative Mortality) - Borderline Resectable and Resectable PC International study group of pancreatic surgery criteria[6]	There was 1 death following preoperative CRT-associated complications	Not estimable	268 (1 study[1])	⊕⊕⊖⊖ low[5]	
Adverse events: Pancreatic fistula (Grade B-C) International study group of pancreatic fistula criteria[9]	Following preoperative CRT there were 15 patients reported pancreatic fistula complications	Not estimable	268 (1 study[1])	⊕⊕⊖⊖ low[5]	

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio;

1 Takashaki 2013
4 NCI Common Terminology Criteria for Adverse Events (CTCAE) v.4. NCI Common Terminology Criteria for Adverse Events (CTCAE) v.4 data files. Available at: http://evs.nci.nih.gov/ftp1/CTCAE/About.html.
5 Non-randomised study with no comparator
6 Wente MN, Bassi C, Dervenis C, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2007;142:761–768.
8 Numbers are too small for precise results to be obtained
9 Bassi C, Dervenis C, Butturini G, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery. 2005;138:8–13

Table 123: Summary clinical evidence profile for neoadjuvant chemotherapy followed by surgery in patients with in patients with borderline resectable pancreatic cancer.

Outcomes	Effect	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Response to neoadjuvant treatment pre-surgery Percent frequency of complete/partial response following neoadjuvant therapy – RECIST criteria	The weighted fraction of patients with complete/partial response at restaging was 23.6% (95% CI: 8.0-28%)	Not estimable	45 (3 studies[1])	⊕⊖⊖⊖ very low[2,3]	
Resection rate	R0 resection rate was 87.6 % in those patients who underwent surgery and received the neoadjuvant CRT intervention (95% CI: 43.9-98.5%)	Not estimable	45 (3 studies[1])	⊕⊖⊖⊖ very low[2,3]	
Adverse events: toxicity rates (grade 3-4)	35.9% of patients had grade 3-4 toxicities as consequence of the neoadjuvant intervention (95% CI: 23.1-51.1%)	Not estimable	45 (3 studies[1])	⊕⊖⊖⊖ very low[2,3]	
The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). *CI: Confidence interval; RR: Risk ratio;*					
1 Festa et al. 2013 (included studies: Lee et al. 2012; Sahora et al. 2011a; Sahora et al. 2011b) *2 Non-randomised study with no comparator* *3 Numbers are too small for precise results to be obtained*					

Table 124: Summary clinical evidence profile for neoadjuvant chemotherapy then chemoradiotherapy followed by surgery in patients with resectable pancreatic cancer.

Outcomes	Effect	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Overall Survival Follow-up: 5 years	Median survival for the patients who completed chemo-CRT was 18.7 months, with a median survival of 31 months for the 52 patients who underwent PD and 10.5 months for the 27 patients who did not undergo surgical resection of their primary tumour	Not estimable	79 (1 study[1])	⊕⊕⊖⊖ low[3]	

Outcomes	Effect	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Resection rate Follow-up: - unclear	R0 resection rate was 96% in those patients who underwent PD and received the intervention	Not estimable	62 (1 study[1])	⊕⊕⊖⊖ low[3]	
Time from initiating treatment to Surgery Follow-up: - unclear	The median time from completion of the neoadjuvant intervention to surgery in the patients who went to surgery for planned PD was 5.6 weeks	Not estimable	62 (1 study[1])	⊕⊕⊖⊖ low[3]	
Adverse effects: Hematologic toxicities (Grade 3-4) (Anaemia; Leukopenia; Granulocytopenia; Thrombocytopenia; Neutropenic fever) No of events Follow-up: - unclear	24 patients experienced hematologic toxicities	Not estimable	79 (1 study[1])	⊕⊕⊖⊖ low[3]	
Adverse effects: Constitutional toxicities (Grade 3-4) (Fatigue; Anorexia; Pain; Failure to thrive) No of events Follow-up: - unclear	30 patients experienced constitutional toxicities	Not estimable	79 (1 study[1])	⊕⊕⊖⊖ low[3]	
Adverse effects: Gastrointestinal toxicities (Grade 3-4) (Nausea; Emesis; Diarrhoea/enteritis; Dehydration; Constipation; Abdominal pain) No of events Follow-up: - unclear	20 patients experienced gastrointestinal toxicities	Not estimable	79 (1 study[1])	⊕⊕⊖⊖ low[3]	
Adverse effects: Liver and biliary toxicities (Grade 3-4) No of events Follow-up: - unclear	29 patients experienced liver and biliary toxicities	Not estimable	79 (1 study[1])	⊕⊕⊖⊖ low[3]	
Adverse effects: Cardiovascular toxicities(Grade 3-4) (Deep venous thrombosis) No of events Follow-up: - unclear	7 patients experienced cardiovascular toxicities	Not estimable	79 (1 study[1])	⊕⊕⊖⊖ low[3]	
Adverse effects: Pulmonary embolism toxicities (Grade 3-4) No of events Follow-up: - unclear	3 patients experienced pulmonary embolism toxicities	Not estimable	79 (1 study[1])	⊕⊕⊖⊖ low[3]	

Outcomes	Effect	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Adverse effects: Other toxicities (Grade 3-4) No of events Follow-up: - unclear	19 patients experienced other toxicities	Not estimable	79 (1 study[1])	⨁⨁⊖⊖ low[3]	
The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). *CI: Confidence interval; RR: Risk ratio;*					
1 Varadhachary et al. 2008 *2 Single-arm phase II clinical trial (non-comparative)* *3 Non-randomised study with no comparator*					

10.1.5 Economic evidence

10.1.5.1 Systematic literature review

References to all included studies and evidence tables for all economic evaluations included in the systematic literature review of the economic evidence are presented in Appendix L. Economic evidence profiles of these studies are presented in Appendix K.

One study (Abbott et al. 2013) was identified by the review of published economic evidence for this topic. The study was a cost utility analysis of a surgery first approach versus a neoadjuvant therapy approach (either gemcitabine or capecitabine based chemotherapy or chemoradiotherapy) in the treatment of pancreatic head cancer. The study reported the results in terms of both cost and Quality Adjusted Life Month (QALM) gained allowing for incremental analysis to be performed for this review. The study considered a US Health Payer perspective. It was deemed partially applicable to the topic primarily because it did not take a NHS+PSS perspective.

Potentially serious limitations were identified with Abbott et al. (2013). Retrospective, observational evidence was used to populate the health outcomes in the economic model from different databases at different centres. It was unlikely that the two patients groups were directly comparable and this may have biased both costs and QALMs. The base case suggested that treating pancreatic head cancer with a neoadjuvant approach would be both less costly and increase QALMs. Deterministic sensitivity analysis suggested this result was robust to alternative clinical assumptions made around the surgery first approach. The deterministic sensitivity analysis did not explore uncertainty around all key clinical assumptions and no probabilistic sensitivity analysis was reported.

References to all included studies and evidence tables for all economic evaluations included in the systematic literature review of the economic evidence are presented in Appendix L. Economic evidence profiles of these studies are presented in Appendix K.

10.1.6 Evidence statements

10.1.6.1 Neoadjuvant chemoradiotherapy followed by surgery versus surgery alone

Response to neoadjuvant treatment pre-surgery

Low quality evidence from 2 RCTs (n=47) showed that radiological response to neoadjuvant chemoradiotherapy on a restaging CT scan was rarely seen in adults with resectable

pancreatic cancer receiving neoadjuvant chemoradiotherapy followed by surgery, whereas most patients had no change or progression (relative effect not estimable).

Low quality evidence from 1 RCT (n=18) showed that the most common pathological response to neoadjuvant chemoradiotherapy was small or moderate (n=8) in adults with resectable pancreatic cancer receiving neoadjuvant chemoradiotherapy followed by surgery. By contrast, only one patient had a poor pathological response and two patients had a minimal response (relative effect not estimable).

Disease-free interval

No evidence was identified to inform this outcome

Relapse-free survival

No evidence was identified to inform this outcome

Overall Survival

Very low quality evidence from 2 RCTs (n=154) showed no clinically important difference between neoadjuvant chemoradiotherapy followed by surgery and surgery alone on long-term survival in adults with resectable pancreatic cancer: HR=0.85 (95% CI, 0.58-1.25), where HR less than 1 favours neoadjuvant chemoradiotherapy group.

Resection rate

Low quality evidence from 3 RCTs (n=183) showed no clinically important difference between neoadjuvant chemoradiotherapy followed by surgery and surgery alone on R0 resection rate in adults with resectable pancreatic cancer: RR 1.16 (95% CI, 0.97-1.39), where RR higher than 1 favours neoadjuvant chemoradiotherapy group.

Time from initiating treatment to Surgery

No evidence was identified to inform this outcome

Adverse Events

Very low quality evidence from 2 RCTs (n=104) showed no clinically important difference between neoadjuvant chemoradiotherapy followed by surgery and surgery alone on post-operative complications in adults with resectable pancreatic cancer: RR 0.86 (95% CI, 0.47-1.57), where RR less than 1 favours neoadjuvant CRT group.

Very low quality evidence from 1 retrospective comparative study (n=132) shows that there may be a clinically important difference favouring neoadjuvant chemoradiotherapy followed by surgery on pancreatic fistula compared to surgery alone in adults with resectable pancreatic cancer, although there is some uncertainty: RR 0.56 (95% CI, 0.3-1.05), where RR less than 1 favours neoadjuvant CRT group.

Very low quality evidence from 3 retrospective studies (n=346) showed no clinically important difference between neoadjuvant chemoradiotherapy followed by surgery and surgery alone on post-operative bleeding in adults with resectable pancreatic cancer: RR 0.56 (95% CI, 0.12-2.65), where RR less than 1 favours neoadjuvant CRT group.

Health Related Quality of Life

No evidence was identified to inform this outcome

Patient experience

No evidence was identified to inform this outcome

PROMS

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No evidence was identified to inform this outcome

10.1.6.2 Neoadjuvant chemoradiotherapy followed by surgery

10.1.6.2.1 Adults with resectable pancreatic cancer

Response to neoadjuvant treatment pre-surgery

No evidence was identified to inform this outcome

Disease-free interval

No evidence was identified to inform this outcome

Relapse-free survival

No evidence was identified to inform this outcome

Overall Survival

Low quality evidence from 1 single-arm phase II clinical trial (n=188) showed that the 5-year survival rate was 57% in adults with resectable pancreatic cancer who received neoadjuvant chemoradiotherapy and underwent surgery (relative effect not estimable).

Low quality evidence from 1 single-arm phase II clinical trial (n=86) showed that adults with resectable pancreatic cancer who received neoadjuvant chemoradiotherapy had an overall median survival of 34 months and a 5-year survival of 36% when they went on to have surgery (n=64) compared to a median survival of 7 months and a 5-year overall survival of 0% for those who received neoadjuvant chemoradiotherapy did not have surgery (n=22) (relative effect not estimable).

Resection rate

Low quality evidence from 2 single-arm phase II clinical trial (n=250) showed that the R0 resection rate in adults with resectable pancreatic cancer who received neoadjuvant chemoradiotherapy followed by surgery was relatively high (99% and 89%, in the two studies) (relative effect not estimable).

Time from initiating treatment to Surgery

Low quality evidence from 1 single-arm phase II clinical trial (n=73) showed that the median time from completion of neoadjuvant chemoradiotherapy to surgery was 5.6 weeks in adults with resectable pancreatic cancer (relative effect not estimable).

Adverse Events

Low quality evidence from 1 single-arm phase II clinical trial (n=86) showed that the overall Grade 3 or 4 toxicities experienced by adults with resectable pancreatic cancer who received neoadjuvant chemoradiotherapy was relatively high with 37 participants experiencing haematological toxicities, 32 participants experiencing constitutional toxicities, 30 participants experiencing gastrointestinal toxicities, 24 participants experiencing liver and biliary toxicities, 4 participants experiencing cardiovascular toxicities, 18 participants experiencing other toxicities, and no patients experiencing pulmonary embolism toxicities (relative effect not estimable).

Health Related Quality of Life

No evidence was identified to inform this outcome

Patient experience

No evidence was identified to inform this outcome

PROMS

No evidence was identified to inform this outcome

40.1.6.2.2 Adults with borderline resectable pancreatic cancer

Response to neoadjuvant treatment pre-surgery

Low the percentage of adults with borderline resectable pancreatic cancer with complete/partial response to neoadjuvant chemoradiotherapy before surgery at restaging was 13.5% (95% CI, 7.0-24.6).

Disease-free interval

No evidence was identified to inform this outcome

Relapse-free survival

No evidence was identified to inform this outcome

Overall Survival

Low quality evidence from 1 single-arm phase II clinical trial (n=43) showed that the 5-year overall survival in adults with borderline resectable pancreatic cancer who received neoadjuvant chemoradiotherapy then surgery was 34% (relative effect not estimable).

Resection rate

Low quality evidence from 7 single-arm prospective clinical trials (n=137) showed that the R0 resection rate was 78.5% (95% CI, 62.2-89.1) in adults with borderline resectable pancreatic cancer who received neoadjuvant chemoradiotherapy followed by surgery (relative effect not estimable).

Time from initiating treatment to Surgery

No evidence was identified to inform this outcome

Adverse Events

Low quality evidence from 7 single-arm prospective clinical trials (n=137) showed that there was a relatively high incidence of Grade 3 or 4 toxicities of 28.8% (n=39) in adults with borderline resectable pancreatic cancer who received neoadjuvant chemoradiotherapy followed by surgery (relative effect not estimable).

Health Related Quality of Life

No evidence was identified to inform this outcome

Patient experience

No evidence was identified to inform this outcome

PROMS

No evidence was identified to inform this outcome

50.1.6.2.3 Adults with resectable or borderline pancreatic cancer

Response to neoadjuvant treatment pre-surgery

No evidence was identified to inform this outcome

Disease-free interval

No evidence was identified to inform this outcome

Relapse-free survival

No evidence was identified to inform this outcome

Overall Survival

No evidence was identified to inform this outcome

Resection rate

No evidence was identified to inform this outcome

Time from initiating treatment to Surgery

No evidence was identified to inform this outcome

Adverse Events

Low quality evidence from 1 single-arm phase II clinical trial (n=268) showed that the overall Grade 3 or 4/Grade B/C toxicities was relatively high in adults with resectable or borderline resectable pancreatic cancer who received neoadjuvant chemoradiotherapy followed by surgery, with 132 participants experiencing Grade 3/4 leukopenia. 14 participants experiencing associated Grade 3/4 thrombocytopenia; 4 participants experienced gastrointestinal toxicities (grade 3-4); 23 participants experiencing Grade B/C delayed gastric emptying complications, and 15 participants experiencing Grade B/C pancreatic fistula complications. There was also 1 death following preoperative chemoradiotherapy-associated complications (relative effect not estimable).

Health Related Quality of Life

No evidence was identified to inform this outcome

Patient experience

No evidence was identified to inform this outcome

PROMS

No evidence was identified to inform this outcome

10.1.6.3 Neoadjuvant chemotherapy followed by surgery

Response to neoadjuvant treatment pre- surgery

Very low quality evidence from 3 single-arm prospective clinical trials (n=45) showed that the percentage of adults with borderline resectable pancreatic cancer with complete/partial response to neoadjuvant chemotherapy followed by surgery at restaging was 23.6% (95% CI: 8.0-28%).

Disease-free interval

No evidence was identified to inform this outcome

Relapse-free survival

No evidence was identified to inform this outcome

Overall Survival

.

No evidence was identified to inform this outcome

Resection rate

Very low quality evidence from 3 single-arm prospective clinical trials (n=45) showed that the R0 resection rate in adults with borderline resectable pancreatic cancer who received neoadjuvant chemotherapy followed by surgery was 87.6% (95% CI, 43.9-98.5).

Time from initiating treatment to Surgery

No evidence was identified to inform this outcome

Adverse Events

Very low quality evidence from 3 single-arm prospective clinical trials (n=45) showed that the incidence of Grade 3 or 4 toxicities was relatively high at 35.9% (95% CI, 23.1-51.1) in adults with borderline resectable pancreatic cancer who received neoadjuvant chemotherapy followed by surgery.

Health Related Quality of Life

No evidence was identified to inform this outcome

Patient experience

No evidence was identified to inform this outcome

PROMS

No evidence was identified to inform this outcome

10.1.6.4 Neoadjuvant chemotherapy then chemoradiotherapy followed by surgery

Response to neoadjuvant treatment pre- surgery

No evidence was identified to inform this outcome

Disease-free interval

No evidence was identified to inform this outcome

Relapse-free survival

No evidence was identified to inform this outcome

Overall Survival

Low quality evidence from 1 single-arm phase II clinical trial (n=79) showed that the median survival of adults with resectable pancreatic cancer who received neoadjuvant chemotherapy then chemoradiotherapy followed by surgery (n=52) was 31 months compared to a median survival of 10.5 months for adults with resectable pancreatic cancer who received neoadjuvant chemotherapy then chemoradiotherapy and did not have surgery (n=27) (relative effect not estimable).

Resection rate

Low quality evidence from 1 single-arm phase II clinical trial (n=62) showed that the R0 resection rate was 96% in adults with resectable pancreatic cancer who received neoadjuvant chemotherapy then chemoradiotherapy followed by surgery (relative effect not estimable).

Time from initiating treatment to Surgery

.

Low quality evidence from 1 single-arm phase II clinical trial (n=62) showed that the median time from completion of neoadjuvant chemotherapy then chemoradiotherapy to surgery was 5.6 weeks (relative effect not estimable).

Adverse Events

Low quality evidence from 1 single-arm phase II clinical trial (n=79) showed that there was a relatively high incidence of adverse events in adults with resectable pancreatic cancer who received neoadjuvant chemotherapy then chemoradiotherapy followed by surgery, with 24 participants experiencing haematological toxicities, 30 participants experiencing constitutional toxicities; 20 participants experiencing gastrointestinal toxicities; 29 participants experiencing liver and biliary toxicities; 7 participants experiencing cardiovascular toxicities; 3 participants experiencing pulmonary embolism toxicities, and 19 participants experiencing other toxicities (relative effect not estimable).

Health Related Quality of Life

No evidence was identified to inform this outcome

Patient experience

No evidence was identified to inform this outcome

PROMS

No evidence was identified to inform this outcome

10.1.7 Recommendations

35. **Only consider neoadjuvant therapy for people with borderline resectable pancreatic cancer as part of a clinical trial.**

36. **Only consider neoadjuvant therapy for people with resectable pancreatic cancer as part of a clinical trial.**

10.1.8 Evidence to recommendations

10.1.8.1 Relative value placed on the outcomes considered

Response to neoadjuvant therapy, disease-free survival, relapse-free survival, resection rate, overall survival, time from initiation of treatment to surgery, adverse events, health-related quality of life and patient experience were considered to be the critical outcomes for this question.

Resection rate and adverse events were reported for all comparisons of interest. Overall survival was reported for all comparisons except chemotherapy followed by surgery. Time from initiating treatment to surgery was only reported for the comparisons of chemoradiotherapy followed by surgery and chemotherapy followed by chemoradiotherapy before surgery. Response to neoadjuvant treatment pre-surgery was not reported for chemotherapy followed by chemoradiotherapy before surgery. Health-related quality of life, patient experience, patient reported outcome measures, disease free interval or relapse free survival were not reported for any of the comparisons of interest.

The committee noted that the evidence of time from initiating treatment to surgery did not help when making recommendations because it was only available for chemoradiotherapy and it wasn't available for the other comparisons of interest.

10.1.8.2 Quality of evidence

The quality of the evidence was assessed by GRADE and the Cochrane risk of bias checklist.

The quality of the evidence for the comparison of chemoradiotherapy followed by surgery against surgery alone ranged from very low to moderate quality across all outcomes. The quality of the evidence for chemoradiotherapy followed by surgery, chemotherapy followed by surgery and chemotherapy followed by chemoradiotherapy before surgery was very low for all outcomes.

The committee noted that several of the studies were from outside the UK and therefore may have limited relevance to the UK population. They also noted that most of the data came from single arm studies with no comparator. The committee applied less weight to this data as the lack of a comparator made it difficult to evaluate the relative effectiveness of the different interventions. The committee also noted that the one comparative study that had been identified used neoadjuvant interventions would be considered sub-optimal compared with current treatments, making it difficult to be certain about the toxicity results. Because of these issues the committee were not able to make any strong recommendations but they agreed to recommend further research in this area to help provide additional data using current treatments.

The committee noted, based on the evidence, that the extent of efficacy and toxicity of neoadjuvant treatment was uncertain because the studies used sub-optimal interventions compared with modern non-surgical therapy. Furthermore, the studies were single arm and non-randomised.

The committee also noted that the data on pathological assessment of the response to neoadjuvant therapy need to be interpreted with caution. Macroscopically, it can be very difficult to distinguish tumour, fibrotic areas of tumour regression, and the fibrosis of obstructive or chronic pancreatitis in pancreatic resection specimens. Therefore, tissue sampling by the pathologist is critical for evaluating whether residual tumour is present or not. The only way to confirm complete tumour regression is for the pathologist to sample the entire pancreas from the resection specimen. It was not always clear from the evidence whether this has been done. Inadequate sampling can lead to a false impression of complete response, because residual tumour was not sampled.

Assessment of resection margin status (R0 or R1) in pancreatic resection specimens post neoadjuvant therapy is also dependent upon tissue sampling. The committee noted that there is no standardised protocol for pancreas resection margin assessment by pathologists and, therefore, R0/R1 rates can be influenced by the number of margins sampled by the pathologist. There is also no universally agreed definition of what constitutes an R1 resection in a pancreatic resection specimen. In pancreatic resections without neoadjuvant therapy, most pathologists use either <1mm clearance or 0mm clearance to define an R1 resection. The clearance required for an R0 resection in a specimen following neoadjuvant therapy is probably much more than 1mm. The evidence does not always specify how R1 has been defined. The R1 rates in pancreatic resection specimens post neoadjuvant therapy range from 0-100%. The variation in specimen/margin sampling by pathologists, and the differing definitions of R1, probably contribute to this wide range of R1 rates.

10.1.8.3 Consideration of clinical benefits and harms

Given the limited, low quality evidence available and the issues around interpreting the data on resection rates, the committee agreed it was difficult to be certain of the balance of benefits and harms from the use of neoadjuvant therapy. They noted that neoadjuvant therapy is currently being used outside of clinical trials. They agreed that the ideal use of neoadjuvant therapy is in the context of ongoing clinical trials in order to collect the required comparative data for both resectable and borderline resectable disease.

10.1.8.4 Consideration of economic benefits and harms

The economic evidence review identified one study reporting an economic model comparing neoadjuvant therapy (either gemcitabine or capecitabine based chemotherapy or chemoradiotherapy) compared to a surgery first approach in people with resectable pancreatic head cancer from a US health payer perspective. The study concluded that neoadjuvant therapy was both cost saving and health improving and this conclusion was robust to alternative assumptions.

The committee noted that retrospective, observational evidence was used to populate the health outcomes in the economic model and from different databases at different centres. It was likely that people receiving neoadjuvant therapy had a better prognosis and were less likely to incur significant costs from adverse events associated with pancreatic cancer than people receiving immediate surgery and this would have counted somewhat towards the cost and health outcome differences in the model. Given this and the low applicability to an NHS setting the CG could not use the study to strongly influence their recommendations.

The committee did agree with the study that neoadjuvant therapy could be cost saving if it successfully selected out people who were unlikely to respond well to resection, therefore potentially avoiding unnecessary expensive surgery. The committee noted that this would account for approximately 20% of resections. However, the committee acknowledge that there was not strong evidence to support this.

10.1.9 Research recommendation

6. Prospective randomised trials should be undertaken to compare preoperative (neoadjuvant) therapy with standard postoperative therapy in people with resectable pancreatic cancer.

Why this is important

The survival rate of pancreatic cancer after surgical resection is very low, which suggests that most patients have metastatic disease at the time of surgery. In addition, complications of surgery may stop people from having adjuvant therapy. This makes neoadjuvant therapy an attractive option. However, the evidence for neoadjuvant therapy is limited and low quality. Using neoadjuvant therapy means delaying surgery, and it is possible that during this delay pancreatic cancer will progress and become unresectable in some people, negating any benefit of neoadjuvant therapy.

Research is needed to compare neoadjuvant treatments (which might be chemotherapy, radiotherapy or both) with surgery followed by adjuvant chemotherapy. The outcomes of interest are:

- feasibility of delivering neoadjuvant treatment
- feasibility of randomising patients
- objective response rate of neoadjuvant therapy
- R0 resection rate
- surgical complications, length of hospital stay, mortality of surgery
- delivery of planned treatment
- disease-free survival and overall survival after surgery
- quality of life, patient experience and patient-reported outcome measures.

10.1.10 References

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10.2 Resectable and borderline resectable pancreatic cancer

Review question: What is the most effective surgery (type and extent) for adults with newly diagnosed resectable and borderline resectable pancreatic cancer?

10.2.1 Introduction

Resectional surgery is the only cure for pancreatic cancer and is indicated in a proportion of people with this disease. The possibility of a resection in an individual depends on the stage of the tumour and their fitness for surgery. For surgery to be successful, in terms of improving survival, a complete resection of the tumour is necessary. The type of surgery is therefore important.

Prior to surgery the person's tumour is assessed with imaging tests to determine whether the tumour might be resectable. Based on the information provided by these tests it is usually possible to identify whether the tumour might be: resectable (one that would be expected to be removed surgically); borderline resectable (one that might be); locally advanced (not resectable but still confined to the pancreas and surrounding tissues); or metastatic (where the tumour has spread to lymph-nodes or other organs).

Resectional surgery is not performed on tumours identified as locally advanced or metastatic. For tumours identified as resectable or borderline resectable, a variety of different types of surgery, surgical access and surgical dissection are used depending on the site of the tumour in the pancreas and involvement of other structures.

Guidance is needed on the most effective type and extent surgery for people with resectable and borderline resectable pancreatic cancer in order to standardise practice.

10.2.1.1 Review protocol summary

The review protocol summary used for this question can be found in Table 125. Full details of the review protocol can be found in Appendix C.

Table 125: Clinical review protocol summary for the review of type and extent of surgery

Population	Adults with • Resectable pancreatic cancer • Borderline resectable pancreatic cancer	
Intervention/Comparator	Minimally invasive surgery • Laparoscopic • Robotic	Open surgery
	Extended surgery (e.g. venous arterial, extent of lymph nodes resection, other organs to be removed)	Standard surgery
Outcomes	• Local Recurrence • Distant Recurrence • Overall Survival • Post-operative death (30 day/90 day) • Treatment related morbidity • Treatment related mortality • Lymph node harvest • Health Related Quality of Life • Patient experience • PROMS	

10.2.2 Description of Clinical Evidence

Eleven studies were included in this review: ten systematic reviews/meta-analyses (Doula et al., 2016; Giovianazzo et al., 2016; Huttner et al., 2016; Ke et al., 2014; Mollber et al., 2011; Sui et al., 2012; Venkat et al., 2012; Yu et al., 2014; Zhang et al., 2013; Zhou et al., 2012) and one RCT (Kawai et al., 2014). A summary of the included studies is presented in Table 126.

One systematic review/meta-analysis (Doula et al., 2016) of 14 retrospective cohort studies (n=1063;) compared minimally invasive (laparoscopic and robotic) pancreaticoduodenectomy with open pancreaticoduodenectomy (Asbun & Stauffer 2010; Bao et al., 2014; Buchs et al., 2011; Chalikonda et al., 2012; Cho et al., 2009; Gumbs et al., 2008; Kuroki et al., 2012; Lai et al., 2012; Langan et al., 2014; Mesleh et al., 2013; Pugliese et al.,2008; Speicher et al., 2014; Zhou et al., 2011; Zureikat et al., 2011).

One systematic review/meta-analysis (Huttner et al., 2016) of 8 retrospective cohort studies (n=512; Bloechle et al., 1999; Lin & Lin, 1999; Paquet, 1998; Seiler et al., 2005; Srinarmwong et al., 2008; Taher et al., 2015; Tran et al., 2004; Wenger et al., 1999) and 1 RCT (n=130; Kawai et al. 2014) compared Pylorus-preserving Whipple with Classic Whipple.

Two systematic reviews/meta-analyses (Venkat et al., 2012; Sui et al., 2012) of 21 retrospective cohort studies (n=1992) compared minimally invasive laparoscopic distal pancreatectomy with open pancreatectomy (Aly et al., 2010; Bruzoni & Sasson, 2008; Casedei et al., 2010; DiNorcia et al., 2010; Eom et al., 2008; Finan et al., 2009; Jayaraman et al., 2010; Kim et al., 2008; Kooby et al., 2010; Matsumoto et al., 2008; Misawa et al., 2007; Nakamura et al., 2009; Shimura et al., 2006; Tang et al., 2007; The et al., 2007; Velanovich et al., 2006; Vijan et al., 2010; Waters et al., 2010; Zhao et al., 2010).

One systematic review/meta-analysis (Zhang et al., 2013) of 7 retrospective cohort studies (n=340) compared minimally invasive robotic pancreatectomy with open pancreatectomy (Buchs et al., 2011; Chalikonda et al., 2012; Hammill et al., 2010; Kang et al., 2011; Walsh et al., 2011; Waters et al., 2010; Zhou et al., 2011).

One systematic review/meta-analysis (Ke et al., 2014) of 4 RCTs (n=428) compared extended lymphadectomy with standard lymphadectomy (Farnell et al., 2005; Nimura et al., 2012; Pedrazzoli et al., 1998; Riall et al., 2005).

One systematic review/meta-analysis (Mollberg et al., 2011) of 26 retrospective observational studies (n=2609) compared arterial resection with no arterial resection (Allendorf et al., 2008; Amano et al., 2009; Bockhorn et al., 2011; Boggi et al., 2009; Denecke et al., 2010; Fortner et al., 2009; Hartwig W et al., 2009; Hirano et al., 2007; Hishinuma et al., 2007; Kato et al., 2009; Kinoshita et al., 2001; Klempnauer et al., 1996; Martin et al., 2009; Miyakawa et al., 2002; Miyazaki, 2003; Ogata et al., 1997; Ouaissi et al., 2010; Park et al., 2001; Settmacher et al., 2004; Shimada et al., 2006; Sperti et al., 2010; Stitzenberg et al., 2008; Sugiura et al., 2009; Wang et al., 2008; Wu et al., 2008).

Three systematic reviews/meta-analyses (Giovinazzo et al., 2016; Yu et al., 2014; Zhou et al., 2012) of 34 retrospective cohort studies (n=9937) compared venous resection with no venous resection (Al-Haddad et al., 2007; Allema et al., 1994; Banz et al., 2012; Bachellier et al., 2001; Carrere et al., 2006; Castleberry et al., 2012; Chakravarty et al., 2010; Furhman et al., 2007; Fukuda et al., 2007; Gong et al., 2013; Harrison et al., 1996; Hartel et al., 2002; Howard et al., 2003; Illumnati et al., 2008; Kaneoka et al., 2009; Kawada et al., 2002; Kelly et al., 2013; Kurosaki et al., 2008; Launois et al., 1999; Leach et al., 1998; Martin et al., 2009; Murakami et al., 2013; Nakagohri et al., 2003; Ouaissi et al., 2010; Poon et al., 2004; Ravikumar et al., 2014; Riediger et al., 2006; Shibata et al., 2001; Shimada et al., 2006; Shrikhande et al., 2011; Sperti et al., 1996; Tseng et al., 2004; Yang et al., 2016)

Where possible, the risk of bias information was taken from the systematic reviews. In some cases, where there was not enough detail included in the review (Ke et al., 2014; Zhang et al., 2013), the original study was used to determine risk of bias.

Further information about the search strategy can be found in Appendix D. See study selection flow chart in Appendix E, forest plots in Appendix H, GRADE tables in Appendix I, study evidence tables in Appendix F and list of excluded studies in Appendix G.

10.2.31 Summary of included studies

2 A summary of the studies that were included in this review is presented in Table 126.

3 **Table 126: Summary of included studies**

Study	N	# of studies	Design of studies	Intervention	Comparison	Outcomes
Doula et al. (2016)	1063	13	Retrospective cohort	Minimally invasive (laparoscopic & robotic) pancreaticoduodenectomy	Open pancreaticoduodenectomy	Post-operative mortality R0 resection rate Operation time Delayed gastric emptying Pancreatic fistula Reoperation rate Blood loss Retrieved lymph nodes
Huttner et al. (2016); Kawai et al. (2014)a	642	9	RCT	Pylorus-preserving Whipple	Classic Whipple	Overall survival Post-operative mortality R0 resection rate Operation time Delayed gastric emptying Pancreatic fistula Biliary leakage Reoperation rate Intraoperative blood loss Surgical site infection Length of hospital stay
Venkat et al. (2012); Sui et al. (2012)	1992	21	Retrospective cohort	Minimally invasive laparoscopic distal pancreatectomy	Open pancreatectomy	Mortality Positive margin rate Pancreatic fistula Reoperation rate Operative blood loss Surgical site infection Operation time

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Study	N	# of studies	Design of studies	Intervention	Comparison	Outcomes
						Length of hospital stay Time to oral intake
Zhang et al. (2013)	340	7	Retrospective cohort	Minimally invasive robotic pancreatectomy	Open Pancreatectomy	Post-operative mortality Positive margin rate Pancreatic fistula Operation time Length of hospital stay
Ke et al. (2014)	428	4	RCT	Extended lymphadenectomy	Standard lymphadenectomy	Overall survival Positive/negative margin status Positive/negative lymph nodes
Mollberg et al. (2011)	2609	26	Retrospective observational	Arterial resection	No arterial resection	Overall survival Post-operative mortality Reoperation rate R0 resection rate Positive lymph nodes Post-operative morbidity
Giovinazzo et al. (2016); Zhou et al. (2012); Yu et al. (2014)	9937	34	Retrospective cohort	Venous resection	No venous resection	Overall survival Post-operative mortality Reoperation rate R1/R2 resection rate Operative morbidity

Notes: a, all articles are systematic reviews and meta-analyses except for Kawai et al. (2014).

10.2.4 Clinical Evidence Profile

The clinical evidence profiles for this review question are presented in Table 127 to Table 133.

Table 127: Summary clinical evidence profile for minimally invasive (laparoscopic & robotic) versus open pancreaticoduodenectomy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Open pancreaticoduodenectomy	Minimally invasive (laparoscopic and robotic) pancreaticoduodenectomy				
Postoperative Mortality	52 per 1000	46 per 1000 (21 to 100)	RR 0.88 (0.4 to 1.92)	768 (9 studies)	⊕⊖⊖⊖ very low[1,2,3]	
R0 resection rate	816 per 1000	882 per 1000 (833 to 931)	RR 1.08 (1.02 to 1.14)	672 (9 studies)	⊕⊖⊖⊖ very low[1,2]	
Operation Time (mins)	The mean operation time (mins) ranged across control groups from 264.9-559 mins	The mean operation time (mins) in the intervention groups was 109.99 higher (2.74 to 217.24 higher)		535 (6 studies)	⊕⊖⊖⊖ very low[2,4,5,6]	
Delayed Gastric Emptying	112 per 1000	117 per 1000 (71 to 193)	RR 1.04 (0.63 to 1.72)	758 (8 studies)	⊕⊖⊖⊖ very low[1,2,3]	
Pancreatic Fistula	191 per 1000	199 per 1000 (153 to 257)	RR 1.04 (0.8 to 1.34)	972 (13 studies)	⊕⊖⊖⊖ very low[1,2,3]	
Reoperation	86 per 1000	64 per 1000 (39 to 105)	RR 0.75 (0.45 to 1.23)	845 (8 studies)	⊕⊖⊖⊖ very low[1,2,7]	
Blood loss (ml)	The mean blood loss (ml) ranged across control groups from 210-1509.5 mls	The mean blood loss (ml) in the intervention groups was 398.6 lower		180 (5 studies)	⊕⊖⊖⊖ very low[1,2,8,9]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Open pancreaticoduodenectomy	**Minimally invasive (laparoscopic and robotic) pancreaticoduodenectomy**				
		(746.26 to 50.95 lower)				
Retrieved lymph nodes	The mean retrieved lymph nodes ranged across control groups from 10-19.1	The mean retrieved lymph nodes in the intervention groups was 1.23 higher (2.29 lower to 4.75 higher)		228 (4 studies)	⊕⊖⊖⊖ very low[1,2,10]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

CI: Confidence interval; RR: Risk ratio;

1 Not Randomised
2 Not all malignancy was pancreatic malignancy
3 95% CI crosses 2 default MIDs (0.8 and 1.25).
4 High heterogeneity between studies (I2=96%)
5 MID is +/- 54 mins (Median SD of control arm at follow up=108 mins).
6 95% CI crosses 1 MID for this outcome.
7 95% CI crosses 1 default MID (0.8 or 1.25).
8 Between studies heterogeneity I2=93%
9 MID for this outcome is +/- 97.3 ml (Median SD of control arm at follow up=194.5 ml).
10 Between studies heterogeneity I2=63%

Table 128: Summary clinical evidence profile for pylorus preserving Whipple versus classic Whipple

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	**Pylorus Preserving Whipple**				
Overall Survival Follow-up: 1-115 months1	625 per 1000	511 per 1000 (344 to 698)	HR 0.73 (0.43 to 1.22)	335 (3 studies)	⊕⊕⊖⊖ low[2,3,4]	
Postoperative Mortality Follow-up: 1-115 months5	60 per 1000	42 per 1000 (19 to 93)	RR 0.7 (0.31 to 1.55)	464 (7 studies)	⊕⊖⊖⊖ very low[2,6,7]	
R0 Resection Rate	819 per 1000	810 per 1000 (606 to 860)	RR 0.99 (0.74	359 (3 studies)	⊕⊖⊖⊖ very low[2,6,8]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Pylorus Preserving Whipple				
			to 1.05)			
Operation Time		The mean operation time in the intervention groups was 45.22 lower (74.67 to 15.78 lower)		472 (7 studies)	⊕⊖⊖⊖ very low[2,6,9]	
Delayed Gastric Emptying Follow-up: 1-115 weeks5	365 per 1000	785 per 1000 (358 to 1000)	RR 2.15 (0.98 to 4.71)	459 (7 studies)	⊕⊖⊖⊖ very low[2,6,8,10]	
Pancreatic Fistula Follow-up: 1-115 months	93 per 1000	90 per 1000 (52 to 158)	RR 0.97 (0.56 to 1.69)	468 (7 studies)	⊕⊖⊖⊖ very low[2,6,7]	
Biliary Leakage Follow-up: 1-115 months5	21 per 1000	20 per 1000 (4 to 109)	RR 0.95 (0.18 to 5.16)	380 (5 studies)	⊕⊖⊖⊖ very low[2,6,7]	
Necessity for Reoperation	115 per 1000	94 per 1000 (50 to 175)	RR 0.82 (0.44 to 1.53)	320 (3 studies)	⊕⊖⊖⊖ very low[2,6,7]	
Intraoperative Blood Loss Follow-up: 1-115 months5	The mean intraoperative blood loss in the control groups was 0.1 litres	The mean intraoperative blood loss in the intervention groups was 0.37 lower (0.77 lower to 0.04 higher)		404 (5 studies)	⊕⊖⊖⊖ very low[2,6,9,11]	
Surgical site infection	98 per 1000	85 per 1000 (38 to 185)	RR 0.86 (0.39 to 1.88)	251 (4 studies)	⊕⊖⊖⊖ very low[2,4,6]	
Hospital Stay (days)		The mean hospital stay (days) in the intervention groups was 0.26 higher		366 (5 studies)	⊕⊕⊖⊖ low[2,4,6,9]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Pylorus Preserving Whipple				
		(2.04 lower to 2.56 higher)				

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;

1 Lin et al Not Reported; Seiler et al 4-93 months; Tran et al 1-115 months;
2 Inadequate reporting of sequence generation and allocation concealment. Small sample size (Lin et al), no power calculations, no intention to treat analysis,
3 Subgroup analysis of pancreatic head carcinoma
4 The committee decided to downgrade survival outcomes by one level for imprecision only if there was a significant difference between the groups.
5 Follow-up not reported in all studies
6 Includes patients with periampullary cancer
7 95% CI crosses both default MIDs (0.8 and 1.25).
8 95% CI crosses 1 default MID (0.8 or 1.25).
9 Distribution of continuous outcomes is known to be skewed and may introduce bias to the analysis. MID for continuous outcomes, calculated from median SD of control arm at follow up, are as follows: operating time is +/- 26.8 mins (Median SD=53.5 min); intraoperative blood loss is +/- 0.202 litres (Median SD=0.404 litres); hospital stay is +/- 6.9 days (Median SD=13.8 days).
10 Heterogeneity I2>50%
11 95% CI crosses 1 MID.

Table 129: Summary clinical evidence profile for minimally invasive laparoscopic distal pancreatectomy versus open pancreatectomy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Open Pancreatectomy	Laparoscopic distal pancreatectomy				
Mortality	13 per 1000	8 per 1000 (3 to 27)	RR 0.63 (0.2 to 2.01)	1723 (17 studies)	⊕⊖⊖⊖ very low[1,2,3]	
Positive Margins	52 per 1000	32 per 1000 (14 to 77)	RR 0.61 (0.26 to 1.48)	1331 (7 studies)	⊕⊖⊖⊖ very low[1,2,3]	
Pancreatic Fistula (All)	205 per 1000	190 per 1000 (158 to 231)	RR 0.93 (0.77 to 1.13)	1814 (18 studies)	⊕⊖⊖⊖ very low[1,2,4]	
Pancreatic Fistula Grade B-C	150 per 1000	135 per 1000 (95 to 194)	RR 0.90 (0.63	834 (6 studies)	⊕⊖⊖⊖ very low[1,2,3]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Open Pancreatectomy	Laparoscopic distal pancreatectomy				
			to 1.29)			
Reoperation Rates	31 per 1000	25 per 1000 (9 to 67)	RR 0.79 (0.29 to 2.15)	847 (5 studies)	⊕⊖⊖⊖ very low[1,2,3]	
Operative Blood Loss		The mean operative blood loss in the intervention groups was 332.22 lower (480.99 to 183.65 lower)		1341 (16 studies)	⊕⊖⊖⊖ very low[1,2,5,6,7]	
Surgical Site Infection	79 per 1000	39 per 1000 (22 to 69)	RR 0.49 (0.28 to 0.87)	1127 (11 studies)	⊕⊖⊖⊖ very low[1,2]	
Operation Time		The mean operation time in the intervention groups was 8.88 higher (6.46 lower to 24.24 higher)		1562 (18 studies)	⊕⊖⊖⊖ very low[1,2,6,8]	
Length of hospital stay		The mean length of hospital stay in the intervention groups was 3.88 lower (4.92 to 2.83 lower)		1811 (20 studies)	⊕⊖⊖⊖ very low[1,2,6,7,9]	
Time to Oral Intake		The mean time to oral intake in the intervention groups was 1.48 lower (2.43 to 0.53 lower)		388 (6 studies)	⊕⊖⊖⊖ very low[1,2,3,10]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

CI: Confidence interval; RR: Risk ratio;

1 Not randomised comparisons
2 Population not all pancreatic cancer patients
3 95% CI crosses 2 default MIDs (0.8 and 1.25).
4 95% CI crosses 1 MID (0.8 or 1.25).

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Open Pancreatectomy	Laparoscopic distal pancreatectomy				

5 Between Studies heterogeneity I2=81%
6 MIDs for continuous outcomes, calculated from median SD of control arm at follow up, are as follows: operative blood loss is +/- 291.5 litres (Median SD=583 litres); operation time is +/- 33.3 mins (Median SD=66.7 mins); length of hospital stay is +/- 2.9 days (median SD=5.7 days); time to oral intake is +/- 2.8 days (median SD=5.4 days).
7 95% CI crosses 1 MID for this outcome.
8 Between Studies heterogeneity I2=81%
9 Between studies heterogeneity I2=84%
10 Between studies heterogeneity I2=68%

Table 130: Summary clinical evidence profile for minimally invasive robotic pancreatectomy versus open pancreatectomy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Open pancreatectomy	Robotic pancreatectomy				
Overall Complication Rate	365 per 1000	259 per 1000 (190 to 354)	RR 0.71 (0.52 to 0.97)	340 (7 studies1)	⊕⊖⊖⊖ very low[2,3,4]	
Postoperative Mortality	15 per 1000	25 per 1000 (7 to 91)	RR 1.67 (0.45 to 6.16)	340 (7 studies1)	⊕⊖⊖⊖ very low[2,3,4]	
Positive Margin Rate	224 per 1000	69 per 1000 (25 to 202)	RR 0.31 (0.11 to 0.9)	124 (4 studies)	⊕⊖⊖⊖ very low[2,3,5]	
Operation Time (mins)		The mean operation time (mins) in the intervention groups was 117.71 higher (139.76 lower to 375.18 higher)		114 (3 studies)	⊕⊖⊖⊖ very low[2,3,4,6]	
Length of hospital stay (days)		The mean length of hospital stay (days) in the intervention groups was 4.71 lower (9.45 lower to 0.03 higher)		114 (3 studies)	⊕⊖⊖⊖ very low[2,3,4]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Open pancreatectomy	Robotic pancreatectomy				
Pancreatic Fistula	163 per 1000	134 per 1000 (69 to 227)	RR 0.82 (0.42 to 1.39)	209 (5 studies)	⊕⊖⊖⊖ very low[2,3,4]	
The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio;						
1 5 full studies/2 abstracts 2 Not randomised 3 Includes patients with benign disease and malignancies other than pancreatic cancer (N=138 patient with malignant disease) 4 95% CI crosses 2 default MIDs (0.8 and 1.25). 5 95% CI crosses 1 default MID (0.8 or 1.25). 6 High heterogeneity between studies (I2=96%)						

Table 131: Summary clinical evidence profile for extended versus standard lymphadenectomy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Standard lymphadenectomy	Extended lymphadenectomy				
Overall Survival Follow-up: 60-96 months	879 per 1000	900 per 1000 (831 to 949)	HR 1.09 (0.84 to 1.41)	412 (4 studies)	⊕⊕⊖⊖ low[1,2,3]	
Lymph nodes (positive) Follow-up: 60-96 months	936 per 1000	943 per 1000 (876 to 980)	HR 1.04 (0.76 to 1.42)	280 (4 studies)	⊕⊕⊖⊖ low[1,2,4]	
Lymph Nodes (negative) Follow-up: 60-96 months	773 per 1000	792 per 1000 (577 to 944)	HR 1.06 (0.58 to 1.94)	132 (4 studies)	⊕⊖⊖⊖ very low[1,2,4]	
No postoperative adjuvant treatment Follow-up:	899 per 1000	1000 per 1000 (602 to 1000)	RR 1.16 (0.67 to 1.98)	178 (2 studies)	⊕⊖⊖⊖ very low[1,2,4]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Standard lymphadenectomy	Extended lymphadenectomy				
77-96 months						
Margin Status Negative	805 per 1000	853 per 1000 (748 to 974)	RR 1.06 (0.93 to 1.21)	428 (4 studies)	⊕⊕⊕⊖ moderate[1,2]	
Margin Status (positive)	186 per 1000	121 per 1000 (61 to 244)	RR 0.65 (0.33 to 1.31)	428 (4 studies)	⊕⊖⊖⊖ very low[1,2,4]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;

1 Inadequate reporting of randomisation and allocation concealment, no assessor blinding, incomplete outcome data
2 Only data relevant to patients with pancreatic cancer were extracted and included in the systematic review
3 The committee decided to downgrade survival outcomes by one level for imprecision only if there was a significant difference between the groups.
4 95% CI crosses 2 default MIDs (0.8 and 1.25).

Table 132: Summary clinical evidence profile for arterial resection versus no arterial resection

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No Arterial Resection	Arterial Resection				
1-year Overall survival	659 per 1000	547 per 1000 (442 to 672)	RR 0.83 (0.67 to 1.02)	1810 (12 studies)	⊕⊖⊖⊖ very low[1,2]	
3-year Overall survival	249 per 1000	115 per 1000 (57 to 234)	RR 0.46 (0.23 to 0.94)	1804 (12 studies)	⊕⊖⊖⊖ very low[1,2]	
Post-operative mortality	35 per 1000	155 per 1000 (89 to 271)	RR 4.40 (2.52 to 7.69)	2093 (14 studies)	⊕⊖⊖⊖ very low[1]	
Reoperation Rate	105 per 1000	254 per 1000 (143 to 451)	RR 2.42 (1.36 to 4.3)	1558 (7 studies)	⊕⊖⊖⊖ very low[1]	
R0 Resection Rate	741 per 1000	675 per 1000 (497 to 912)	RR 0.91 (0.67 to 1.23)	1471 (9 studies)	⊕⊖⊖⊖ very low[1,3,4]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No Arterial Resection	Arterial Resection				
Positive lymph nodes	601 per 1000	679 per 1000 (565 to 817)	RR 1.13 (0.94 to 1.36)	1201 (6 studies)	⊕⊖⊖⊖ very low[1,4]	
Postoperative morbidity	396 per 1000	523 per 1000 (365 to 749)	RR 1.32 (0.92 to 1.89)	1379 (7 studies)	⊕⊖⊖⊖ very low[4,5]	
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio;						
1 Not randomised studies 2 The committee decided to downgrade survival outcomes by one level for imprecision only if there was a significant difference between the groups. 3 I2 81% indicating between studies heterogeneity 4 95% CI crosses 1 default MID (0.8 or 1.25). 5 I2 was 64% indicating between studies heterogeneity						

Table 133: Summary clinical evidence profile for venous resection versus no venous resection

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No venous resection	Venous resection				
1-year overall survival	See comment	See comment	HR 1.38 (1.04 to 1.83)	1935 (6 studies)	⊕⊖⊖⊖ very low[1,2]	
5-year overall survival	See comment	See comment	HR 3.12 (1.55 to 6.29)	525 (4 studies)	⊕⊖⊖⊖ very low[1,2]	
5-year overall survival (b)	172 per 1000	117 per 1000 (77 to 173)	RR 0.68 (0.45 to 1.01)	1532 (11 studies)	⊕⊖⊖⊖ very low[1,2]	
Post-operative mortality	32 per 1000	49 per 1000 (37 to 65)	RR 1.53 (1.16 to 2.02)	8624 (28 studies)	⊕⊖⊖⊖ very low[1,3]	
Reoperation Rate	90 per 1000	122 per 1000 (102 to 146)	RR 1.35 (1.13 to 1.62)	6398 (11 studies)	⊕⊖⊖⊖ very low[1,3]	
R1-R2 resection rate	345 per 1000	472 per 1000 (414 to 538)	RR 1.37 (1.2 to 1.56)	3303 (18 studies)	⊕⊖⊖⊖ very low[3,4]	
Overall operative morbidity	330 per 1000	390 per 1000 (333 to 456)	RR 1.18 (1.01 to 1.38)	6249 (16 studies)	⊕⊖⊖⊖ very low[1,3,5]	
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes.						

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No venous resection	Venous resection				
The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). *CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;*						
1 No randomised, blinding or allocation concealment *2 The committee decided to downgrade survival outcomes by one level for imprecision only if there was a significant difference between the groups.* *3 95% CI crosses 1 default MID (0.8 or 1.25).* *4 I2 is 68% indicating high between studies heterogeneity* *5 I2 is 55% indicating high between studies heterogeneity*						

10.2.5 Economic evidence

A literature review of published cost effectiveness analyses did not identify any relevant studies for this topic. Although there were potential implications for resource use associated with making recommendations in this area, other topics in the guideline were agreed as a higher economic priority. Consequently, bespoke economic modelling was not done for this topic.

10.2.6 Evidence Statements

10.2.6.1 Minimally invasive (laparoscopic & robotic) versus open pancreaticoduodenectomy

Local or distant recurrence

No evidence was identified to inform this outcome

Overall Survival

No evidence was identified to inform this outcome

Postoperative Mortality

Very low quality evidence from 9 retrospective cohort studies (n=768) showed no clinically important difference between minimally invasive pancreaticoduodenectomy and open pancreaticoduodenectomy on post-operative mortality in adults with resectable or borderline resectable pancreatic cancer: RR 0.75 (95% CI, 0.45-1.23).

R0 Resection Rate

Very low quality evidence from 9 retrospective cohort studies (n=672) showed that there is a clinically important difference favouring minimally invasive pancreaticoduodenectomy on achieving an R0 resection compared to open pancreaticoduodenectomy in adults with resectable or borderline resectable pancreatic cancer: RR 1.08 (95% CI, 1.02-1.14).

Operation time (mins)

Very low quality evidence from 6 retrospective cohort studies (n=535) showed that there is a clinically important difference favouring open pancreaticoduodenectomy on operation time

(mins) compared to minimally invasive pancreaticoduodenectomy in adults with resectable or borderline resectable pancreatic cancer: MD 109.99 (95% CI, 2.74-217.24).

Treatment Related Morbidity

Delayed Gastric Emptying

Very low quality evidence from 8 retrospective cohort studies (n=758) showed no clinically important difference between minimally invasive pancreaticoduodenectomy and open pancreaticoduodenectomy on delayed gastric emptying in adults with resectable or borderline resectable pancreatic cancer: RR 1.04 (95% CI, 0.63-1.72).

Pancreatic Fistula

Very low quality evidence from 13 retrospective cohort studies (n=972) showed no clinically important difference between minimally invasive pancreaticoduodenectomy and open pancreaticoduodenectomy on pancreatic fistula formation in adults with resectable or borderline resectable pancreatic cancer: RR 1.04 (95% CI, 0.8-1.34).

Reoperation Rate

Very low quality evidence from 8 retrospective cohort studies (n=845) showed no clinically important difference between minimally invasive pancreaticoduodenectomy and open pancreaticoduodenectomy on the relative rates of reoperation in adults with resectable or borderline resectable pancreatic cancer: RR 0.75 (95% CI, 0.45-1.23).

Blood Loss (mls)

Very low quality evidence from 5 retrospective cohort studies (n=180) showed that there is a clinically important difference favouring minimally invasive pancreaticoduodenectomy on blood loss compared with open pancreaticoduodenectomy in adults with resectable or borderline resectable pancreatic cancer: MD = -398.6 (95% CI, -746.26 to -50.95).

Lymph Node Harvest/Retrieval

Very low quality evidence from 4 retrospective cohort studies (n=228) patients showed no clinically important difference between minimally invasive pancreaticoduodenectomy and open pancreaticoduodenectomy on lymph node retrieval in adults with resectable or borderline resectable pancreatic cancer: MD 1.23 (95% CI, -2.29 to 4.75).

Quality of Life

No evidence was identified to inform this outcome

Patient Experience

No evidence was identified to inform this outcome

PROMs

No evidence was identified to inform this outcome

10.2.6.2 Pylorus preserving Whipple (PPW) versus Classic Whipple (CW)

Local or distant recurrence

No evidence was identified to inform this outcome

Overall Survival

Low quality evidence from 3 RCTs (n=335) showed no clinically important difference between Pylorus-preserving Whipple and Classic Whipple on overall survival in adults with resectable or borderline resectable pancreatic cancer: HR=0.73 (95% CI, 0.43-1.22).

Postoperative Mortality

Very low quality evidence from 7 RCTs (n=464) showed no clinically important difference between Pylorus-preserving Whipple and Classic Whipple on post-operative mortality in adults with resectable or borderline resectable pancreatic cancer: RR 0.7 (95% CI, 0.31-1.55).

R0 Resection Rate

Very low quality evidence from 3 RCTs (n=359) showed no clinically important difference between Pylorus-preserving Whipple and Classic Whipple on achieving an R0 resection in adults with resectable or borderline resectable pancreatic cancer patients: RR 0.99 (95% CI, 0.74-1.05).

Operation Time (mins)

Very low quality evidence from 7 RCTs (n=472) showed that there is a clinically important difference favouring Pylorus-preserving Whipple on operation time compared to Classic Whipple in adults with resectable or borderline resectable pancreatic cancer: MD -45.22 (95% CI, -74.67 to -15.78).

Treatment related morbidity

Delayed Gastric Emptying

Very low quality evidence from 7 RCTs (n=459) showed no clinically important difference between Pylorus-preserving Whipple and Classic Whipple on frequency of delayed gastric emptying in adults with resectable or borderline resectable pancreatic cancer: RR 2.15 (95% CI, 0.98-4.71).

Pancreatic Fistula

Very low quality evidence from 7 RCTs (n=468) showed no clinically important difference between Pylorus-preserving Whipple and Classic Whipple on pancreatic fistula formation in adults with resectable or borderline resectable pancreatic cancer: RR 0.97 (95% CI, 0.56-1.69).

Biliary Leakage

Very low quality evidence from 5 RCTs (n=380) showed no clinically important difference between Pylorus-preserving Whipple and Classic Whipple on biliary leakage in adults with resectable or borderline resectable pancreatic cancer: RR 0.95 (95% CI, 0.18-5.16).

Reoperation Rate

Very Low quality evidence from 3 RCTs (n=320) showed no clinically important difference between Pylorus-preserving Whipple and Classic Whipple on reoperation rate in adults with resectable or borderline resectable pancreatic cancer: RR 0.82 (95% CI, 0.44-1.53).

Intraoperative Blood Loss (mls)

Very low quality evidence from 5 RCTs (n=404) showed that there is a clinically important difference favouring Pylorus-preserving Whipple on blood loss compared to Classic Whipple

in adults with resectable or borderline resectable pancreatic cancer: MD -0.32 (95% CI, -0.62 to -0.03).

Surgical Site Infection

Very low quality evidence from 4 RCTs (n=251) showed no clinically important difference between Pylorus-preserving Whipple and Classic Whipple on surgical site infection in adults with resectable or borderline resectable pancreatic cancer: RR 0.86 (95% CI, 0.39-1.88).

Hospital Stay (days)

Low quality evidence from 5 RCTs (366) showed no clinically important difference between Pylorus-preserving Whipple and Classic Whipple on length of hospital stay in adults with resectable or borderline resectable pancreatic cancer: MD 0.26 (95% CI -2.04 to 2.56).

Lymph Node Harvest

No evidence was identified to inform this outcome.

Quality of Life

No evidence was identified to inform this outcome

Patient Experience

No evidence was identified to inform this outcome

PROMs

No evidence was identified to inform this outcome

10.2.6.3 Minimally invasive laparoscopic distal pancreatectomy versus open pancreatectomy

Local or distant recurrence

No evidence was identified to inform this outcome

Overall Survival

No evidence was identified to inform this outcome

Postoperative Mortality

Very low quality evidence from 17 retrospective cohort studies (n=1723) showed no clinically important difference between minimally invasive laparoscopic distal pancreatectomy and open pancreatectomy on post-operative mortality in adults with resectable or borderline resectable pancreatic cancer: RR 0.63 (95% CI, 0.2-2.01).

Treatment Related Morbidity

Positive Margins

Very low quality evidence from 7 retrospective cohort studies (n=1331) showed no clinically important difference between minimally invasive laparoscopic distal pancreatectomy and open pancreatectomy on positive margin rate in adults with resectable or borderline resectable pancreatic cancer: RR 0.61 (95% CI, 0.26-1.48).

Pancreatic Fistula

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Very low quality evidence from 18 retrospective cohort studies (n=1814) showed no clinically important difference between minimally invasive laparoscopic distal pancreatectomy and open pancreatectomy on frequency of any pancreatic fistula formation in adults with resectable or borderline resectable pancreatic cancer: RR 0.93 (95% CI, 0.77-1.13).

Very low quality evidence from 6 retrospective cohort studies (n=834) showed no clinically important difference between minimally invasive laparoscopic distal pancreatectomy and open pancreatectomy on frequency of ISGPF Grade B-C pancreatic fistula formation in adults with resectable or borderline resectable pancreatic cancer: RR 0.90 (95% CI, 0.63-1.29).

Reoperation Rate

Very low quality evidence from 5 retrospective cohort studies (n=847) showed no clinically important difference between minimally invasive laparoscopic distal pancreatectomy and open pancreatectomy on reoperation rate in adults with resectable or borderline resectable pancreatic cancer: RR 0.79 (95% CI, 0.29-2.15).

Operative Blood Loss (mls)

Very low quality evidence from 16 retrospective cohort studies (n=1341) showed that there is a clinically important difference favouring minimally invasive laparoscopic distal pancreatectomy on blood loss (mls) compared to open pancreatectomy in adults with resectable or borderline resectable pancreatic cancer: MD -332.2 (95% CI, -480.99 to -183.45).

Surgical Site Infection

Very low quality evidence from 11 retrospective cohort studies (n=1127) showed that there is a clinically important difference favouring minimally invasive laparoscopic distal pancreatectomy on rate of surgical site infection compared to open pancreatectomy in adults with resectable or borderline resectable pancreatic cancer: RR 0.49 (95% CI, 0.28-0.87).

Operation Time (mins)

Very low quality evidence from 18 retrospective cohort studies (n=1562) showed no clinically important difference between minimally invasive laparoscopic distal pancreatectomy and open pancreatectomy on operation time (minutes) in adults with resectable or borderline resectable pancreatic cancer: MD 8.88 (95% CI, -6.46 to 24.23).

Hospital Stay (days)

Very low quality evidence from 20 retrospective cohort studies (n=1811) showed that there is a clinically important difference favouring minimally invasive laparoscopic distal pancreatectomy on length of hospital stay (days) compared to open pancreatectomy in adults with resectable or borderline resectable pancreatic cancer: MD -3.88 (95% CI, -4.92 to -2.83).

Time to Oral Intake

Very low quality evidence from 6 retrospective cohort studies (n=388) showed that there is a clinically important difference favouring minimally invasive laparoscopic distal pancreatectomy on time to oral intake compared to open pancreatectomy in adults with resectable or borderline resectable pancreatic cancer: MD -1.48 (95% CI, -2.43 to -0.53).

Lymph Node Harvest

No evidence was identified to inform this outcome

.

Quality of Life

No evidence was identified to inform this outcome

Patient Experience

No evidence was identified to inform this outcome

PROMs

No evidence was identified to inform this outcome

10.2.6.4 Minimally invasive robotic pancreatectomy versus open pancreatectomy

Local or distant recurrence

No evidence was identified to inform this outcome

Overall Survival

No evidence was identified to inform this outcome

Postoperative Mortality

Very low quality evidence from 7 retrospective cohort studies (n=340) showed no clinically important difference between minimally invasive robotic pancreatectomy and open pancreatectomy on post-operative mortality in adults with resectable or borderline resectable pancreatic cancer: RR 1.67 (95% CI, 0.45-6.16).

Treatment Related Morbidity

Positive Margins

Very low quality evidence from 4 retrospective cohort studies (n=124) showed that there is a clinically important difference favouring minimally invasive robotic pancreatectomy on positive margin rate compared to open pancreatectomy in adults with resectable or borderline resectable pancreatic cancer: RR 0.31 (95% CI, 0.11-0.90).

Pancreatic Fistula

Very low quality evidence from 5 retrospective cohort studies (n=209) showed no clinically important difference between minimally invasive robotic pancreatectomy and open pancreatectomy on rate of pancreatic fistula formation in adults with resectable or borderline resectable pancreatic cancer: RR 0.82 (95% CI, 0.42-1.39).

Reoperation Rate

No evidence was identified to inform this outcome

Operative Blood Loss

No evidence was identified to inform this outcome

Operative Time (mins)

Very low quality evidence from 3 retrospective cohort studies (n=114) showed no clinically important difference between minimally invasive robotic pancreatectomy and open pancreatectomy on operative time (mins) in adults with resectable or borderline resectable pancreatic cancer: MD 117.71 (95% CI, -139.76 to 375.18).

Hospital Stay (days)

Very low quality evidence from 3 retrospective cohort studies (n=114) showed no clinically important difference between minimally invasive robotic pancreatectomy and open pancreatectomy on length of hospital stay (days) in adults with resectable or borderline resectable pancreatic cancer: MD 4.71 (95% CI, -9.45 to 0.03).

Time to Oral Intake

No evidence was identified to inform this outcome

Lymph Node Harvest

No evidence was identified to inform this outcome

Quality of Life

No evidence was identified to inform this outcome

Patient Experience

No evidence was identified to inform this outcome

PROMs

No evidence was identified to inform this outcome

10.2.6.5 Extended versus standard lymphadenectomy

Local or distant recurrence

No evidence was identified to inform this outcome

Overall Survival

Low quality evidence from 4 RCTs (n=412) showed no clinically important difference between extended lymphadenectomy and standard lymphadenectomy on overall survival in adults with resectable or borderline resectable pancreatic cancer: HR=1.09 (95% CI, 0.84-1.41).

Margin Status

Very low quality evidence from 4 RCTs (n=428) showed no clinically important difference between extended lymphadenectomy and standard lymphadenectomy on survival in adults with a positive margin status and resectable or borderline resectable pancreatic cancer: RR 0.65 (95% CI, 0.33-1.31).

Moderate quality evidence from 4 RCTs (n=428) showed no clinically important difference between extended lymphadenectomy and standard lymphadenectomy on survival in adults with negative margin status and resectable or borderline resectable pancreatic cancer: RR 1.06 (95% CI, 0.93-1.21).

Lymph Node Status

Low to very low quality evidence from 4 RCTs showed no clinically important difference between extended lymphadenectomy and standard lymphadenectomy on overall survival in adults with either positive lymph node status (n=280; HR=1.04 [95% CI, 0.76-1.42]) or

negative lymph node status (n=132; HR=1.06 [95% CI, 0.58-1.94]) and resectable or borderline resectable pancreatic cancer.

Postoperative Mortality

No evidence was identified to inform this outcome

Treatment Related Morbidity

Pancreatic Fistula

No evidence was identified to inform this outcome

Reoperation Rate

No evidence was identified to inform this outcome

Operative Time (mins)

No evidence was identified to inform this outcome

Hospital Stay (days)

No evidence was identified to inform this outcome

Lymph Node Harvest

No evidence was identified to inform this outcome

Quality of Life

No evidence was identified to inform this outcome

Patient Experience

No evidence was identified to inform this outcome

PROMs

No evidence was identified to inform this outcome

10.2.6.6 Arterial resection versus no arterial resection

Local or distant recurrence

No evidence was identified to inform this outcome

Overall Survival

Very low quality evidence from 12 retrospective observational studies (n=1810) showed no clinically important difference between arterial resection and no arterial resection on 1-year overall survival in adults with resectable or borderline resectable pancreatic cancer: RR 0.83 (95% CI, 0.67-1.02).

Very low quality evidence from 12 retrospective observational studies (n=1787) showed that there is a clinically important difference favouring no arterial resection on 3-year overall survival compared to arterial resection in adults with resectable or borderline resectable pancreatic cancer: RR 0.46 (95% CI, 0.23-0.94).

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Postoperative Mortality

Very low quality evidence from 14 retrospective observational studies (n=2093) showed that there is a clinically important difference favouring no arterial resection on post-operative mortality (including in-hospital, 30-day and 60-day mortality) compared to arterial resection (concomitant with pancreatectomy) in adults with resectable or borderline resectable pancreatic cancer: RR 4.40 (95% CI, 2.52-7.69).

Treatment Related Morbidity

Reoperation Rate

Very low quality evidence from 7 retrospective observational studies (n=1558) showed there is a clinically important difference favouring no arterial resection on reoperation rate compared to arterial resection in adults with resectable or borderline resectable pancreatic cancer: RR 2.42 (95% CI, 1.36 to 4.30).

R0 Resection Rates

Very low quality evidence from 9 retrospective observational studies (n=1471) showed no clinically important difference between arterial resection and no arterial resection on achieving an R0 resection in adults with resectable or borderline resectable pancreatic cancer: RR 0.91 (95% CI, 0.67-1.23).

Positive Lymph Nodes

Very low quality evidence from 6 retrospective observational studies (n=1201) showed no clinically important difference between arterial resection and no arterial resection on positive lymph nodes in adults with resectable or borderline resectable pancreatic cancer: RR 1.13 (95% CI, 0.94-1.36).

Postoperative Morbidity

Very low quality evidence from 7 retrospective observational studies (n=1379) showed no clinically important difference between arterial resection and no arterial resection on post-operative morbidity in adults with resectable or borderline resectable pancreatic cancer: RR 1.32 (95% CI, 0.92-1.89).

Quality of Life

No evidence was identified to inform this outcome

Patient Experience

No evidence was identified to inform this outcome

PROMs

No evidence was identified to inform this outcome

10.2.6.7 Venous resection versus no venous resection

Local or distant recurrence

No evidence was identified to inform this outcome

Overall Survival

Very low quality evidence from 6 retrospective cohort studies (n=1935) showed that there is a clinically important difference favouring no venous resection on 1-year overall survival compared to venous resection in adults with resectable or borderline resectable pancreatic cancer: HR=1.38 (95% CI, 1.04-1.83).

Very low quality evidence from 4 retrospective cohort studies (n=525) showed that there is a clinically important difference favouring no venous resection on 5-year overall survival compared to venous resection in adults with resectable or borderline resectable pancreatic cancer: HR=3.12 (95% CI, 1.55-6.29). By contrast, if the raw survival data from all 11 retrospective cohort studies (n=1532) are considered, venous resection is favoured on 5-year overall survival compared to no venous resection, although there is some uncertainty: RR 0.68 (95% CI, 0.45-1.01).

Postoperative Mortality

Very low quality evidence from 28 retrospective cohort studies (n=8624) showed that there is a clinically important difference favouring no venous resection on post-operative mortality compared to venous resection in adults with resectable or borderline resectable pancreatic cancer: RR 1.53 (95% CI, 1.16-2.02).

Treatment related morbidity

Reoperation Rates

Very low quality evidence from 11 retrospective cohort studies (n=6398) showed that there is a clinically important difference favouring no venous resection on reoperation rate compared to venous resection in adults with resectable or borderline resectable pancreatic cancer: RR 1.35 (95% CI, 1.13-1.62).

R1-2 Resection Rates

Very low quality evidence from 18 retrospective cohort studies (n=3303) showed that there is a clinically important difference favouring no venous resection on R1 and R2 resection rates compared to venous resection in adults with resectable or borderline resectable pancreatic cancer: RR 1.37 (95% CI, 1.2-1.56).

Postoperative Morbidity

Very low quality evidence from 16 retrospective cohort studies (n=6249) showed that there is a clinically important difference favouring no venous resection on post-operative morbidity compared to venous resection in adults with resectable or borderline resectable pancreatic cancer: RR 1.18 (95% CI, 1.01-1.38).

Lymph node harvest

No evidence was identified to inform this outcome

Quality of Life

No evidence was identified to inform this outcome

Patient Experience

No evidence was identified to inform this outcome

PROMs

No evidence was identified to inform this outcome

10.2.7 Recommendations

37. For people having surgery for head of pancreas cancer, consider pylorus-preserving resection if the tumour can be adequately resected.

38. Consider standard lymphadenectomy[a] for people having head of pancreas resection.

10.2.8 Evidence to recommendations

10.2.8.1 Relative value placed on the outcomes considered

Local and distant recurrence, overall survival, post-operative death (30 day/90 day), treatment related morbidity and mortality, lymph node harvest, health related quality of life, patients experience and PROMs were considered to be the critical outcomes to this question.

Lymph node harvest was considered to be a particularly important outcome when comparing the extent of lymphadenectomy as it was a way to determine whether surgery did in fact include extended lymphadenectomy according to current definitions.

The outcomes of local/distant recurrence, health-related quality of life, patient experience and patient reported outcome measures were not reported for any of the comparisons of interest.

Post-operative mortality and treatment-related morbidity were not reported for the comparison of extended lymphadenectomy against standard lymphadenectomy. Overall survival was not reported for comparisons of minimally invasive pancreatoduodenectomy against open pancreatoduodenectomy or minimally invasive pancreatectomy (either laparoscopic or robotic) against open pancreatectomy. Lymph node harvest was not reported for any comparisons other than minimally invasive pancreatoduodenectomy against open pancreatoduodenectomy.

R0 resection rates were reported for some of the comparisons of interest, but the Committee did not use this information when agreeing recommendations due to the limitations of the evidence.

10.2.8.2 Quality of evidence

The quality of the evidence was assessed by GRADE and the Cochrane risk of bias checklist.

The quality of the evidence for comparisons of minimally invasive surgery versus open surgery was very low for all outcomes. The committee noted that the populations included in the studies were not exclusively people with pancreatic cancer and that this mixed population represented a high risk of overestimating the benefit of minimally invasive and/or robotic surgery as people with periampullary cancer, benign disease or other malignancies were likely to have better outcomes. In addition they noted that there was a risk of selection bias - studies included in the review were not randomised trials and therefore it is possible that the people selected for surgery represent the proportion of pancreatic patients who were considered likely to benefit from surgery and have favourable outcomes.

[a] As defined by Tol et al. (2014) Definition of a standard lymphadenectomy in surgery for pancreatic ductal adenocarcinoma: a consensus statement by the International Study Group on Pancreatic Surgery (ISGPS). Surgery 156(3): 591–600

Due to the limitations with the evidence, the committee were unable to determine which form of pancreatoduodenectomy was the most effective; whether minimally invasive laparoscopic or open distal pancreatectomy was the most effective; or whether minimally invasive robotic or open pancreatectomy was the most effective. They agreed not to make any recommendations for clinical practice in these areas but to recommend further research instead.

The quality of the evidence comparing pylorus preserving Whipple (PPW) with classic Whipple (CW) was very low quality for all outcomes except overall survival which was low quality. In addition, there was not enough detail reported to determine whether the trials were at risk of selective outcome reporting and many of the included trials did not adequately report the randomisation methods or blinding. In addition the populations included in the studies were not exclusively people with pancreatic cancer and there was a risk of selection bias in the non-randomised studies as it was possible that the people selected for surgery represent the proportion of pancreatic cancer patients who were considered likely to benefit from surgery and have favourable outcomes. Therefore the committee were not able to make any strong recommendations.

The quality of the evidence for extended lymphadenectomy versus standard lymphadenectomy was low and only reported survival outcomes. The committee noted that whilst this evidence included randomised trials, in a number of cases these trials were underpowered or there was insufficient detail to ascertain whether the study was powered. In addition, there was not enough detail reported to determine whether the trials were at risk of selective outcome reporting and many of the included trials did not adequately report the randomisation methods or blinding. However, the committee considered that the reasons for the low quality evaluation were a result of the randomised trials being small and underpowered. They also noted that the evidence for this comparison was directly relevant as it only included people with pancreatic cancer. The committee considered whether or not to make a recommendation for future research in this area but agreed not to do so as only a small population group are affected and there were likely to be higher priorities for research funding. Therefore the committee agreed to make recommendations for clinical practice but were not able to make any strong recommendations.

The quality of the evidence for the comparisons of arterial resection versus no arterial resection and venous resection versus no venous resection was very low for all outcomes. The committee noted that whilst the evidence was a systematic review it only included observational studies, with small sample sizes and high heterogeneity between studies for overall survival and mortality. Given the very low quality of the evidence the committee agreed not to make any recommendations for clinical practice. Arterial resection is a high-risk procedure, the benefits of which are uncertain based on the available evidence so the committee agreed not to make any recommendations for clinical practice about this type of surgery. The committee acknowledged that portal venous resection in an effort to obtain a clear surgical margin (R0) appeared, based on the evidence, to be safe and is an increasingly frequent practice in high-volume centres. However, given the low quality of this evidence, the committee agreed not to make any recommendations for clinical practice. The committee discussed whether or not to make a recommendation for future research but agreed that RCTs would be difficult to construct, and only a small number of people would be suitable for enrolment. It would therefore take too long to collect the necessary data.

10.2.8.3 Consideration of clinical harms and benefits

The committee did not make clinical practice recommendations for a number of the comparisons of interest as they considered the evidence to be of too low quality to allow them to adequately balance the benefits and harms for people with pancreatic cancer.

The committee noted, based on the evidence, that blood loss and operative time appeared to be significantly reduced with PPW (compared with CW), but no difference in survival was

found between the two techniques. The committee acknowledged there were limitations with the evidence, but agreed that it was possible to make recommendations for clinical practice because although there were mixed populations in the evidence the patient populations were comparable and the differences were in the Whipple's procedure. They recommended PPW based on the evidence of reduced blood loss and operative time and their clinical experience that it is a less extensive procedure and preserving the pylorus and stomach is potentially beneficial to people, particularly in terms of minimising the number or severity of side effects and surgical risks.

Whilst the committee acknowledged that there may be some differences between what the evidence reported as 'standard' and 'extended' lymphadenectomy and what is used in current practice, the committee noted, based on the evidence, that no survival difference had been shown between standard and extended lymphadenectomy. Based on their clinical experience that the extended procedure would result in increased morbidity, because it is more complex surgery, the committee agreed to recommend standard lymphadenectomy (as defined by Tol et al. (2014.

The committee considered standard lymphadenectomy to be sufficient to ensure adequate clearance of lymph nodes. The evidence did not provide any details of the morbidity around the extended procedure. However the committee reported clinical experience which suggests greater morbidity from the extended procedure. The committee therefore considered that recommending the standard procedure should help to standardise the approach to lymphadenectomy and minimise the potential risks associated with the extended procedure.

It was agreed that there needs to be a balance between the most effective surgery in terms of achieving the most favourable survival and/or recurrence outcomes while minimising the number or severity of side effects and surgical risks. The committee therefore recommended the less extensive procedure for both Whipple's surgery and lymphadenectomy.

10.2.8.4 Consideration of economic benefits and harms

The committee noted that no relevant published economic evaluations had been identified and no additional economic analysis had been undertaken in this area.

The committee considered that the recommendations were unlikely to result in a substantial increase in costs because the less extensive procedure had been recommended in both instances which were likely to have shorter surgery times and reduced morbidity. Consequently the committee considered it was possible that the recommendations could result in a small cost saving compared with current practice.

10.2.8.5 Other considerations

Having reviewed the evidence for the most effective type of surgery for people with resectable or borderline resectable pancreatic cancer, the committee noted that the available data was limited, of low quality and often included mixed populations. Given these issues there was a lot of uncertainty over the effects reported by the evidence which severely restricted the ability of the committee to evaluate the effectiveness of several surgical interventions.

10.2.9 Research Recommendations

7. Prospective randomised trials should be undertaken to compare the effectiveness of minimally invasive pancreatectomy (laparoscopic or robotic) with open pancreatectomy in people with pancreatic cancer.

Minimally invasive surgery is generally considered to be more acceptable to patients than open surgery. It has been introduced successfully for several other types of cancer and has

been shown to improve quality of life. However, there is not enough evidence to determine whether minimally invasive surgery improves morbidity and mortality for people with pancreatic cancer, compared with open surgery. Prospective randomised trials are therefore needed in this area. The outcomes of interest are:

- conversion rate to open surgery
- R0 resection rate
- lymph node yield
- blood loss
- duration of surgery
- complications
- need for critical care
- length of hospital stay
- time to return to normal activity
- mortality of surgery
- long-term survival after surgery
- quality of life, patient experience and patient-reported outcome measures.

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Ogata Y, Hishinuma S, Takahashi S et al. (1997) Indication and results of pancreatectomy with combined resection of vessels for adenocarcinoma of the pancreas. Nippon Geka Gakkai Zasshi 98: 615-621

Ouaissi M, Hubert C, Verhelst R et al. (2010) Vascular resection during pancreatectomy for ductal adenocarcinoma of the pancreas improves resectability but does not achieve cure. World Journal of Surgery 34: 2648-2661

Park DI, Lee JK, Kim JE et al. (2001) The analysis of resectability and survival in pancreatic cancer patients with vascular invasion. Journal of Clinical Gastroenterology 32: 231-234

Settmacher U, Langrehr JM, Husmann I et al. (2004) Reconstruction of visceral arteries with homografts in excision of the pancreas. Chirurg; Zeitschrift fur alle Gebiete der operativen Medizen 75: 1199-1206

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Shimada K, Sakamoto Y, Sano T et al. (2006) Prognostic factors after distal pancreatectomy with extended lymphadenectomy for invasive pancreatic adenocarcinoma of the body and tail. Surgery 139: 288-295

Sperti C, Berselli M, Pedrazzoli S (2010) Distal pancreatectomy for body-tail pancreatic cancer: is there a role for celiax axis resection. Pancreatology 10: 491-498

Stitzenberg KB, Watson JC, Roberts A et al. (2008) Survival after pancreatectomy with major arterial resection and reconstruction. Annals of Surgical Oncology 15: 1399-1406

Sugiura Y, Horio T, Aiko S et al. (2009) Pancreatectomy for pancreatic cancer with reference to combined resection of the vessels, twenty nine year experience by a single surgeon. The Keio Journal of Medicine 58: 103-109

Tamura K, Kin S, Ono K et al. (1989) Operative results in cancer of the pancreas, especially complicated with large vascular involvement. Nippon Geka Gakkai Zasshi 90: 1032-1042

Wang C, Wu H, Xiong J et al. (2008) Pancreaticoduodenectomy with vascular resection for local advanced pancreatic cancer: a single centre retrospective study. Journal of Gastrointestinal Surgery 12: 2183-2190

Wu X, Tao R, Lei R et al. (2008) Distal pancreatectomy combined with celiac axis resection in treatment of carcinoma of the body/tail of the pancreas: a single -centre experience. Annals of Surgical Oncology 17: 1359-1366

10.2.10.6 Studies included in “Sui et al. 2012” (n=3)

Kooby DA, Hawkins WG, Schmidt CM et al. (2010) A multicentre analysis of distal pancreatectomy for adenocarcinoma: is laparoscopic resection appropriate? Journal of the American College of Surgeons 62: 171-174

Shimura T, Suehiro T, Mochida Y et al. (2006) Laparoscopy assisted distal pancreatectomy with mobilisation of the distal pancreas and spleen outside the abdominal cavity. Surgical Laparoscopy, Endoscopy & Percutaneous Techniques 16: 387-389

Zhao GD, Hu MG, Liu R (2010) A comparative study of laparoscopic distal pancreatectomy and open distal pancreatectomy. Nan Fang Yi Ke Da Xue Xue Bao [Journal of Southern Medical University] 30: 2756-2758

10.2.10.7 Studies included in “Venkat et al. 2012” (n=18)

Aly MY, Tsutsumi K, Nakamura M et al. (2010) Comparative Study of laparoscopic and open distal pancreatectomy. Journal of Laparoendoscopic Advanced Surgical Techniques 20: 435-440

Baker MS, Bentrem DJ, Ujiki MB et al. (2009) A prospective single institution comparison of peri-operative outcomes for laparoscopic and open distal pancreatectomy. Surgery 146: 635-643

Bruzoni M and Sasson AR (2008) Open and laparoscopic spleen preserving, splenic vessel preerving distal pancreatectomy: indications and outcomes. Journal of Gastrointesinal Surgery 12: 1202-1206

Casesdei R, Ricci C, D'Ambra M et al. (2010) Laparoscopic versus open distal pancreatectomy in pancreatic tumours: a case control study. Updates in Surgery 62: 171-174

DiNorcia J, Schrope BA, Lee MK et al. (2010) Laparoscopic distal pancreatectomy offers shorter hospital stays with fewer complications. Journal of Gastrointestinal Surgery 14: 1804-1812

Eom BW, Jang JY, Lee SE et al. (2008) Clinical outcomes compared between laparoscopic and open distal pancreatectomy. Surgical Endoscopy 22: 1334-1338

Finan KR, Cannon EE, Kim EL et al. (2009) Laparoscopic and open distal pancreatectomy: a comparison of outcomes. The American Surgeon 75: 671-679

Jayaraman S, Gonen M, Brennan MF et al. (2010) Laparoscopic distal pancreatectomy: evaluation of a technique at a single institution. Journal of the American College of Surgeons 211: 503-509

Kim SC, Park KT, Hwang JW et al. (2008) Comparative analysis of clincal outcomes for laparoscopic distal pancreatic resection and open distal pancreatic resection at a single institution. Surgical Endoscopy 22(10): 2261-2268

Kooby DA, Gillespie T, Bentrem D et al. (2008) Left sided pancreatectomy: a multicentre comparison of laparoscopic and open approaches. Annals of Surgery 248: 438-446

Matsumoto T, Shibata K, Ohta M et al. (2008) Laparoscopic distal pancreatectomy and open distal pancreatectomy: a non ramdomised comparative study. Surgical Laparoscopy, Endoscopy & Percutaneouss Techniques 18: 340-343

Misawa T, Shiba K, Usuba T et al. (2007) Systemic inflammatory response syndrome after hand assisted laparoscopic distal pancreatectomy. Surgical Endoscopy 21: 1446-1449

Nakamura Y, Uchida E, Aimoto T et al. (2009) Clinical outcome of laparoscopic distal pancreatectomy. Journal of Hepatobiliary Pancreatic Surgery 16: 35-41

Tang CN, Tsui KK, Ha JP et al. (2007) Laparoscopic distal pancreatectomy: a comparative study. Hepatogastroenterology 54: 265-271

The, SH, Tseng, D, Sheppard, BC (2007) Laparoscopic and open distal pancreatic resection for benign pancreatic disease. Journal of Gastrointestinal Surgery 11: 1120-1125

Velanovich V (2006) Case control comparison of laparoscopic versus open distal pancreatectomy. Journal of Gastrointestinal Surgery 10: 95-98

Vijan SS, Ahmed KA, Harmsen WS (2010) Laparoscopic versus open distal pancreatectomy: a single institution comparative study. Archives of Surgery 145: 616-621

Waters JA, Canal DF, Wiebke EA et al. (2010) Robotic distal pancreatectomy: cost effective. Surgery 148: 814-823

10.2.10.8 Studies included in “Yu et al. 2014” (n=4)

Banz VM, Croagh D, Coldham C et al. (2012) Factors influencing outcome in patients undergoing portal vein resection with adjuvant chemotherapy for adenocarcinoma of the pancreas. European Journal of Surgical Oncology 38: 72-9

Illumnati G, Carboni F, Lorusso R et al. (2008) Results of a pancreatectomy with a limited venous resection for pancreatic cancer. Surgery Today 38: 517-523

Kaneoka Y, Yamaguchi A, Isogai M (2009) Portal or superior mesenteric vein resection for pancreatic head adenocarcinoma: prognostic value of the length of venous resection. Surgery 145: 417-425

Yang KX, Shi KW, Xi PC et al. (2016) Pancreaticoduodenectomy combined with resection of PV/SMV for carcinoma of the head of the pancreas. Chinese Journal of Hepatobiliary Surgery 16: 176-178

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10.2.10.9 Studies included in "Zhang et al. 2013" (n=7)

Buchs NC, Addeo P, Bianco FM et al. (2011) Robotic versus open pancreaticodudenectomy: a comparative study at a single institution. World Journal of Surgery 35: 2739-2746

Chalikonda S, Aguilar-Saavedra JR, Walsh RM (2012) Laparoscopic robot assisted pancreaticoduodenectomy: a case matched comparison with open resection. Surgical Endoscopy 26: 2397-2402

Hammill C, Cassera M, Swanstrom L et al. (2010) Robotic Assistance may provide the technical capability to perform a safe, minimally invasive pancreaticoduodenectomy. HPB 12: 198 (abstract)

Kang CM, Kim DH, Lee WJ et al. (2011) Initial experiences using robot assisted central pancreatectomy with pancreaticogastrostomy: a potential way to advanced pancreatectomy. Surgical Endoscopy 25: 1101-1106

Walsh M, Chalikonda S, Saavedra JRA et al. (2011) Laparoscopic robotic assisted Whipple: early results of a novel technique and comparison with the standard open procedure. Surgical Endoscopy 25: S221

Waters JA, Canal DF, Wiebke EA et al. (2010) Robotic Distal Pancreatectomy: cost effective. Surgery 148: 814-823

Zhou NX, Chen JZ, Liu Q et al. (2011) Outcomes of pancreatoduodenectomy with robotic surgery versus open surgery. The International Journal of Medical Robotics and Computer Assisted Surgery 7: 131-137

10.2.10.10 Studies included in "Zhou et al. 2012" (n=2)

Allema JH, Reinders ME, Van Gulik TM et al. (1994) Portal vein resection in patients undergoing pancreaticoduodenectomy for carcinoma of the pancreatic head. British Journal of Surgery 81: 1642-1646

Howard TJ, Villanustre N, Moore SA et al. (2003) Effiicacy of venous reconstruction in patients with adenocarcinoma of the pancreatic head. Journal of Gastrointestinal Surgery 7: 1089-1095

10.3 Adjuvant treatment

Review question: What is the most effective adjuvant therapy (chemotherapy, chemoradiotherapy, biological therapy, immunotherapy, combinations of therapies) for adults who have undergone surgical resection of pancreatic adenocarcinoma?

10.3.1 Introduction

Outcomes after surgery for pancreatic cancer are very poor. Most people die from metastatic pancreatic cancer, so non-surgical treatments are often used after surgery with the aim of improving patient survival. Clinical trials have been conducted to evaluate a number of different adjuvant treatment strategies and it is generally accepted that adjuvant therapy has increased 5 year survival after surgery for pancreatic cancer.

Whilst adjuvant therapy is now established as standard of care, there is still uncertainty regarding what is the optimal treatment modality and regimen. Treatment modalities which have been tested in this setting include chemotherapy, radiotherapy, immunotherapy and combinations of these approaches.

Guidance is needed what is the most effective adjuvant therapy for people who have undergone surgical resection of primary pancreatic cancer.

10.3.1.1 Review protocol summary

The review protocol summary used for this question can be found in Table 134. Full details of the review protocol can be found in Appendix C.

Table 134: Clinical review protocol summary for the review of most effective adjuvant therapy

Population	Patients who have undergone resection of primary pancreatic cancer	
Intervention/comparison	Chemotherapy	• Difference chemo types/combination regimens • Chemoradiotherapy • No adjuvant therapy
	Combination chemotherapy with chemoradiotherapy	• Combination chemotherapy with chemoradiotherapy • Chemotherapy only • Chemoradiotherapy only • No adjuvant therapy
	Immunotherapy	• Other adjuvant therapy • No adjuvant therapy
	Biological therapy	
Outcomes	• Disease-free survival • Relapse-free survival • Overall Survival • Adverse Events • Health-related quality of life • Patient experience • Patient-reported outcome measures (PROMs)	

10.3.2 Description of clinical evidence

Seventeen RCTs (n=4617) were included in the review (Buchler et al. 1991; Kosuge et al. 2006; Lygidakis et al. 2002; Neoptolemos 2001; Neoptolemos et al. 2004/2009; Neoptolemos et al. 2010/Valle et al. 2014; Neoptolemos et al. 2017; Oettle et al. 2007/Oettle et al. 2013; Regine et al. 2008/2011; Reni et al. 2012; Schmidt et al. 2012; Takada et al. 2002; Ueno et al. 2009; Uesaka et al. 2016; Valle et al. 2014; van Laethem et al. 2010; Yoshitomi et al. 2008). All of the studies were in adults with resected pancreatic cancer.

All the included studies were RCTs, several of which were international multicentre studies. Ten direct comparisons were found with the majority of evidence concerning the efficacy of chemotherapy (predominantly a flouroracil and folinic acid combination, or gemcitabine) compared to no adjuvant therapy. There were only a few identified studies that examined a combined adjuvant option with chemotherapy either preceding or following chemoradiotherapy. Only single studies were found that examined immunotherapy, chemoimmunotherapy, or chemoradioimmunotherapy as adjuvant therapies, whilst no studies were found that examined adjuvant biological therapy. Three of the identified studies were phase II studies (Yoshitomi et al. 2008; Reni et al. 2012; van Laethem et al. 2010).

Eight RCTs were found that compared chemotherapy with no adjuvant therapy (Kosuge et al. 2006; Lygidakis et al. 2002; Neoptolemos 2001; Neoptolemos et al. 2004, 2009; Oettle et al. 2007; Oettle et al. 2013; Takada et al. 2002; Ueno et al. 2009).

Four RCTs were found that compared chemotherapy using gemcitabine with another type of chemotherapy (Neoptolemos et al. 2010/Valle et al. 2014; Neoptolemos et al. 2017; Uesaka et al. 2016; Yoshitomi et al. 2008).

Two RCTs were found that compared chemotherapy with chemoradiotherapy (Neoptolemos, Stocken et al. 2004; van Laethem, Hammel et al. 2010).

One RCT was found that compared chemotherapy with chemoimmunotherapy (Lygidakis, Sgourakis et al. 2002).

One RCT was found that compared chemotherapy with chemoradioimmunotherapy (Schmidt, Abel et al. 2012).

One RCT was found that compared chemoradiotherapy followed by chemotherapy with no adjuvant therapy, chemotherapy only and chemoradiotherapy only (Neoptolemos, Stocken et al. 2004).

Two RCTs were found that compared chemotherapy using gemcitabine followed by chemoradiotherapy with chemotherapy using another type of drug followed by chemoradiotherapy (Regine, Winter et al 2008; Reni, Balzano et al. 2012).

One RCT was found that compared immunotherapy with no adjuvant therapy (Buchler, Friess et al. 1991).

One RCT was found that compared chemoimmunotherapy with no adjuvant therapy (Lygidakis, Sgourakis et al. 2002).

Evidence from these are summarised in the clinical evidence profiles below (Table 136 to Table 146).

10.3.31 Summary of included studies

2 A summary of the studies that were included in this review are presented in Table 135.

3 **Table 135: Summary of included studies**

Study (Country/ies)	N	Intervention	Comparison(s)	Outcomes	Overall risk of bias
Büchler et al. 1991 (Germany)	61	Immunotherapy (MoAb 494/32)	No adjuvant therapy	Overall survival Adverse events	HIGH
Kosuge et al. 2006 (Japan)	89	Chemotherapy (cisplatin + 5-FU)	No adjuvant therapy	Overall survival Disease-free survival Adverse events	HIGH
Lygidakis et al. 2002 (Greece)	128	Chemotherapy (gemcitabine, carboplatin + mitoxantrone + mitomycin C + fluororacil + folinic acid)	No adjuvant therapy Chemoimmunotherapy (chemotherapy course followed by interleukin-2)	Overall survival Disease-free survival Adverse events	HIGH
Neoptolemos et al. 2001 [ESPAC-1+] (11 European countries)	192	Chemotherapy (5-FU + FA)	No adjuvant therapy	Overall survival Quality of life	HIGH
Neoptolemos et al. 2004 [ESPAC-1 2x2] (11 European countries)	289	Chemotherapy (5-FU + FA)	No adjuvant therapy Chemoradiotherapy (20 Gy in 10 fractions) Chemoradiotherapy (5-FU with 20 Gy) then chemotherapy (5-FU)	Overall survival Adverse events	HIGH
Neoptolemos et al. 2009 ESPAC-3, v.1 (17 countries)	122	Chemotherapy (5-FU + FA)	No adjuvant therapy	Overall survival	HIGH
Neoptolemos et al. 2010/Valle et al. 2014 [ESPAC-3, v.2]	1088	Chemotherapy (gemcitabine)	Chemotherapy (5-FU + FA)	Overall survival Disease-free survival Adverse events	LOW

Study (Country/ies)	N	Intervention	Comparison(s)	Outcomes	Overall risk of bias
(17 countries)				Quality of life	
Neoptolemos et al. 2017 [ESPAC-4] (6 countries)	730	Chemotherapy (gemcitabine)	Chemotherapy (Gemcitabine + Capecitabine)	Overall Survival Relapse-free Survival Adverse Events	HIGH
Oettle et al. 2007/Oettle et al. 2013 (Germany and Austria)	368	Chemotherapy (gemcitabine)	No adjuvant therapy	Overall survival Disease-free survival Adverse events	HIGH
Regine et al. 2008/2011 (USA and Canada)	451	Chemotherapy (gemcitabine) then chemoradiotherapy (50.4 Gy with 5-FU) then chemotherapy (gemcitabine)	Chemotherapy (5-FU) then chemoradiotherapy (50.4 Gy in 28 fractions with 5-FU) then chemotherapy (5-FU)	Overall survival Adverse events	UNCLEAR
Reni et al. 2012a (Italy)	102	Chemotherapy (gemcitabine) with chemoradiotherapy (54-60 Gy in 27-30 fractions with 5-FU or capecitabine) then chemotherapy (gemcitabine)	Chemotherapy (PEFG) with chemoradiotherapy (54-60 Gy in 27-30 fractions with 5-FU or capecitabine) then chemotherapy (PEFG)	Overall survival Disease-free survival Adverse events	HIGH
Schmidt et al. 2012 (Germany and Italy)b	132	Chemotherapy (5-FU + FA)	Chemotherapy with chemoradioimmunotherapy (50.4 Gy in 28 fractions, 5-FU + FA + cisplatin, 3 million units of interferon α-2b)	Overall survival Disease-free survival Adverse events Quality of life	HIGH
Takada et al. 2002 (Japan)	173	Chemotherapy (5-FU and mitomycin C)	No adjuvant therapy	Overall survival Disease-free survival Quality of life	HIGH
Ueno et al. 2009 (Japan)	118	Chemotherapy (gemcitabine)	No adjuvant therapy	Overall survival Disease-free survival Adverse events	LOW
Uesaka et al. 2016 (Japan)	375	Chemotherapy (gemcitabine)	Chemotherapy (S-1)	Overall survival Disease-free survival	LOW

Study (Country/ies)	N	Intervention	Comparison(s)	Outcomes	Overall risk of bias
				Adverse events Quality of life	
Van Laethem et al. 2010 (Various European countries)a	90	Chemotherapy (gemcitabine)	Chemoradiotherapy (50.4 Gy in 28 fractions with gemcitabine)	Overall survival Disease-free survival Adverse events	HIGH
Yoshitomi et al. 2008a (Japan)	99	Chemotherapy (gemcitabine)	Chemotherapy (gemcitabine + UFT)	Overall survival Disease-free survival Adverse events	HIGH
Notes: All studies were RCTs; a, Phase II trials; b; unclear whether study involved other countries.					

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10.3.4 Clinical evidence profile

The clinical evidence profiles for this review question are presented in Table 136 to Table 145.

Table 136: Summary clinical evidence profile for adjuvant chemotherapy versus no adjuvant therapy in resected pancreatic cancer patients

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No adjuvant therapy	Chemotherapy				
Overall Survival - Chemotherapy vs No adjuvant therapy	Study population[1]		HR 0.78 (0.69 to 0.89)	1262 (8 studies)	⊕⊕⊖⊖ low[2,3]	
	833 per 1000	752 per 1000 (709 to 796)				
	Moderate[1]					
	300 per 1000	243 per 1000 (218 to 272)				
Overall Survival - 5FU+FA vs No adjuvant therapy	Study population[1]		HR 0.69 (0.56 to 0.85)	458 (3 studies)	⊕⊕⊖⊖ low[3,4]	
	844 per 1000	723 per 1000 (647 to 794)				
	Moderate[1]					
	300 per 1000	218 per 1000 (181 to 262)				
Overall Survival - Cisplatin+5FU vs No adjuvant therapy	Study population[1]		HR 1.02 (0.64 to 1.62)5	89 (1 study)	⊕⊕⊖⊖ low[3,6,7]	
	818 per 1000	824 per 1000 (664 to 937)				
	Moderate[1]					
	300 per 1000	305 per 1000 (204 to 439)				
Overall Survival - Gemcitabine vs No adjuvant therapy	Study population[1]		HR 0.76 (0.63 to 0.93)	472 (2 studies)	⊕⊕⊖⊖ low[3,8]	
	906 per 1000	835 per 1000 (775 to 890)				
	Moderate[1]					
	300 per 1000	237 per 1000 (201 to 282)				
Overall Survival - Gemcitabine, Carboplatin, Mitomycin C, 5FU+FA vs No adjuvant therapy	Study population1		HR 0.52 (0.27 to 1)5	85 (1 study)	⊕⊖⊖⊖ very low[3,7,9]	
	375 per 1000	217 per 1000 (119 to 375)				
	Moderate[1]					
	300 per 1000	169 per 1000 (92 to 300)				
Overall Survival - Mitomycin C+5FU vs No adjuvant therapy	Study population[1]		HR 1.15 (0.82 to 1.61)[5]	158 (1 study)	⊕⊖⊖⊖ very low[3,7,10]	
	818 per 1000	859 per 1000 (753 to 936)				
	Moderate[1]					

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No adjuvant therapy	Chemotherapy				
	300 per 1000	336 per 1000 (254 to 437)				
Disease-free Survival - Chemotherapy vs No adjuvant therapy	Study population[1]		HR 0.79 (0.68 to 0.92)	803 (5 studies)	⊕⊖⊖⊖ very low[3,11,12]	
	904 per 1000	843 per 1000 (797 to 884)				
	Moderate[1]					
	200 per 1000	162 per 1000 (141 to 186)				
Disease-free Survival - Cisplatin+5FU vs No adjuvant therapy	Study population[1]		HR 1.06 (0.66 to 1.72)[5]	88 (1 study)	⊕⊕⊖⊖ low[3,6,7]	
	773 per 1000	792 per 1000 (624 to 922)				
	Moderate[1]					
	200 per 1000	211 per 1000 (137 to 319)				
Disease-free Survival - Gemcitabine vs No adjuvant therapy	Study population[1]		HR 0.72 (0.59 to 0.87)	472 (2 studies)	⊕⊕⊖⊖ low[3,8]	
	906 per 1000	818 per 1000 (753 to 873)				
	Moderate[1]					
	200 per 1000	148 per 1000 (123 to 176)				
Disease-free Survival - Gemcitabine, Carboplatin, Mitomycin C, 5FU+FA vs No adjuvant therapy	Study population[1]		HR 0.41 (0.21 to 0.81)5	85 (1 study)	⊕⊖⊖⊖ very low[3,7,9]	
	375 per 1000	175 per 1000 (94 to 317)				
	Moderate[1]					
	200 per 1000	87 per 1000 (46 to 165)				
Disease-free Survival - Mitomycin C+5FU vs No adjuvant therapy	Study population[1]		HR 0.97 (0.7 to 1.34)5	158 (1 study)	⊕⊖⊖⊖ very low[3,7,10]	
	922 per 1000	916 per 1000 (832 to 967)				
	Moderate[1]					
	200 per 1000	195 per 1000 (145 to 258)				
# patients with serious adverse events - Gemcitabine vs No adjuvant therapy	82 per 1000	140 per 1000 (77 to 255)	RR 1.7 (0.93 to 3.1)	368 (1 study)	⊕⊖⊖⊖ very low[13,14]	
# patients with any Grade 3 or 4 haematological toxicities - 5FU+FA vs No adjuvant therapy	0 per 1000	0 per 1000 (0 to 0)	RR 4.61 (0.22 to 94.27)	144 (1 study)	⊕⊖⊖⊖ very low[4,15]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No adjuvant therapy	Chemotherapy				
UICC Common Toxicity Criteria						
# patients with any Grade 3 or 4 non-haematological toxicities - 5FU+FA vs No adjuvant therapy UICC Common Toxicity Criteria	0 per 1000	0 per 1000 (0 to 0)	RR 17.5 (1.04 to 295.13)	144 (1 study)	⊕⊖⊖⊖ very low[4,15]	
# patients with Grade 3 or 4 Abscess - Gemcitabine vs No adjuvant therapy NCI Common Terminology Criteria for Adverse Events	0 per 1000	0 per 1000 (0 to 0)	RR 3.16 (0.13 to 75.9)	117 (1 study)	⊕⊕⊖⊖ low[15]	
# patients with Grade 3 or 4 Alanine Aminotransferase - Gemcitabine vs No adjuvant therapy NCI Common Terminology Criteria for Adverse Events	0 per 1000	0 per 1000 (0 to 0)	RR 9.47 (0.52 to 171.95)	117 (1 study)	⊕⊕⊖⊖ low[15]	
# patients with Grade 3 or 4 Anaemia - Gemcitabine vs No adjuvant therapy NCI Common Terminology Criteria for Adverse Events	0 per 1000	0 per 1000 (0 to 0)	RR 5.26 (0.26 to 107.22)	117 (1 study)	⊕⊕⊖⊖ low[15]	
# patients with Grade 3 or 4 Anorexia - Gemcitabine vs No adjuvant therapy NCI Common Terminology Criteria for Adverse Events	0 per 1000	0 per 1000 (0 to 0)	RR 5.26 (0.26 to 107.22)	117 (1 study)	⊕⊕⊖⊖ low[15]	
# patients with Grade 3 or 4 Aspartate Aminotransferase - Gemcitabine vs No adjuvant therapy NCI Common	0 per 1000	0 per 1000 (0 to 0)	RR 7.36 (0.39 to 139.44)	117 (1 study)	⊕⊕⊖⊖ low[15]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No adjuvant therapy	Chemotherapy				
Terminology Criteria for Adverse Events						
# patients with Grade 3 or 4 Diarrhoea - Chemotherapy vs No adjuvant therapy UICC Common Toxicity Criteria; NCI Common Terminology Criteria for Adverse Events			RR 3.9 (0.44 to 34.75)	261 (2 studies)	⊕⊖⊖⊖ very low[4,15]	
# patients with Grade 3 or 4 Diarrhoea - 5FU+FA vs No adjuvant therapy UICC Common Toxicity Criteria	0 per 1000	0 per 1000 (0 to 0)	RR 4.61 (0.22 to 94.27)	144 (1 study)	⊕⊖⊖⊖ very low[4,15]	
# patients with Grade 3 or 4 Diarrhoea - Gemcitabine vs No adjuvant therapy NCI Common Terminology Criteria for Adverse Events	0 per 1000	0 per 1000 (0 to 0)	RR 3.16 (0.13 to 75.9)	117 (1 study)	⊕⊕⊖⊖ low[15]	
# patients with Grade 3 or 4 Fatigue - Gemcitabine vs No adjuvant therapy NCI Common Terminology Criteria for Adverse Events	0 per 1000	0 per 1000 (0 to 0)	RR 3.16 (0.13 to 75.9)	117 (1 study)	⊕⊕⊖⊖ low[15]	
# patients with Grade 3 or 4 Fever - Gemcitabine vs No adjuvant therapy NCI Common Terminology Criteria for Adverse Events	0 per 1000	0 per 1000 (0 to 0)	RR 3.16 (0.13 to 75.9)	117 (1 study)	⊕⊕⊖⊖ low[15]	
# patients with Grade 3 or 4 Granulocytopenia - Cisplatin+5FU vs No adjuvant therapy WHO Toxicity criteria	0 per 1000	0 per 1000 (0 to 0)	RR 10.38 (0.58 to 186.87)	82 (1 study)	⊕⊖⊖⊖ very low[6,15]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No adjuvant therapy	Chemotherapy				
# patients with Grade 3 or 4 Hepatic - Cisplatin+5FU vs No adjuvant therapy WHO Toxicity criteria	0 per 1000	0 per 1000 (0 to 0)	RR 8.08 (0.43 to 151.56)	82 (1 study)	⊕⊖⊖⊖ very low[6,15]	
# patients with Grade 3 or 4 Leukopenia - Chemotherapy vs No adjuvant therapy WHO Toxicity criteria; NCI Common Terminology Criteria for Adverse Events	0 per 1000	0 per 1000 (0 to 0)	RR 18.43 (2.45 to 138.47)	199 (2 studies)	⊕⊕⊖⊖ low[6,16]	
# patients with Grade 3 or 4 Leukopenia - Cisplatin+5FU vs No adjuvant therapy WHO Toxicity criteria	0 per 1000	0 per 1000 (0 to 0)	RR 5.77 (0.29 to 116.57)	82 (1 study)	⊕⊖⊖⊖ very low[6,15]	
# patients with Grade 3 or 4 Leukopenia - Gemcitabine vs No adjuvant therapy NCI Common Terminology Criteria for Adverse Events	0 per 1000	0 per 1000 (0 to 0)	RR 30.5 (1.86 to 499.65)	117 (1 study)	⊕⊕⊕⊖ moderate[16]	
# patients with Grade 3 or 4 Neutropenia - Gemcitabine vs No adjuvant therapy NCI Common Terminology Criteria for Adverse Events	0 per 1000	0 per 1000 (0 to 0)	RR 85.19 (5.36 to 1353.55)	117 (1 study)	⊕⊕⊕⊖ moderate[16]	
# patients with Grade 3 or 4 Mucositis - Cisplatin+5FU vs No adjuvant therapy WHO Toxicity criteria	0 per 1000	0 per 1000 (0 to 0)	RR 5.77 (0.29 to 116.57)	82 (1 study)	⊕⊖⊖⊖ very low[6,15]	
# patients with Grade 3 or 4 Nausea/Vomiting -	0 per 1000	0 per 1000 (0 to 0)	RR 5.97	284 (3 studies)	⊕⊖⊖⊖ very low[6,9,14]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No adjuvant therapy	Chemotherapy				
Chemotherapy vs No adjuvant therapy WHO toxicity criteria; NCI Common Terminology Criteria for Adverse Events			(1.1 to 32.48)			
# patients with Grade 3 or 4 Nausea/Vomiting - Cisplatin+5FU vs No adjuvant therapy WHO toxicity criteria	0 per 1000	0 per 1000 (0 to 0)	RR 12.69 (0.72 to 222.32)	82 (1 study)	⊕⊖⊖⊖ very low[6,15]	
# patients with Grade 3 or 4 Nausea/Vomiting - Gemcitabine, Carboplatin, Mitoxantrone, mitomycin C, 5FU+FA vs No adjuvant therapy Not stated in study	0 per 1000	0 per 1000 (0 to 0)	RR 2.67 (0.11 to 63.84)	85 (1 study)	⊕⊖⊖⊖ very low[9,15]	
# patients with Grade 3 or 4 Nausea/Vomiting - Gemcitabine vs No adjuvant therapy NCI Common Terminology Criteria for Adverse Events	0 per 1000	0 per 1000 (0 to 0)	RR 3.16 (0.13 to 75.9)	117 (1 study)	⊕⊕⊖⊖ low[15]	
# patients with Grade 3 or 4 Stomatitis - 5FU+FA vs No adjuvant therapy UICC Common Toxicity Criteria	0 per 1000	0 per 1000 (0 to 0)	RR 8.29 (0.45 to 151.2)	144 (1 study)	⊕⊖⊖⊖ very low[4,15]	
# patients with Grade 3 or 4 Thrombocytopenia - Gemcitabine vs No adjuvant therapy NCI Common Terminology Criteria for Adverse Events	0 per 1000	0 per 1000 (0 to 0)	RR 3.16 (0.13 to 75.9)	117 (1 study)	⊕⊕⊖⊖ low[15]	
Quality of life - change scores - 5FU+FA vs No		The mean quality of life - change scores -		473 (1 study)	⊕⊖⊖⊖ very low[4,17]	SMD 0 (-0.18 to 0.18)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No adjuvant therapy	Chemotherapy				
adjuvant therapy ESPAC-1 QoL		5fu+fa vs no adjuvant therapy in the intervention groups was 0 standard deviations higher (0.18 lower to 0.18 higher)				
# patients with improving ESPAC-1 QoL Role Functioning scores - 5FU+FA vs No adjuvant therapy		The mean # patients with improving espac-1 QOL role functioning scores - 5fu+fa vs no adjuvant therapy in the intervention groups was 0.27 standard deviations lower (0.46 to 0.09 lower)		473 (1 study)	⨁⊖⊖⊖ very low[4,17]	SMD -0.27 (-0.46 to -0.09)
# patients improved >=1 ECOG PS Grade - Mitomycin C+5FU vs No adjuvant therapy	709 per 1000	709 per 1000 (560 to 893)	RR 1 (0.79 to 1.26)	113 (1 study)	⨁⊖⊖⊖ very low[10,15]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes.*

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;

1 Thirty percent 2-year overall survival rate and 20% 2-year disease-free survival rate assumed for no adjuvant therapy control group.
2 Majority of studies have high risk of bias (Lygidakis et al. 2002; Neoptolemos et al. 2001, 2004, 2009; Oettle et al. 2007/2013; Takada et al. 2002). Main reasons include: unclear risk for randomisation method/allocation concealment; unclear or high risk for selective reporting (primary outcomes not fully reported); other sources of bias (Kaplan-Meier curves cross, proportional hazards not satisfied).
3 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant.
4 Overall high risk of bias (Neoptolemos et al. 2001, 2004 and 2009). Main reasons include: unclear risk randomisation method; selective reporting (one or more outcomes of interest reported incompletely); other sources of bias (clinicians chose which ESPAC-1 trial patients were randomised to [ESPAC-1 2x2, ESPAC-1+ chemotherapy only trial, ESPAC-1+ chemoradiotherapy only trials]); other sources of bias (Kaplan-Meier curves for overall survival cross, proportional hazards not satisfied).
5 Hazard ratio estimated from Kaplan-Meier curve and/or summary statistics using method 7 in Tierney et al. (2007).
6 Overall unclear risk of bias for Kosuge et al. 2006 (unclear risk allocation concealment; selective reporting (insufficient information); other sources of bias (Kaplan-Meier curves for overall and disease-free survival

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No adjuvant therapy	Chemotherapy				

cross, proportional hazards not satisfied).
7 Not statistically significant (p>0.5).
8 Overall high risk of bias (Oettle et al. 2007/2013). Main reasons include: selective reporting (one or more outcomes of interest not fully reported; other sources of bias (Kaplan-Meier curves for overall survival cross, proportional hazards not satisfied).
9 Overall high risk of bias for Lygidakis et al. 2002. Main reasons include unclear risk randomisation method/allocation method; high risk selective reporting (fails to report survival results in expected manner); other sources of bias (power calculation not reported; Kaplan-Meier curves for overall survival cross, proportional hazards not satisfied).
10 Overall high risk of bias for Takada et al. 2002. Main reasons include: unclear randomisation method/allocation concealment; selective reporting (one or more outcomes of interest not fully reported); other sources of bias (No Kaplan-Meier curve, not clear whether proportional hazards satisfied).
11 Majority of studies have high risk of bias (Lygidakis et al. 2002; Oettle et al. 2007/2013; Takada et al. 2002). Main reasons include: unclear risk for randomisation method/allocation concealment; high risk for selective reporting (primary outcomes not fully reported);
12 High heterogeneity (i2>50%).
13 Overall high risk of bias for Oettle et al. 2007/2013. Main reasons include: selective reporting (one or more outcomes of interest not fully reported.
14 Crosses 1 default MID (0.8 or 1.25).
15 Crosses 2 default MIDs (0.8 and 1.25).
16 Small sample size (<300 events).
17 Data from both ESPAC-1 2x2 trial (Neoptolemos et al. 2001, 2004) and ESPAC-1+ (Neoptolemos et al. 2009) trial. Chemotherapy group (n=238) includes 72 patients who received both chemotherapy and chemoradiotherapy, in addition to 168 patients who received chemotherapy only. Comparison group (n=235) includes 70 patients who received chemoradiotherapy only, in addition to165 patients who received no treatment after resection.

Table 137: Summary clinical evidence profile for adjuvant chemotherapy-1 (gemcitabine) versus adjuvant chemotherapy-2 (other) in resected pancreatic cancer patients

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Chemotherapy-2 (other)	Chemotherapy-1 (gemcitabine)				
Overall Survival - Gemcitabine vs Other chemotherapy (Random Effects)	Study population1		HR 1.15 (0.85 to 1.55)	2302 (4 studies)	⊕⊖⊖⊖ very low[2,3,4,5]	
	650 per 1000	701 per 1000 (590 to 803)				
	Moderate[1]					
	400 per 1000	444 per 1000 (352 to 547)				
Overall Survival - Gemcitabine vs 5FU+FA (Fixed Effects)	Study population[1]		HR 0.94 (0.81	1088 (1 study)	⊕⊕⊕⊖ moderate [4,5]	
	704 per 1000	682 per 1000 (627 to 735)				

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Chemotherapy-2 (other)	Chemotherapy-1 (gemcitabine)				
	Moderate[1]		to 1.09)			
	400 per 1000	381 per 1000 (339 to 427)				
Overall Survival - Gemcitabine vs S-1(Fixed Effects)	Study population[1]		HR 1.75 (1.37 to 2.24)	385 (1 study)	⊕⊕⊕⊕ high[4]	
	594 per 1000	793 per 1000 (709 to 867)				
	Moderate[1]					
	400 per 1000	591 per 1000 (503 to 682)				
Overall Survival - Gemcitabine vs Gemcitabine+UFT (Fixed Effects)	Study population[1]		HR 0.75 (0.45 to 1.26)[6]	99 (1 study)	⊕⊕⊖⊖ low[4,5,7]	
	620 per 1000	516 per 1000 (353 to 705)				
	Moderate[1]					
	400 per 1000	318 per 1000 (205 to 475)				
Overall Survival - Gemcitabine vs Gemcitabine+Capecitabine (Fixed Effects)	Study population[1]		HR 1.22 (1.02 to 1.46)[6]	730 (1 study)	⊕⊕⊕⊖ moderate [4,8]	
	602 per 1000	675 per 1000 (609 to 739)				
	Moderate[1]					
	400 per 1000	464 per 1000 (406 to 526)				
Relapse-Free Survival - Gemcitabine vs Gemcitabine+Capecitabine	648 per 1000	703 per 1000 (641 to 761)	HR 1.16 (0.98 to 1.37)	730 (1 study)	⊕⊕⊖⊖ low[4,5,8]	
Disease-free Survival - Gemcitabine vs Other chemotherapy	Study population[1]		HR 1.11 (0.99 to 1.25)	1461 (3 studies)	⊕⊖⊖⊖ very low[2,3,4,5]	
	787 per 1000	820 per 1000 (783 to 855)				
	Moderate[1]					
	400 per 1000	433 per 1000 (397 to 472)				
	Study population[1]					

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Chemotherapy-2 (other)	Chemotherapy-1 (gemcitabine)				
Disease-free Survival - Gemcitabine vs 5FU+FA	836 per 1000	833 per 1000 (792 to 872)	HR 0.99 (0.87 to 1.14)	985 (1 study)	⊕⊕⊕⊖ moderate [4,5]	
	Moderate[1]					
	400 per 1000	397 per 1000 (359 to 441)				
Disease-free Survival - Gemcitabine vs S-1	Study population[1]		HR 1.67 (1.31 to 2.12)	377 (1 study)	⊕⊕⊕⊕ high[4]	
	658 per 1000	833 per 1000 (755 to 897)				
	Moderate[1]					
	400 per 1000	574 per 1000 (488 to 661)				
Disease-free Survival - Gemcitabine vs Gemcitabine+UFT	Study population[1]		HR 0.91 (0.58 to 1.43)[6]	99 (1 study)	⊕⊖⊖⊖ very low[4,5,7]	
	780 per 1000	748 per 1000 (584 to 885)				
	Moderate1					
	400 per 1000	372 per 1000 (256 to 518)				
# patients with serious treatment-related adverse events - Gemcitabine vs Other (Random Effects)	179 per 1000	138 per 1000 (68 to 272)	RR 0.77 (0.38 to 1.52)	1813 (2 studies)	⊕⊖⊖⊖ very low[3,8,9]	
# patients with serious treatment-related adverse events - Gemcitabine vs 5FU+FA (Fixed Effects)	140 per 1000	74 per 1000 (52 to 108)	RR 0.53 (0.37 to 0.77)	1088 (1 study)	⊕⊕⊕⊕ high	
# patients with serious treatment-related adverse events - Gemcitabine vs Gemcitabine+Capecitabine (Fixed Effects)	240 per 1000	256 per 1000 (199 to 331)	RR 1.07 (0.83 to 1.38)	725 (1 study)	⊕⊕⊖⊖ low[8,10]	
# patients with Grade 3 or 4 Alanine Aminotransferase/Aspartate Aminotransferase - Gemcitabine vs Other chemotherapy (Random Effects)	174 per 1000	337 per 1000 (45 to 1000)	RR 1.94 (0.26 to 14.2)	1564 (3 studies)	⊕⊖⊖⊖ very low[3,9]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Chemotherapy-2 (other)	Chemotherapy-1 (gemcitabine)				
NCI Common Toxicity Criteria						
# patients with Grade 3 or 4 Alanine Aminotransferase/Aspartate Aminotransferase - Gemcitabine vs S-1 (Fixed Effects) NCI Common Toxicity Criteria	80 per 1000	726 per 1000 (444 to 1000)	RR 9.05 (5.53 to 14.83)	377 (1 study)	⊕⊕⊕⊕ high[11]	
# patients with Grade 3 or 4 Alanine Aminotransferase/Aspartate Aminotransferase - Gemcitabine vs 5FU+FA (Fixed Effects) NCI Common Toxicity Criteria	220 per 1000	222 per 1000 (178 to 277)	RR 1.01 (0.81 to 1.26)	1088 (1 study)	⊕⊕⊕⊖ moderate [10]	
# patients with Grade 3 or 4 Alanine Aminotransferase/Aspartate Aminotransferase - Gemcitabine vs Gemcitabine+UFT (Fixed Effects) NCI Common Toxicity Criteria	20 per 1000	7 per 1000 (0 to 163)	RR 0.34 (0.01 to 8.15)	99 (1 study)	⊕⊕⊖⊖ low[9]	
# patients with Grade 3 or 4 Anorexia - Gemcitabine vs Other chemotherapy NCI Common Toxicity Criteria	68 per 1000	50 per 1000 (24 to 103)	RR 0.74 (0.36 to 1.53)	476 (2 studies)	⊕⊕⊖⊖ low[9]	
# patients with Grade 3 or 4 Anorexia - Gemcitabine vs Gemcitabine+UFT NCI Common Toxicity Criteria	20 per 1000	20 per 1000 (1 to 317)	RR 1.02 (0.07 to 15.86)	99 (1 study)	⊕⊕⊖⊖ low[9]	
# patients with Grade 3 or 4 Anorexia - Gemcitabine vs S-1 NCI Common Toxicity Criteria	80 per 1000	58 per 1000 (27 to 123)	RR 0.72 (0.34 to 1.53)	377 (1 study)	⊕⊕⊖⊖ low[9]	
# patients with Grade 3 or 4 Bilirubin - Gemcitabine vs S-1 NCI Common Toxicity Criteria	11 per 1000	5 per 1000 (1 to 58)	RR 0.49 (0.05 to 5.38)	377 (1 study)	⊕⊕⊖⊖ low[9]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Chemotherapy-2 (other)	Chemotherapy-1 (gemcitabine)				
# patients with Grade 3 or 4 Creatinine - Gemcitabine vs S-1 NCI Common Toxicity Criteria	5 per 1000	5 per 1000 (0 to 84)	RR 0.98 (0.06 to 15.62)	377 (1 study)	⊕⊕⊖⊖ low[9]	
# patients with Grade 3 or 4 Diarrhoea - Gemcitabine vs Other chemotherapy NCI Common Toxicity Criteria	91 per 1000	17 per 1000 (10 to 27)	RR 0.19 (0.11 to 0.3)	2190 (3 studies)	⊕⊕⊕⊕ high[11]	
# patients with Grade 3 or 4 Diarrhoea - Gemcitabine vs S-1 NCI Common Toxicity Criteria	48 per 1000	2 per 1000 (0 to 42)	RR 0.05 (0 to 0.88)	377 (1 study)	⊕⊕⊕⊖ moderate [10]	
# patients with Grade 3 or 4 Diarrhoea - Gemcitabine vs 5FU+FA NCI Common Toxicity Criteria	131 per 1000	22 per 1000 (12 to 41)	RR 0.17 (0.09 to 0.31)	1088 (1 study)	⊕⊕⊕⊕ high[11]	
# patients with Grade 3 or 4 Diarrhoea - Gemcitabine vs Gemcitabine+Capecitabine NCI Common Toxicity Criteria	53 per 1000	16 per 1000 (7 to 41)	RR 0.31 (0.13 to 0.77)	725 (1 study)	⊕⊕⊕⊖ moderate [8]	
# patients with Grade 3 or 4 Fatigue/Tiredness - Gemcitabine vs Other chemotherapy NCI Common Toxicity Criteria	68 per 1000	55 per 1000 (40 to 77)	RR 0.81 (0.58 to 1.12)	2190 (3 studies)	⊕⊕⊖⊖ low[8,10]	
# patients with Grade 3 or 4 Fatigue/Tiredness - Gemcitabine vs S-1 NCI Common Toxicity Criteria	53 per 1000	48 per 1000 (20 to 114)	RR 0.89 (0.37 to 2.13)	377 (1 study)	⊕⊕⊖⊖ low[9]	
# patients with Grade 3 or 4 Fatigue/Tiredness - Gemcitabine vs 5FU+FA NCI Common Toxicity Criteria	82 per 1000	60 per 1000 (38 to 92)	RR 0.73 (0.47 to 1.13)	1088 (1 study)	⊕⊕⊕⊖ moderate [10]	
# patients with Grade 3 or 4 Fatigue/Tiredness - Gemcitabine vs Gemcitabine+Capecitabi	56 per 1000	52 per 1000 (28 to 96)	RR 0.93 (0.51	725 (1 study)	⊕⊖⊖⊖ very low[8,9]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Chemotherapy-2 (other)	Chemotherapy-1 (gemcitabine)				
ne NCI Common Toxicity Criteria			to 1.72)			
# patients with Grade 3 or 4 Febrile Neutropenia - Gemcitabine vs S-1 NCI Common Toxicity Criteria	5 per 1000	16 per 1000 (2 to 150)	RR 2.95 (0.31 to 28.13)	377 (1 study)	⊕⊕⊖⊖ low[9]	
# patients with Grade 3 or 4 Fever - Gemcitabine vs Other NCI Common Toxicity Criteria	20 per 1000	12 per 1000 (5 to 32)	RR 0.62 (0.24 to 1.6)	1102 (1 study)	⊕⊖⊖⊖ very low[8,9]	
# patients with Grade 3 or 4 Fever - Gemcitabine vs S-1 NCI Common Toxicity Criteria	27 per 1000	5 per 1000 (1 to 45)	RR 0.2 (0.02 to 1.67)	377 (1 study)	⊕⊕⊖⊖ low[9]	
# patients with Grade 3 or 4 Fever - Gemcitabine vs Gemcitabine+Capecitabine NCI Common Toxicity Criteria	17 per 1000	16 per 1000 (5 to 50)	RR 0.98 (0.32 to 3.01)	725 (1 study)	⊕⊖⊖⊖ very low[8,9]	
# patients with Grade 3 or 4 Glucose Intolerance - Gemcitabine vs Gemcitabine+UFT NCI Common Toxicity Criteria	980 per 1000	333 per 1000 (10 to 1000)	RR 0.34 (0.01 to 8.15)	99 (1 study)	⊕⊕⊖⊖ low[9]	
# patients with Grade 3 or 4 Haemoglobin - Gemcitabine vs Gemcitabine+UFT NCI Common Toxicity Criteria	40 per 1000	82 per 1000 (16 to 426)	RR 2.04 (0.39 to 10.64)	99 (1 study)	⊕⊕⊖⊖ low[9]	
# patients with Grade 3 or 4 Hand-Foot Syndrome	72 per 1000	1 per 1000 (0 to 22)	RR 0.02 (0 to 0.3)	725 (1 study)	⊕⊕⊕⊖ moderate[8]	
# patients with Grade 3 or 4 Infection - Gemcitabine vs Other NCI Common Toxicity Criteria	20 per 1000	58 per 1000 (29 to 113)	RR 2.86 (1.46 to 5.6)	1102 (2 studies)	⊕⊕⊕⊖ moderate[8]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Chemotherapy-2 (other)	Chemotherapy-1 (gemcitabine)				
# patients with Grade 3 or 4 Infection - Gemcitabine vs S-1 NCI Common Toxicity Criteria	11 per 1000	42 per 1000 (9 to 196)	RR 3.94 (0.85 to 18.3)	377 (1 study)	⊕⊕⊕⊖ moderate [10]	
# patients with Grade 3 or 4 Infection - Gemcitabine vs Gemcitabine+Capecitabine NCI Common Toxicity Criteria	25 per 1000	66 per 1000 (31 to 139)	RR 2.62 (1.23 to 5.55)	725 (1 study)	⊕⊕⊖⊖ low [8,10]	
# patients with Grade 3 or 4 Leukocytes - Gemcitabine vs Gemcitabine+UFT NCI Common Toxicity Criteria	180 per 1000	225 per 1000 (103 to 493)	RR 1.25 (0.57 to 2.74)	99 (1 study)	⊕⊕⊖⊖ low [9]	
# patients with Grade 3 or 4 Nausea - Gemcitabine vs Other chemotherapy NCI Common Toxicity Criteria	35 per 1000	25 per 1000 (14 to 45)	RR 0.7 (0.39 to 1.27)	1465 (2 studies)	⊕⊕⊖⊖ low [9]	
# patients with Grade 3 or 4 Nausea - Gemcitabine vs S-1 NCI Common Toxicity Criteria	37 per 1000	26 per 1000 (9 to 82)	RR 0.7 (0.23 to 2.18)	377 (1 study)	⊕⊕⊖⊖ low [9]	
# patients with Grade 3 or 4 Nausea - Gemcitabine vs 5FU+FA NCI Common Toxicity Criteria	34 per 1000	24 per 1000 (12 to 49)	RR 0.7 (0.35 to 1.41)	1088 (1 study)	⊕⊕⊖⊖ low [9]	
# patients with Grade 3 or 4 Neutrophils - Gemcitabine vs Other chemotherapy (Random Effects) NCI Common Toxicity Criteria	184 per 1000	35 per 1000 (293 to 426)	RR 0.19 (1.59 to 2.31)	1465 (2 studies)	⊕⊕⊖⊖ low [3]	
# patients with Grade 3 or 4 Neutrophils - Gemcitabine vs S-1 (Fixed Effects) NCI Common Toxicity Criteria	80 per 1000	726 per 1000 (444 to 1000)	RR 9.05 (5.53 to 14.83)	377 (1 study)	⊕⊕⊕⊕ high [11]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Chemotherapy-2 (other)	Chemotherapy-1 (gemcitabine)				
# patients with Grade 3 or 4 Neutrophils - Gemcitabine vs 5FU+FA (Fixed Effects) NCI Common Toxicity Criteria	220 per 1000	222 per 1000 (178 to 277)	RR 1.01 (0.81 to 1.26)	1088 (1 study)	⊕⊕⊕⊖ moderate [10]	
# patients with Grade 3 or 4 Platelets - Gemcitabine vs Other chemotherapy NCI Common Toxicity Criteria	15 per 1000	30 per 1000 (17 to 52)	RR 2.04 (1.17 to 3.53)	2289 (4 studies)	⊕⊕⊕⊖ moderate [10]	
# patients with Grade 3 or 4 Platelets - Gemcitabine vs S-1 NCI Common Toxicity Criteria	48 per 1000	95 per 1000 (44 to 206)	RR 1.97 (0.91 to 4.27)	377 (1 study)	⊕⊕⊕⊖ moderate [10]	
# patients with Grade 3 or 4 Platelets - Gemcitabine vs 5FU+FA NCI Common Toxicity Criteria	0 per 1000	0 per 1000 (0 to 0)	RR 17.44 (1.01 to 301.45)	1088 (1 study)	⊕⊕⊕⊖ moderate [10]	
# patients with Grade 3 or 4 Platelets - Gemcitabine vs Gemcitabine+UFT NCI Common Toxicity Criteria	0 per 1000	0 per 1000 (0 to 0)	RR 7.14 (0.38 to 134.71)	99 (1 study)	⊕⊕⊖⊖ low [9]	
# patients with Grade 3 or 4 Platelets - Gemcitabine vs Gemcitabine+Capecitabine NCI Common Toxicity Criteria	22 per 1000	19 per 1000 (7 to 52)	RR 0.86 (0.31 to 2.34)	725 (1 study)	⊕⊖⊖⊖ very low [8,9]	
# patients with Grade 3 or 4 Stomatitis - Gemcitabine vs Other chemotherapy NCI Common Toxicity Criteria	80 per 1000	2 per 1000 (1 to 10)	RR 0.03 (0.01 to 0.13)	1465 (2 studies)	⊕⊕⊕⊕ high [11]	
# patients with Grade 3 or 4 Stomatitis - Gemcitabine vs S-1 NCI Common Toxicity Criteria	27 per 1000	2 per 1000 (0 to 43)	RR 0.09 (0 to 1.61)	377 (1 study)	⊕⊕⊖⊖ low [9]	
# patients with Grade 3 or 4 Stomatitis -	98 per 1000	2 per 1000 (0 to 14)	RR 0.02	1088 (1 study)	⊕⊕⊕⊕ high [11]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Chemotherapy-2 (other)	Chemotherapy-1 (gemcitabine)				
Gemcitabine vs 5FU+FA NCI Common Toxicity Criteria			(0 to 0.14)			
# patients with Grade 3 or 4 Vomiting - Gemcitabine vs Other chemotherapy NCI Common Toxicity Criteria	27 per 1000	18 per 1000 (9 to 36)	RR 0.66 (0.33 to 1.32)	1465 (2 studies)	⊕⊕⊖⊖ low[9]	
# patients with Grade 3 or 4 Vomiting - Gemcitabine vs S-1 NCI Common Toxicity Criteria	16 per 1000	11 per 1000 (2 to 62)	RR 0.66 (0.11 to 3.88)	377 (1 study)	⊕⊕⊖⊖ low[9]	
# patients with Grade 3 or 4 Vomiting - Gemcitabine vs 5FU+FA NCI Common Toxicity Criteria	31 per 1000	20 per 1000 (10 to 43)	RR 0.66 (0.31 to 1.4)	1088 (1 study)	⊕⊕⊖⊖ low[9]	
# patients with Grade 3 or 4 White Blood Cell Count - Gemcitabine vs Other chemotherapy (Random Effects) NCI Common Toxicity Criteria	82 per 1000	135 per 1000 (61 to 297)	RR 1.65 (0.75 to 3.63)	2289 (4 studies)	⊕⊖⊖⊖ very low[3,9]	
# patients with Grade 3 or 4 White Blood Cell Count - Gemcitabine vs S-1 (Fixed Effects) NCI Common Toxicity Criteria	86 per 1000	389 per 1000 (236 to 643)	RR 4.55 (2.76 to 7.51)	377 (1 study)	⊕⊕⊕⊕ high[12]	
# patients with Grade 3 or 4 White Blood Cell Count - Gemcitabine vs 5FU+FA (Fixed Effects) NCI Common Toxicity Criteria	58 per 1000	99 per 1000 (64 to 150)	RR 1.7 (1.11 to 2.59)	1088 (1 study)	⊕⊕⊕⊖ moderate [10]	
# patients with Grade 3 or 4 White Blood Cell Count - Gemcitabine vs Gemcitabine+UFT (Fixed Effects) NCI Common Toxicity Criteria	180 per 1000	225 per 1000 (103 to 493)	RR 1.25 (0.57 to 2.74)	99 (1 study)	⊕⊕⊖⊖ low[9]	
# patients with Grade 3 or 4 White Blood Cell Count - Gemcitabine vs Gemcitabine+Capecitabi	103 per 1000	76 per 1000 (47 to 123)	RR 0.74 (0.46	725 (1 study)	⊕⊕⊖⊖ low[8,10]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Chemotherapy-2 (other)	Chemotherapy-1 (gemcitabine)				
ne (Fixed Effects) NCI Common Toxicity Criteria			to 1.19)			
EQ-5D Quality of Life - Gemcitabine vs S-1, 3 months post-randomisation		The mean eq-5d quality of life - gemcitabine vs s-1, 3 months post-randomisation in the intervention groups was 0.15 standard deviations higher (0.08 lower to 0.37 higher)		311 (1 study)	⨁⊖⊖⊖ very low[13,14]	SMD 0.15 (-0.08 to 0.37)
EQ-5D Quality of Life - Gemcitabine vs S-1, 6 months post-randomisation		The mean eq-5d quality of life - gemcitabine vs s-1, 6 months post-randomisation in the intervention groups was 0.14 standard deviations higher (0.09 lower to 0.37 higher)		291 (1 study)	⨁⊖⊖⊖ very low[13,14]	SMD 0.14 (-0.09 to 0.37)
EQ-5D Quality of Life - Gemcitabine vs S-1, 12 months post-randomisation		The mean eq-5d quality of life - gemcitabine vs s-1, 12 months post-randomisation in the		255 (1 study)	⨁⊖⊖⊖ very low[10,13]	SMD 0.4 (0.15 to 0.65)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Chemotherapy-2 (other)	Chemotherapy-1 (gemcitabine)				
		intervention groups was 0.4 standard deviations higher (0.15 to 0.65 higher)				
EQ-5D Quality of Life - Gemcitabine vs S-1, 24 months post-randomisation		The mean eq-5d quality of life - gemcitabine vs s-1, 24 months post-randomisation in the intervention groups was 0.42 standard deviations higher (0.11 to 0.72 higher)		171 (1 study)	⨁⊖⊖⊖ very low[10,13]	SMD 0.42 (0.11 to 0.72)
Global Quality of Life - Gemcitabine vs 5FU+FA EORTC QLQ-C30 v3; ESPAC-32		The mean global quality of life - gemcitabine vs 5fu+fa in the intervention groups was 0.15 standard deviations higher (0.01 lower to 0.32 higher)		565 (1 study)	⨁⨁⊖⊖ low[15]	SMD 0.15 (-0.01 to 0.32)

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes.*

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;

1 Forty percent 2-year overall survival and disease-free survival rate assumed for other chemotherapy group.
2 Two of 4 studies at high risk of bias: Yoshitomi et al. 2008 (high risk of bias due to other sources of bias (Kaplan-Meier curves for both overall and disease-free survival cross, proportional hazards not satisfied); Neoptolemos et al. 2017 (high risk due to no allocation concealment; no blinding of participants/personnel; relapsed patients received additional chemoradiotherapy, surgery or other treatment).

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Chemotherapy-2 (other)	Chemotherapy-1 (gemcitabine)				

3 High heterogeneity (i2>80%).
4 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant.
5 Not statistically significant (p>0.5).
6 Hazard ratio estimated from Kaplan-Meier curve and summary statistics using method 7 in Tierney et al. (2007).
7 Overall high risk of bias (Yoshitomi et al. 2008) due to high risk other sources of bias (Kaplan-Meier curves for overall and disease-free survival cross, proportional hazards not satisfied).
8 Overall high risk of bias (Neoptolemos et al. 2017: no allocation concealment; no blinding of participants/personnel; relapsed patients received additional chemoradiotherapy, surgery or other treatment).
9 Crosses 2 default MIDs (0.8 and 1.25).
10 Crosses 1 default MID (dichotomous outcomes: 0.8 or 1.25; continuous outcomes: 0.5 or -0.5).
11 Very large effect size (Risk Ratio >5 or <0.2)
12 Large effect size (Risk Ratio >2 or <0.5)
13 Overall high risk of bias (Uesaka et al. 2016). Main reason: high risk blinding of participants and personnel (participants not blinded, quality of life outcomes likely to be influenced by this).
14 Small sample size (<400 participants).
15 Overall high risk of bias (Neoptolemos et al. 2010). Main reason: high risk blinding of participants and personnel (participants not blinded, quality of life outcomes likely to be influenced by this).

Table 138: Summary clinical evidence profile for adjuvant chemotherapy versus adjuvant chemoradiotherapy in resected pancreatic cancer patients

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Chemoradiotherapy	Chemotherapy				
Overall Survival - Chemotherapy vs Chemoradiotherapy	Study population[1]		HR 0.79 (0.59 to 1.07)[2]	238 (2 studies)	⊕⊖⊖⊖ very low[3,4,5]	
	746 per 1000	661 per 1000 (554 to 769)				
	Moderate[1]					
	500 per 1000	422 per 1000 (336 to 524)				
Overall Survival - 5FU+FA vs Chemoradiotherapy	Study population[1]		HR 0.7 (0.49 to 1.01)	148 (1 study)	⊕⊖⊖⊖ very low[3,5,6]	
	863 per 1000	751 per 1000 (622 to 866)				
	Moderate[1]					
	500 per 1000	384 per 1000 (288 to 503)				
Overall Survival - Gemcitabine vs Chemoradiotherapy	Study population[1]		HR 1.02 (0.61 to 1.72)[2]	90 (1 study)	⊕⊖⊖⊖ very low[4,5,6]	
	556 per 1000	563 per 1000 (390 to 752)				
	Moderate[1]					
	500 per 1000	507 per 1000 (345 to 696)				

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Disease-free survival - Gemcitabine vs Chemoradiotherapy	Study population[1]		HR 0.97 (0.62 to 1.52)2	90 (1 study)	⊕⊖⊖⊖ very low[4,5,6]	
	756 per 1000	745 per 1000 (582 to 883)				
	Moderate[1]					
	500 per 1000	489 per 1000 (349 to 651)				
# patients with any Grade 3 or 4 haematological toxicities - 5FU+FA vs Chemoradiotherapy UICC Common Toxicity Criteria	0 per 1000	0 per 1000 (0 to 0)	RR 4.87 (0.24 to 99.7)	148 (1 study)	⊕⊖⊖⊖ very low[3,7]	
# patients with any Grade 3 or 4 non-haematological toxicities - 5FU+FA vs Chemoradiotherapy UICC Common Toxicity Criteria	27 per 1000	120 per 1000 (27 to 537)	RR 4.38 (0.98 to 19.59)	148 (1 study)	⊕⊖⊖⊖ very low[3,8]	
# patients with Grade 3 or 4 Anorexia - Gemcitabine vs Chemoradiotherapy NCI Common Terminology Criteria for Adverse Events	47 per 1000	9 per 1000 (0 to 193)	RR 0.2 (0.01 to 4.14)	85 (1 study)	⊕⊖⊖⊖ very low[4,7]	
# patients with Grade 3 or 4 Diarrhoea - Chemotherapy vs Chemoradiotherapy NCI Common Terminology Criteria for Adverse Events; UCCI Common Toxicity Criteria	9 per 1000	13 per 1000 (2 to 77)	RR 1.49 (0.25 to 8.95)	233 (2 studies)	⊕⊖⊖⊖ very low[3,4,7]	
# patients with Grade 3 or 4 Diarrhoea - Gemcitabine vs Chemoradiotherapy	23 per 1000	7 per 1000 (0 to 189)	RR 0.31 (0.01 to 8.14)	85 (1 study)	⊕⊖⊖⊖ very low[4,7]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
NCI Common Terminology Criteria for Adverse Events						
# patients with Grade 3 or 4 Diarrhoea - 5FU+FA vs Chemoradiotherapy UICC Common Toxicity Criteria	0 per 1000	0 per 1000 (0 to 0)	RR 4.87 (0.24 to 99.7)	148 (1 study)	⊕⊖⊖⊖ very low[3,7]	
# patients with Grade 3 or 4 Fatigue - Gemcitabine vs Chemoradiotherapy NCI Common Terminology Criteria for Adverse Events	70 per 1000	47 per 1000 (8 to 271)	RR 0.68 (0.12 to 3.88)	85 (1 study)	⊕⊖⊖⊖ very low[4,7]	
# patients with Grade 3 or 4 Fever - Gemcitabine vs Chemoradiotherapy NCI Common Terminology Criteria for Adverse Events	70 per 1000	10 per 1000 (1 to 192)	RR 0.15 (0.01 to 2.75)	85 (1 study)	⊕⊖⊖⊖ very low[4,7]	
# patients with Grade 3 or 4 Gastritis - Gemcitabine vs Chemoradiotherapy NCI Common Terminology Criteria for Adverse Events	47 per 1000	9 per 1000 (0 to 193)	RR 0.2 (0.01 to 4.14)	85 (1 study)	⊕⊖⊖⊖ very low[4,7]	
# patients with Grade 3 or 4 Haemoglobin - Gemcitabine vs Chemoradiotherapy NCI Common Terminology Criteria for Adverse Events	70 per 1000	10 per 1000 (1 to 192)	RR 0.15 (0.01 to 2.75)	85 (1 study)	⊕⊖⊖⊖ very low[4,7]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
# patients with Grade 3 or 4 Haemorrhage - Gemcitabine vs Chemoradiotherapy NCI Common Terminology Criteria for Adverse Events	23 per 1000	24 per 1000 (2 to 368)	RR 1.02 (0.07 to 15.84)	85 (1 study)	⊕⊖⊖⊖ very low[4,7]	
# patients with Grade 3 or 4 Nausea - Gemcitabine vs Chemoradiotherapy NCI Common Terminology Criteria for Adverse Events	23 per 1000	8 per 1000 (0 to 189)	RR 0.34 (0.01 to 8.14)	85 (1 study)	⊕⊖⊖⊖ very low[4,7]	
# patients with Grade 3 or 4 Neutrophils - Gemcitabine vs Chemoradiotherapy NCI Common Terminology Criteria for Adverse Events	326 per 1000	430 per 1000 (247 to 746)	RR 1.32 (0.76 to 2.29)	85 (1 study)	⊕⊖⊖⊖ very low[4,7]	
# patients with Grade 3 or 4 Other Gastrointestinal toxicity - Gemcitabine vs Chemoradiotherapy NCI Common Terminology Criteria for Adverse Events	23 per 1000	8 per 1000 (0 to 189)	RR 0.34 (0.01 to 8.14)	85 (1 study)	⊕⊖⊖⊖ very low[3,7]	
# patients with Grade 3 or 4 Platelets - Gemcitabine vs Chemoradiotherapy NCI Common Terminology Criteria for Adverse Events	23 per 1000	8 per 1000 (0 to 189)	RR 0.34 (0.01 to 8.14)	85 (1 study)	⊕⊖⊖⊖ very low[4,7]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
# patients with Grade 3 or 4 Serum Glutamicpyruvic Transaminase - Gemcitabine vs Chemoradiotherapy NCI Common Terminology Criteria for Adverse Events	116 per 1000	119 per 1000 (37 to 381)	RR 1.02 (0.32 to 3.28)	85 (1 study)	⊕⊖⊖⊖ very low[4,7]	
# patients with Grade 3 or 4 Stomatitis - 5FU+FA vs Chemoradiotherapy UICC Common Toxicity Criteria	0 per 1000	0 per 1000 (0 to 0)	RR 8.76 (0.48 to 159.93)	148 (1 study)	⊕⊖⊖⊖ very low[3,7]	
# patients with Grade 3 or 4 Vomiting - Gemcitabine vs Chemoradiotherapy NCI Common Terminology Criteria for Adverse Events	23 per 1000	8 per 1000 (0 to 189)	RR 0.34 (0.01 to 8.14)	85 (1 study)	⊕⊖⊖⊖ very low[3,7]	
# patients with Grade 3 or 4 Weight Loss - Gemcitabine vs Chemoradiotherapy NCI Common Terminology Criteria for Adverse Events	23 per 1000	8 per 1000 (0 to 189)	RR 0.34 (0.01 to 8.14)	85 (1 study)	⊕⊖⊖⊖ very low[4,7]	
# patients with Grade 3 or 4 White Blood Cell count - Gemcitabine vs Chemoradiotherapy (NCI Common Terminology Criteria for Adverse Events	163 per 1000	143 per 1000 (52 to 391)	RR 0.88 (0.32 to 2.4)	85 (1 study)	⊕⊖⊖⊖ very low[4,7]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes.*

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). *CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;*						
1 Fifty percent 2-year overall survival and disease-free survival rate assumed for chemoradiotherapy control group. *2 Hazard ratio for van Laethem et al. 2010 estimated using Kaplan-Meier curve and method 10 in Tierney et al. 2010.* *3 Overall high risk of bias (Neoptolemos et al. 2004). Main reasons include: unclear risk randomisation method; selective reporting (one or more outcomes of interest reported incompletely); other sources of bias (clinicians chose which ESPAC-1 trial patients were randomised to [ESPAC-1 2x2, ESPAC-1+ chemotherapy only trial, ESPAC-1+ chemoradiotherapy only trials]; Kaplan-Meier curves for separate groups not provided, unclear whether proportional hazards satisfied).* *4 Overall high risk of risk (van Laethem et al. 2010). Main reasons include: unclear risk randomisation method/allocation concealment; high risk selective reporting (one or more outcomes of interest not fully reported); other sources of bias (Kaplan-Meier curve cross, proportional hazards not satisfied).* *5 Not statistically significant (p>0.5).* *6 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant.* *7 Crosses 2 default MIDs (0.8 and 1.25).* *8 Crosses 1 default MID (0.8 or 1.25).*						

Table 139: Summary clinical evidence profile for adjuvant chemotherapy versus adjuvant chemoimmunotherapy in resected pancreatic cancer patients

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Chemoimmunotherapy	Chemotherapy				
Overall Survival - Gemcitabine, Carboplatin, Mitomycin C, 5FU+FA vs CT+Interleukin-2	Study population[1]		HR 2.05 (1.12 to 3.76)2	88 (1 study)	⊕⊕⊖⊖ low[3,4]	
	465 per 1000	723 per 1000 (504 to 905)				
	Moderate[1]					
	400 per 1000	649 per 1000 (436 to 853)				
Disease-free Survival - Gemcitabine, Carboplatin, Mitomycin C, 5FU+FA vs CT+Interleukin-2	Study population[1]		HR 1.99 (1.07 to 3.7)[2]	88 (1 study)	⊕⊕⊖⊖ low[3,4]	
	488 per 1000	736 per 1000 (512 to 916)				
	Moderate[1]					
	400 per 1000	638 per 1000 (421 to 849)				
# patients with Grade 3 or 4 Nausea - Gemcitabine, Carboplatin, mitoxantrone,	0 per 1000	0 per 1000 (0 to 0)	RR 2.87 (0.12 to 68.58)	88 (1 study)	⊕⊖⊖⊖ very low[3,5]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
mitomycin C, 5FU+FA vs CT+Interleukin-2 Not stated in study						
# patients with Grade 3 or 4 Vomiting - Gemcitabine, Carboplatin, mitoxantrone, mitomycin C, 5FU+FA vs CT+Interleukin-2 Not stated in study	47 per 1000	9 per 1000 (0 to 180)	RR 0.19 (0.01 to 3.87)	88 (1 study)	⊕⊖⊖⊖ very low[3,5]	
**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes.* *The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).* *CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;*						
1 Forty percent 2-year overall and disease-free survival rate assumed for chemoimmunotherapy control group *2 Hazard ratio estimated from Kaplan-Meier curve and summary statistics using method 7 in Tierney et al. (2007).* *3 Overall high risk of bias for Lygidakis et al. 2002. Main reasons include unclear risk randomisation method/allocation method; high risk selective reporting (fails to report survival results in expected manner); other sources of bias (power calculation not reported; Kaplan-Meier curves for disease-free survival cross, proportional hazards not satisfied).* *4 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant.* *5 Crosses 2 default MIDs (0.8 and 1.25).*						

Table 140: Summary clinical evidence profile for adjuvant chemotherapy versus adjuvant chemoradioimmunotherapy in resected pancreatic cancer patients

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Chemoradioimmunotherapy	Chemotherapy				
Overall Survival - 5FU vs 5FU, Cisplatin + Interferon alpha-2b	Study population[1]		HR 0.96 (0.63 to 1.48)	132 (1 study)	⊕⊖⊖⊖ very low[3,4,5]	
	See comment[2]	See comment[2]				
	Moderate[1]					
	400 per 1000[2]	388 per 1000 (275 to 530)2				

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Disease-free Survival - 5FU vs 5FU, Cisplatin + Interferon alpha-2b (Copy)	Study population[1]		HR 1.02 (0.64 to 1.65)[6]	132 (1 study)	⊕⊖⊖⊖ very low[3,4,5]	
	See comment[2]	See comment2				
	Moderate[1]					
	400 per 1000[2]	406 per 1000 (279 to 570)[2]				
# patients with any Grade 3 or 4 toxicities - 5FU vs 5FU, Cisplatin + Inteferon alpha-2b Common Toxicity Criteria	789 per 1000	174 per 1000 (95 to 316)	RR 0.22 (0.12 to 0.4)	110 (1 study)	⊕⊖⊖⊖ very low[3,7]	
EORTC QLQ-30 Quality of Life - Global Health Status	The mean EORTC qlq-30 quality of life - global health status in the control groups was 55.8 AUC	The mean EORTC qlq-30 quality of life - global health status in the intervention groups was 7 higher (0.41 to 13.59 higher)		86 (1 study)	⊕⊖⊖⊖ very low[3,8]	SMD -0.46 (-0.9 to -0.03)
EORTC QLQ-30 Quality of Life - Nausea/Vomiting	The mean EORTC qlq-30 quality of life - nausea/vomiting in the control groups was -15.9 AUC	The mean EORTC qlq-30 quality of life - nausea/vomiting in the intervention groups was 7.7 higher (1.67 to 13.73 higher)		86 (1 study)	⊕⊖⊖⊖ very low[3,8]	SMD 0.53 (0.09 to 0.97)
EORTC QLQ-30 Quality of Life - Role functioning	The mean EORTC qlq-30 quality of life - role functioning in the control groups was 55.6 AUC	The mean EORTC qlq-30 quality of life - role functioning in the intervention groups was 13.9 higher (4.16 to 23.64 higher)		85 (1 study)	⊕⊖⊖⊖ very low[3,8]	SMD 0.61 (0.17 to 1.05)
EORTC QLQ-30 Quality of	The mean EORTC qlq-30 quality of life - social	The mean EORTC qlq-		85 (1 study)	⊕⊖⊖⊖	SMD -0.45 (-

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Life - Social functioning	functioning in the control groups was 64.5	30 quality of life - social functioning in the intervention groups was 10 higher (0.75 to 19.25 higher)			very low[3,8]	0.88 to -0.01)

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes.*

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;

1 Forty percent 2-year overall survival rate assumed for chemoradioimmunotherapy control group.
2 The number of observed deaths in each group was not provided in the study (Schmidt et al. 2012).
3 Overall high risk of bias (Schmidt et al. 2012). Main reasons include: selective reporting (one or more outcomes of interest not fully reported); high risk blinding of participants and personnel (participants not blinded, quality of life outcomes likely to be influenced by this); high risk other sources of bias (Kaplan-Meier curves for overall and disease-free survival cross, proportional hazards not satisfied).
4 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant.
5 Not statistically significant (p>0.5).
6 Hazard ratio estimated using Kaplan-Meier curve and method 10 of Tierney et al. 2007.
7 Small sample size (<300 events).
8 Crosses 1 MID (+5 or -5, from Osoba et al. 1998)

Table 141: Summary clinical evidence profile for adjuvant chemoradiotherapy followed by chemotherapy versus no adjuvant therapy in resected pancreatic cancer patients

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No adjuvant therapy	Chemoradiotherapy->Chemotherapy				
# patients with any Grade 3 or 4 haematological toxicities - Chemoradiotherapy ->5FU+FA vs No adjuvant therapy UICC Common Toxicity Criteria	0 per 1000	0 per 1000 (0 to 0)	RR 10.55 (0.59 to 187.23)	141 (1 study)	⊕⊖⊖⊖ very low[1,2]	
# patients with any Grade 3 or 4 non-haematological	0 per 1000	0 per 1000 (0 to 0)	RR 22.05 (1.32	141 (1 study)	⊕⊖⊖⊖	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
toxicities - Chemoradiotherapy ->5FU+FA vs No adjuvant therapy UICC Common Toxicity Criteria			to 367.2)		very low[1,3]	
# patients with Grade 3 or 4 Stomatitis - Chemoradiotherapy ->5FU+FA vs No adjuvant therapy UICC Common Toxicity Criteria	0 per 1000	0 per 1000 (0 to 0)	RR 8.29 (0.45 to 151.2)	144 (1 study)	⊕⊖⊖⊖ very low[1,2]	
# patients with Grade 3 or 4 Diarrhoea - Chemoradiotherapy ->5FU+FA vs No adjuvant therapy UICC Common Toxicity Criteria	0 per 1000	0 per 1000 (0 to 0)	RR 4.61 (0.22 to 94.27)	144 (1 study)	⊕⊖⊖⊖ very low[1,2]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes.*

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

1 Overall high risk of bias (Neoptolemos et al. 2004). Main reasons include: unclear risk randomisation method; selective reporting (one or more outcomes of interest reported incompletely); other sources of bias (clinicians chose which ESPAC-1 trial patients were randomised to [ESPAC-1 2x2, ESPAC-1+ chemotherapy only trial, ESPAC-1+ chemoradiotherapy only trials]; Kaplan-Meier overall survival curves for separate groups not provided, unclear whether proportional hazards satisfied).
2 Crosses 2 default MIDs (0.8 and 1.25).
3 Small sample size (<300 events).

Table 142: Summary clinical evidence profile for adjuvant chemoradiotherapy followed by chemotherapy versus adjuvant chemotherapy in resected pancreatic cancer patients

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Chemotherapy	Chemoradiotherapy->Chemotherapy				
Overall Survival - Chemoradiotherapy->5FU+FA vs 5FU+FA	Study population[1]		HR 1.32 (0.9 to 1.92)	147 (1 study)	⊕⊖⊖⊖ very low[2,3,4]	
	867 per 1000	930 per 1000 (837 to 979)				
	Moderate[1]					

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	400 per 1000	490 per 1000 (369 to 625)				
# patients with any Grade 3 or 4 haematological toxicities - Chemoradiotherapy->5FU+FA vs 5FU+FA UICC Common Toxicity Criteria	27 per 1000	69 per 1000 (14 to 347)	RR 2.6 (0.52 to 13)	147 (1 study)	⊕⊖⊖⊖ very low[2,5]	
# patients with any Grade 3 or 4 non-haematological toxicities - Chemoradiotherapy->5FU+FA vs 5FU+FA UICC Common Toxicity Criteria	120 per 1000	152 per 1000 (67 to 347)	RR 1.27 (0.56 to 2.89)	147 (1 study)	⊕⊖⊖⊖ very low[2,5]	
# patients with Grade 3 or 4 Stomatitis - Chemoradiotherapy->5FU+FA vs 5FU+FA UICC Common Toxicity Criteria	0 per 1000	0 per 1000 (0 to 0)	RR 8.29 (0.45 to 151.2)	144 (1 study)	⊕⊖⊖⊖ very low[2,5]	
# patients with Grade 3 or 4 Diarrhoea - Chemoradiotherapy->5FU+FA vs 5FU+FA UICC Common Toxicity Criteria	0 per 1000	0 per 1000 (0 to 0)	RR 5 (0.24 to 102.42)	150 (1 study)	⊕⊖⊖⊖ very low[2,5]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes.*

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;

1 Forty percent 2-year overall survival assumed for chemotherapy control group.
2 Overall high risk of bias (Neoptolemos et al. 2004). Main reasons include: unclear risk randomisation method; selective reporting (one or more outcomes of interest reported incompletely); other sources of bias (clinicians chose which ESPAC-1 trial patients were randomised to [ESPAC-1 2x2, ESPAC-1+ chemotherapy only trial, ESPAC-1+ chemoradiotherapy only trials]; Kaplan-Meier overall survival curves for separate groups not provided, unclear whether proportional hazards satisfied).
3 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant.
4 Not statistically significant (p>0.5).
5 Crosses 2 default MIDs (0.8 and 1.25).

Table 143: Summary clinical evidence profile for adjuvant chemoradiotherapy followed by chemotherapy versus adjuvant chemoradiotherapy in resected pancreatic cancer patients

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Chemoradiotherapy	Chemoradiotherapy->Chemotherapy				
Overall Survival - Chemoradiotherapy->5FU+FA vs Chemoradiotherapy	Study population[1]		HR 0.67 (0.47 to 0.96)	145 (1 study)	⊕⊕⊖⊖ low[2,3]	
	890 per 1000	773 per 1000 (646 to 880)				
	Moderate[1]					
	500 per 1000	371 per 1000 (278 to 486)				
# patients with any Grade 3 or 4 haematological toxicities - Chemoradiotherapy->5FU+FA vs Chemoradiotherapy UICC Common Toxicity Criteria	0 per 1000	0 per 1000 (0 to 0)	RR 11.15 (0.63 to 198.04)	145 (1 study)	⊕⊖⊖⊖ very low[2,4]	
# patients with any Grade 3 or 4 non-haematological toxicities - Chemoradiotherapy->5FU+FA vs Chemoradiotherapy UICC Common Toxicity Criteria	27 per 1000	153 per 1000 (35 to 665)	RR 5.58 (1.28 to 24.28)	145 (1 study)	⊕⊖⊖⊖ very low[2,4]	
# patients with Grade 3 or 4 Stomatitis - Chemoradiotherapy->5FU+FA vs Chemoradiotherapy UICC Common Toxicity Criteria	0 per 1000	0 per 1000 (0 to 0)	RR 8.76 (0.48 to 159.93)	148 (1 study)	⊕⊖⊖⊖ very low[2,4]	
# patients with Grade 3 or 4 Diarrhoea - Chemoradiotherapy->5FU+FA vs Chemoradiotherapy UICC Common Toxicity Criteria	0 per 1000	0 per 1000 (0 to 0)	RR 4.61 (0.22 to 94.27)	144 (1 study)	⊕⊖⊖⊖ very low[2,4]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;						
1 Fifty percent 2-year overall survival assumed for chemoradiotherapy control group. 2 Overall high risk of bias (Neoptolemos et al. 2004). Main reasons include: unclear risk randomisation method; selective reporting (one or more outcomes of interest reported incompletely); other sources of bias (clinicians chose which ESPAC-1 trial patients were randomised to [ESPAC-1 2x2, ESPAC-1+ chemotherapy only trial, ESPAC-1+ chemoradiotherapy only trials]; Kaplan-Meier overall survival curves for separate groups not provided, unclear whether proportional hazards satisfied). 3 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant. 4 Crosses 2 default MIDs (0.8 and 1.25).						

Table 144: Summary clinical evidence profile for adjuvant chemotherapy-1 (gemcitabine) followed by chemoradiotherapy versus adjuvant chemotherapy-2 (other) followed by chemoradiotherapy in resected pancreatic cancer patients

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Chemotherapy-2 (other)->Chemoradiotherapy	Chemotherapy-1 (gemcitabine)->Chemoradiotherapy				
Overall Survival - Gemcitabine->CRT->Gemcitabine vs 5-FU->CRT->5FU	817 per 1000	794 per 1000 (725 to 859)	HR 0.93 (0.76 to 1.15)	451 (1 study)	⊕⊕⊖⊖ low[1,2,3]	
Disease-free Survival - Gemcitabine->CRT vs PEFG->CRT	Study population[4]		HR 1.33 (0.86 to 2.06)[6]	100 (1 study)	⊕⊖⊖⊖ very low[2,3,7]	
	See comment[5]	See comment[5]				
	Moderate[4]					
	400 per 1000[5]	493 per 1000 (356 to 651)5				
# patients with any Grade 4 toxicity - Gemcitabine->CRT->gemcitabine vs 5FU->CRT->5FU Monitored by RTOG Data	13 per 1000	145 per 1000 (45 to 466)	RR 11.1 (3.45 to 35.73)	451 (1 study)	⊕⊕⊕⊖ moderate[1]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Monitoring Committee						
# patients with Grade 3 or 4 Diarrhoea - Gemcitabine->CRT->gemcitabine vs 5FU->CRT->5FU Monitored by RTOG Data Monitoring Committee	191 per 1000	149 per 1000 (99 to 226)	RR 0.78 (0.52 to 1.18)	451 (1 study)	⊕⊕⊖⊖ low[1,8]	
# patients with Grade 3 or 4 Neutropenia - Gemcitabine->CRT vs PEFG->CRT NCI Common Terminology Criteria for Adverse Events		The mean # patients with grade 3 or 4 neutropenia - gemcitabine->CRT vs PEFG->CRT in the intervention groups was 0.8 standard deviations lower (1.21 to 0.4 lower)		102 (1 study)	⊕⊖⊖⊖ very low[7,8]	SMD 0.8 (0.4 to 1.21)
# patients with Grade 3 or 4 Stomatitis - Gemcitabine->CRT->gemcitabine vs 5FU->CRT->5FU Monitored by RTOG Data Monitoring Committee	152 per 1000	99 per 1000 (61 to 164)	RR 0.65 (0.4 to 1.08)	451 (1 study)	⊕⊕⊖⊖ low[1,8]	
# patients with Grade 3 or 4 Thrombocytopenia - Gemcitabine->CRT vs PEFG->CRT NCI Common Terminology Criteria for Adverse Events		The mean # patients with grade 3 or 4 thrombocytopenia - gemcitabine->CRT vs PEFG->CRT in the intervention groups was 0.8 standard deviations lower (1.21 to 0.4 lower)		102 (1 study)	⊕⊖⊖⊖ very low[7,8]	SMD 0.8 (0.4 to 1.21)
# patients with Grade 3 or 4 Worst haematological	96 per 1000	583 per 1000 (386 to 882)	RR 6.1 (4.04	451 (1 study)	⊕⊕⊕⊖	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
AEs - Gemcitabine->CRT->gemcitabine vs 5FU->CRT->5FU Monitored by RTOG Data Monitoring Committee			to 9.22)		moderate[1]	
# patients with Grade 3 or 4 Worst non-haematological AEs - Gemcitabine->CRT->gemcitabine vs 5FU->CRT->5FU Monitored by RTOG Data Monitoring Committee	596 per 1000	584 per 1000 (500 to 679)	RR 0.98 (0.84 to 1.14)	451 (1 study)	⊕⊕⊕⊖ moderate[1]	
# patients with Grade 3 or 4 Worst overall AEs - Gemcitabine->CRT->gemcitabine vs 5FU->CRT->5FU Monitored by RTOG Data Monitoring Committee	622 per 1000	790 per 1000 (703 to 895)	RR 1.27 (1.13 to 1.44)	451 (1 study)	⊕⊕⊖⊖ low[1,8]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes.*

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;

1 Overall unclear risk of bias (Regine et al. 2008/2011). Main reasons include: unclear risk randomisation method/allocation concealment (insufficient information).
2 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant.
3 Not statistically significant (p>0.5).
4 Forty percent 2-year overall survival and disease-free survival assumed for chemotherapy then chemoradiotherapy group.
5 Observed disease-free events not provided by authors (Reni et al. 2012).
6 Hazard ratio estimated from Kaplan-Meier survival curve using method 11 in Tierney et al. (2007).
7 Overall high risk of bias (Reni et al. 2012) due to high risk selective reporting (primary outcomes not fully reported).
8 Crosses 1 default MID (dichotomous outcomes: 0.8 or 1.25; continuous outcomes: 0.5 or -0.5).

Table 145: Summary clinical evidence profile for immunotherapy versus no adjuvant therapy in resected pancreatic cancer patients

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No adjuvant therapy	Immunotherapy				
Overall Survival - IgG1 murine Monoclonal Antibody 494/32 vs Observation	Study population[1]		HR 1.12 (0.21 to 6.03)[2]	61 (1 study)	⊕⊖⊖⊖ very low[3,4,5]	
	531 per 1000	572 per 1000 (147 to 990)				
	Moderate[1]					
	300 per 1000	329 per 1000 (72 to 884)				
# patients with Grade 3 or 4 Abdominal Pain - IgG1 murine Monoclonal Antibody 494/32 vs No adjuvant therapy	0 per 1000	0 per 1000 (0 to 0)	RR 3.3 (0.14 to 77.95)	61 (1 study)	⊕⊖⊖⊖ very low[3,6]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes.*

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;

1 Thirty percent 2-year overall survival rate assumed for no adjuvant therapy control group.
2 Hazard ratio estimated from Kaplan-Meier curve using method 10 in Tierney et al. (2007).
3 Overall high risk of bias (Buchler et al. 1991). Main reasons include: unclear randomisation method/allocation concealment (insufficient information); selective reporting (primary outcome not fully reported); other sources of bias (Kaplan-Meier curve crosses, proportional hazards not satisfied).
4 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant.
5 Not statistically significant (p>0.5).
6 Crosses 2 default MIDs (0.8 and 1.25).

Table 146: Summary clinical evidence profile for chemoimmunotherapy versus no adjuvant therapy in resected pancreatic cancer patients

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No adjuvant therapy	Chemoimmunotherapy				
Overall Survival - Gemcitabine, Carboplatin, Mitomycin C,	Study population[1]		HR 0.45 (0.23	83 (1 study)	⊕⊕⊖⊖ low[3,4]	
	375 per 1000	191 per 1000 (102 to 339)				
	Moderate[1]					

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
5FU+FA+Interleukin -2 vs No adjuvant therapy	300 per 1000	148 per 1000 (79 to 269)	to 0.88)[2]			
Disease-free Survival - Gemcitabine, Carboplatin, Mitomycin C, 5FU+FA+Interleukin -2 vs No adjuvant therapy	Study population[1]		HR 0.33 (0.17 to 0.64)[2]	83 (1 study)	⊕⊕⊖⊖ low[3,4]	
	375 per 1000	144 per 1000 (77 to 260)				
	Moderate[1]					
	200 per 1000	71 per 1000 (37 to 133)				
# patients with Grade 3 or 4 Vomiting - Gemcitabine, Carboplatin, mitoxantrone, mitomycin C, 5FU+FA+Interleukin -2 vs No adjuvant therapy Not stated in study	0 per 1000	0 per 1000 (0 to 0)	RR 4.66 (0.23 to 94.18)	83 (1 study)	⊕⊖⊖⊖ very low[3,5]	

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes.*

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;

1 Thirty percent 2-year overall survival rate and 20% 2-year disease-free survival rate assumed for no adjuvant therapy control group.
2 Hazard ratio estimated from Kaplan-Meier curve and summary statistics using method 7 in Tierney et al. (2007).
3 Overall high risk of bias for Lygidakis et al. 2002. Main reasons include unclear risk randomisation method/allocation method; high risk selective reporting (fails to report survival results in expected manner); other sources of bias (power calculation not reported).
4 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant.
5 Crosses 2 default MIDs (0.8 and 1.25).

10.3.5 Economic evidence

A literature review of published cost effectiveness analyses did not identify any relevant studies for this topic. Although there were potential implications for resource use associated with making recommendations in this area, other topics in the guideline were agreed as a higher economic priority. Consequently, bespoke economic modelling was not done for this topic.

10.3.6 Evidence statements

10.3.6.1 Adjuvant chemotherapy versus no adjuvant therapy

Disease-free survival

Very low quality evidence from 5 RCTs (n=803) showed that there is a clinically important difference favouring adjuvant chemotherapy on disease-free survival compared to no adjuvant therapy in adults with resected pancreatic cancer: HR 0.79 (95% CI 0.68-0.92).

- Low quality evidence from 1 RCT (n=88) showed no clinically important difference between adjuvant cisplatin combined with fluororacil and no adjuvant therapy on disease-free survival in adults with resected pancreatic cancer: HR 1.06 (95% CI 0.66-1.72).
- Low quality evidence from 1 RCT (n=) showed that there is a clinically important difference favouring adjuvant gemcitabine on overall survival compared to no adjuvant therapy in adults with resected pancreatic cancer: HR 0.72 (95% CI 0.59-0.87).
- Very low quality evidence from 1 RCT (n=85) showed that there is a clinically important difference favouring adjuvant gemcitabine combined with carboplatin, mitomycin C, fluororacil and folinic acid on disease-free survival compared to no adjuvant therapy in adults with resected pancreatic cancer: HR 0.41 (95% CI 0.21-0.81).
- Very low quality evidence from 1 RCT (n=158) showed no clinically important difference between adjuvant mitomycin C combined with fluororacil and no adjuvant therapy on disease-free survival in adults with resected pancreatic cancer: HR 0.97 (95% CI 0.7-1.34).

Relapse-free survival

- No evidence was identified to inform this outcome.

Overall survival

Low quality evidence from 8 RCTs (n=1262) showed that there is a clinically important difference favouring adjuvant chemotherapy on overall survival compared to no adjuvant therapy in adults with resected pancreatic cancer: HR 0.78 (0.69-0.89).

- Low quality evidence from 3 RCTs (n=458) showed that there is a clinically important difference favouring adjuvant fluororacil and folinic acid on overall survival compared to no adjuvant therapy in adults with resected pancreatic cancer: HR 0.69 (95% CI 0.56-0.85).
- Low quality evidence from 1 RCT (n=89) showed no clinically important difference between adjuvant cisplatin and fluororacil and no adjuvant therapy on overall survival in adults with resected pancreatic cancer: HR 1.02 (95% CI 0.64-1.62).
- Low quality evidence from 2 RCTs (n=472) showed that there is a clinically important difference favouring adjuvant gemcitabine on overall survival compared to no adjuvant therapy in adults with resected pancreatic cancer: HR 0.76 (95% CI 0.63-0.93).
- Very low quality evidence from 1 RCT (n=85) showed that there is a clinically important difference favouring adjuvant gemcitabine, carboplatin, mitomycin C, fluororacil and folinic acid on overall survival compared to no adjuvant therapy in adults with resected pancreatic cancer: HR 0.52 (95% CI 0.27-1.0).
- Very low quality evidence from 1 RCT (n=158) showed no clinically important difference between adjuvant mitomycin C combined with fluororacil and no adjuvant therapy on overall survival in adults with resected pancreatic cancer: HR 1.15 (95% CI 0.82-1.61).

Adverse events

Very low quality evidence from 1 RCT (n=368) showed that there may be a clinically important difference favouring no adjuvant therapy on the number of people who experience

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serious adverse events compared to adjuvant gemcitabine in adults with resected pancreatic cancer, although there is some uncertainty: RR 1.7 (95% CI 0.93-3.1).

Very low quality evidence from 1 RCT (n=144) showed that there is a clinically important difference favouring no adjuvant therapy in the number of people who experience grade 3 or 4 non-haematological toxicities compared to adjuvant chemotherapy (fluororacil and folinic acid) in adults with resected pancreatic cancer: RR 17.5 (95% CI 1.04-295.13).

Very low quality evidence from 1 RCT (n=144) showed no clinically important difference between adjuvant chemotherapy (fluororacil and folinic acid) and no adjuvant therapy on the number of people who experience a grade 3 or 4 haematological toxicity (RR 4.61 [95% CI 0.22-94.27]), nor on the number of people who experience grade 3 or 4 stomatitis (RR 8.29 [95% CI 0.45-151.2]) in adults with resected pancreatic cancer.

Very low quality evidence from 1 RCT (n=82) showed no clinically important difference between adjuvant chemotherapy (cisplatin and fluororacil) and no adjuvant therapy on the number of people who experience a grade 3 or 4 granulocytopenic (RR 10.38 [95% CI 0.58-186.87]), hepatic (RR 8.08 [95% CI 0.43 to 151.56]), or mucositic (RR 5.77 [95% CI 0.29 to 116.57]) toxicity in adults with resected pancreatic cancer.

Low quality evidence from 2 RCTs (n=199) showed that there is a clinically important difference favouring no adjuvant therapy on the number of people who experience grade 3 or 4 leukopenic toxicities compared to adjuvant chemotherapy (cisplatin and fluororacil; gemcitabine) in adults with resected pancreatic cancer: RR 18.43 (95% CI 2.45-138.47).

Very low quality evidence from 3 studies (n=284) showed that there is a clinically important difference favouring no adjuvant therapy on the number of people who experience grade 3 or 4 nausea/vomiting compared to adjuvant chemotherapy (cisplatin and fluororacil; gemcitabine, carboplatin, mitoxantrone, mitomycin C, fluorouracil, and folinic acid; gemcitabine) in adults with resected pancreatic cancer: RR 5.97 (95% CI 1.1-32.48).

Very low quality evidence from 2 RCTs (n=261) showed no clinically important difference between adjuvant chemotherapy (fluorouracil and folinic acid; gemcitabine) and no adjuvant therapy on the number of people who experience grade 3 or 4 diarrhoea in adults with resected pancreatic cancer: RR 3.9 (95% CI 0.44-34.75).

Moderate quality evidence from 1 RCT (n=117) that there is a clinically important difference favouring no adjuvant therapy on the number of people who experience grade 3 or 4 neutropenic toxicities compared to adjuvant gemcitabine in adults with resected pancreatic cancer: RR 85.19 (95% CI 5.36-1353.55).

Low quality evidence from 1 RCT (n=117) showed no clinically important difference between adjuvant chemotherapy (gemcitabine) and no adjuvant therapy on the number of people who experience grade 3 or 4 abscess (RR 3.16 [95% CI 0.13-75.9]), alanine aminotransferase (RR 9.47 [95% CI 0.52-171.95]), anaemia (RR 5.26 [95% CI 0.26-107.22]), anorexia (RR 5.26 [95% CI 0.26-107.22]), aspartate aminotransferase (RR 7.36 [95% CI 0.39-139.44]), fatigue (RR 3.16 [95% CI 0.13-75.9]), fever (RR 3.16 [95% CI 0.13-75.9]), and thrombocytopenia (RR 3.16 [95% CI 0.13-75.9]) in adults with resected pancreatic cancer.

Very low quality evidence from 3 RCTs (n=284) showed that there is a clinically important difference favouring no adjuvant therapy on the number of people who have grade 3 or 4 nausea/vomiting compared to adjuvant chemotherapy in adults with resected pancreatic cancer: RR 5.97 (95% CI 1.1-32.48).

- Very low quality evidence from 1 RCT (n=82) showed no clinically important difference between adjuvant cisplatin combined with fluororacil and no adjuvant therapy on the number of people who experience grade 3 or 4 nausea/vomiting in adults with resected pancreatic cancer: RR 12.69 (95% CI 0.72-222.32).

- Very low quality evidence from 1 RCT (n=85) showed no clinically important difference between adjuvant gemcitabine combined with adjuvant chemotherapy (carboplatin, mitoxantrone, mitomycin C, fluororacil and folinic acid) and no adjuvant therapy on the number of people who experience grade 3 or 4 nausea/vomiting in adults with resected pancreatic cancer: RR 2.67 (95% CI 0.11-63.84).
- Very low quality evidence from 1 RCT (n=117) showed no clinically important difference between adjuvant gemcitabine and no adjuvant therapy on the number of people who experience grade 3 or 4 nausea/vomiting in adults with resected pancreatic cancer: RR 3.16 (95% CI 0.13-75.9).

Health-related quality of life

Very low quality evidence from 1 RCT (n=473) showed no clinically important difference between adjuvant chemotherapy (fluororacil and folinic acid) and no adjuvant therapy on quality of life (ESPAC-1 QoL) change scores in adults with resected pancreatic cancer: SMD 0 (95% CI -0.18 to 0.18).

Very low quality evidence from 1 RCT (n=473) showed that no clinically important difference between adjuvant fluororacil combined with folinic acid and no adjuvant therapy on quality of life-role functioning score in adults with resected pancreatic cancer: SMD 0.27 (95% CI -0.46- -0.09).

Very low quality evidence from 1 CT (n=113) showed no clinically important difference between adjuvant chemotherapy (mitomycin C and fluororacil) and no adjuvant therapy on the number of people whose ECOG performance status score improved by one or more grade in adults with resected pancreatic cancer: RR 1 (95% CI 0.79-1.26).

Patient experience

No evidence was identified to inform this outcome.

PROMS

No evidence was identified to inform this outcome.

10.3.6.2 Adjuvant chemotherapy-1 (gemcitabine) versus adjuvant chemotherapy-2 (other)

Disease-free survival

Very low quality evidence from 3 RCTs (n=1461) showed no clinically important difference between adjuvant gemcitabine and any other type of adjuvant chemotherapy on disease-free survival in adults with resected pancreatic cancer: HR 1.11 (95% CI95% CI 0.99-1.25).

- Moderate quality evidence from 1 RCT (n=985) showed no clinically important difference between adjuvant gemcitabine and adjuvant fluororacil and folinic acid on disease-free survival in adults with resected pancreatic cancer: HR 0.99 (95% CI 0.87-1.14).
- High quality evidence from 1 RCT (n=377) showed that there is a clinically important difference favouring adjuvant S-1 on disease-free survival compared to adjuvant gemcitabine in adults with resected pancreatic cancer: HR 1.67 (95% CI 1.31-2.12).
- Very low quality evidence from 1 RCT (n=99) showed no clinically important difference between adjuvant gemcitabine only and adjuvant gemcitabine combined with UFT on disease-free survival in adults with resected pancreatic cancer: HR 0.91 (95% CI 0.58-1.43).

Relapse-free survival

Low quality evidence from 1 RCT (n=730) showed no clinically important difference between adjuvant gemcitabine only and adjuvant gemcitabine combined with capecitabine on relapse-free survival in adults with resected pancreatic cancer: HR 1.16 (95% CI 0.98-1.37).

Overall survival

Very low quality evidence from 4 RCTs (n=2301) showed no clinically important difference between adjuvant gemcitabine and any other type of adjuvant chemotherapy on overall survival compared in adults with resected pancreatic cancer: HR 1.15 (95% CI 0.85-1.55) [random effects analysis].

- Moderate quality evidence from 1 RCT (n=1088) showed no clinically important difference between adjuvant gemcitabine and adjuvant fluororacil and folinic acid on overall survival in adults with resected pancreatic cancer: HR 0.94 (95% CI 0.81-1.09) [fixed effects analysis].
- High quality evidence from 1 RCT (n=385) showed that there is clinically important difference favouring adjuvant S-1 on overall survival compared to adjuvant gemcitabine in adults with resected pancreatic cancer: HR 1.75 (95% CI 1.37-2.24) [fixed effects analysis].
- Very low quality evidence from 1 RCT (n=99) showed no clinically important difference between adjuvant gemcitabine only and adjuvant gemcitabine combined with UFT on overall survival in adults with resected pancreatic cancer: HR 0.75 (95% CI 0.45-1.26) [fixed effects analysis].
- Moderate quality evidence from 1 RCT (n=730) showed that there is clinically important difference favouring adjuvant gemcitabine combined with capecitabine on overall survival compared to adjuvant gemcitabine only in adults with resected pancreatic cancer: HR 1.22 (95% CI 1.02-1.46) [fixed effects analysis].

Adverse events

Very low quality evidence from 2 RCTs (n=1813) showed no clinically important difference between adjuvant gemcitabine and any other type of adjuvant chemotherapy on the number of people who experience serious treatment-related adverse events in adults with resected pancreatic cancer: RR 0.77 (95% CI 0.38-1.52).

- High quality evidence from 1 RCT (n=1088) showed that there is a clinically important difference favouring adjuvant gemcitabine on the number of people who experience serious treatment-related adverse events compared to adjuvant fluororacil and folinic acid in adults with resected pancreatic cancer: RR 0.53 (95% CI 0.37-0.77) [fixed effects analysis].
- Low quality evidence from 1 RCT (n=725) showed no clinically important difference between adjuvant gemcitabine only and adjuvant gemcitabine combined with capecitabine on the number of people who experience serious treatment-related adverse events in adults with resected pancreatic cancer: RR 1.07 (0.83-1.38) [fixed effects analysis].

Very low quality evidence from 3 RCTs (n=1564) showed no clinically important difference between adjuvant gemcitabine and any other type of adjuvant chemotherapy on the number of people who experience grade 3 or 4 alanine and aspartate aminotransferase toxicities in adults with resected pancreatic cancer: RR 1.94 (95% CI 0.26-14.2) [random effects].

- High quality evidence from 1 RCT (n=377) showed there is a clinically important difference favouring adjuvant S-1 on the number of people who experience grade 3 or 4 alanine and aspartate aminotransferase toxicities compared to adjuvant gemcitabine in adults with resected pancreatic cancer: RR 9.05 (95% CI 5.53-14.83) [fixed effects].

- Moderate quality evidence from 1 RCT (n=1088) showed no clinically important difference between adjuvant gemcitabine only and adjuvant fluororacil combined with folinic acid on the number of people who experience grade 3 or 4 alanine and aspartate aminotransferase toxicities in adults with resected pancreatic cancer: RR 1.01 (95% CI 0.81-1.26) [fixed effects].
- Very low quality evidence from 1 RCT (n=99) showed no clinically important difference between adjuvant gemcitabine only and adjuvant gemcitabine combined with UFT on the number of people who experience grade 3 or 4 alanine and aspartate aminotransferase toxicities in adults with resected pancreatic cancer: RR 0.34 (95% CI 0.01-8.15) [fixed effects].

Low quality evidence from 2 RCTs (n=476) showed no clinically important difference between adjuvant gemcitabine and any other type of adjuvant chemotherapy on the number of people who experience grade 3 or 4 anorexia in adults with resected pancreatic cancer: RR 0.74 (95% CI 0.36-1.53).

- Low quality evidence from 1 RCT (n=99) showed no clinically important difference between adjuvant gemcitabine only and adjuvant gemcitabine combined with UFT on the number of people who experience grade 3 or 4 anorexia in adults with resected pancreatic cancer: RR 1.02 (95% CI 0.07-15.86).
- Low quality evidence from 1 RCT (n=377) showed no clinically important difference between adjuvant gemcitabine and adjuvant S-1 on the number of people who experience grade 3 or 4 anorexia in adults with resected pancreatic cancer: RR 0.72 (95% CI 0.34-1.53).

Low quality evidence from 1 study (n=377) showed no clinically important difference between adjuvant gemcitabine and adjuvant S-1 on the number of people who experience grade 3 or 4 bilirubin (RR 0.49 [95% CI 0.05 to 5.38]), creatinine (RR 0.98 [95% CI 0.06 to 15.62]) and febrile neutropenia (RR 2.95 [95% CI 0.31-28.13]) in adults with resected pancreatic cancer.

High quality evidence from 3 RCTs (n=2190) showed there is a clinically important difference favouring adjuvant gemcitabine on the number of people who experience grade 3 or 4 diarrhoea compared to any other type of adjuvant chemotherapy in adults with resected pancreatic cancer: RR 0.19 (95% CI 0.11-0.3).

- Moderate quality evidence from 1 RCT (n=377) showed there is a clinically important difference favouring adjuvant gemcitabine on the number of people who experience grade 3 or 4 diarrhoea compared to adjuvant S-1 in adults with resected pancreatic cancer: RR 0.05 (95% CI 0-0.88).
- High quality evidence from 1 RCT (n=1088) showed there is a clinically important difference favouring adjuvant gemcitabine on the number of people who experience grade 3 or 4 diarrhoea compared to adjuvant fluororacil and folinic acid in adults with resected pancreatic cancer: RR 0.17 (95% CI 0.09-0.31).
- Moderate quality evidence from 1 RCT (n=725) showed there is a clinically important difference favouring adjuvant gemcitabine only on the number of people who experience grade 3 or 4 diarrhoea compared to adjuvant gemcitabine and capecitabine in adults with resected pancreatic cancer: RR 0.31 (95% CI 0.13-0.77).

Low quality evidence from 3 RCTs (n=2190) showed no clinically important difference between adjuvant gemcitabine and any other type of adjuvant chemotherapy on the number of people who experience grade 3 or 4 fatigue/tiredness in adults with resected pancreatic cancer: RR 0.81 (95% CI 0.58-1.12).

- Low quality evidence from 1 RCT (n=377) showed no clinically important difference between adjuvant gemcitabine and adjuvant S-1 on the number of people who experience grade 3 or 4 fatigue/tiredness in adults with resected pancreatic cancer: RR 0.89 (95% CI 0.37-2.13).

- Moderate quality evidence from 1 RCT (n=1088) showed no clinically important difference between adjuvant gemcitabine and adjuvant fluororacil and folinic acid on the number of people who experience grade 3 or 4 fatigue/tiredness in adults with resected pancreatic cancer: RR 0.73 (95% CI 0.47-1.13).
- Very low quality evidence from 1 RCT (n=725) showed no clinically important difference between adjuvant gemcitabine only and adjuvant gemcitabine combined with capecitabine on the number of people who experience grade 3 or 4 fatigue/tiredness in adults with resected pancreatic cancer: RR 0.93 (95% CI 0.51-1.72).

Very low quality evidence from 2 RCTs (n=1102) showed no clinically important difference between adjuvant gemcitabine and any other adjuvant chemotherapy on the number of people who experience grade 3 or 4 fever in adults with resected pancreatic cancer: RR 0.62 (95% CI 0.24-1.6).

- Low quality evidence from 1 RCT (n=377) showed no clinically important difference between adjuvant gemcitabine and adjuvant S-1 on the number of people experience grade 3 or 4 fever in adults with resected pancreatic cancer: RR 0.2 (95% CI 0.02-1.67).
- Very low quality evidence from 1 RCT (n=725) showed no clinically important difference between adjuvant gemcitabine only and adjuvant gemcitabine combined with capecitabine on the number of people who experience grade 3 or 4 fever in adults with resected pancreatic cancer: RR 0.98 (95% CI 0.32-3.01).

Moderate quality evidence from 1 RCT (n=725) showed there is a clinically important difference favouring adjuvant gemcitabine on the number of people who experience grade 3 or 4 hand foot syndrome compared to adjuvant gemcitabine and capecitabine in adults with resected pancreatic cancer: RR 0.02 (95% CI 0.0-0.3).

Moderate quality evidence from 2 RCTs (n=1102) showed there is a clinically important difference favouring any other adjuvant chemotherapy on the number of people who experience grade 3 or 4 infections compared to adjuvant gemcitabine in adults with resected pancreatic cancer: RR 2.86 (95% CI 1.46-5.6).

- Moderate quality evidence from 1 RCT (n=377) showed that there may be a clinically important difference favouring adjuvant S-1 on the number of people who experience grade 3 or 4 infections compared to adjuvant gemcitabine in adults with resected pancreatic cancer, although there is some uncertainty: RR 3.94 (95% CI 0.85-18.3).
- Low quality evidence from 1 RCT (n=725) showed that there may be a clinically important difference favouring adjuvant gemcitabine and capecitabine on the number of people who experience grade 3 or 4 infections compared to adjuvant gemcitabine only in adults with resected pancreatic cancer: RR 2.62 (95% CI 1.23-5.55).

Low quality evidence from 2 RCTs (n=1465) showed no clinically important difference between adjuvant gemcitabine and any other type of adjuvant chemotherapy on the number of people who experience grade 3 or 4 nausea (RR 0.7 [95% CI 0.39-1.27]) and vomiting (RR 0.66 [95% CI 0.33-1.32]) in adults with resected pancreatic cancer.

- Low quality evidence from 1 RCT (n=377) showed no clinically important difference between adjuvant gemcitabine and adjuvant S-1 on the number of people who experience grade 3 or 4 nausea in adults with resected pancreatic cancer: RR 0.7 (95% CI 0.23-2.18).
- Low quality evidence from 1 RCT (n=1088) showed no clinically important difference between adjuvant gemcitabine and adjuvant fluororacil combined with folinic acid on the number of people who experience grade 3 or 4 nausea in adults with resected pancreatic cancer: RR 0.7 (95% CI 0.35-1.41).
- Low quality evidence from 1 RCT (n=377) showed no clinically important difference between adjuvant gemcitabine and adjuvant S-1 on the number of people who experience grade 3 or 4 vomiting in adults with resected pancreatic cancer: RR 0.66 (95% CI 0.11-3.88).

- Low quality evidence from 1 RCT (n=1088) showed no clinically important difference between adjuvant gemcitabine and adjuvant fluororacil and folinic acid on the number of people who experience grade 3 or 4 vomiting in adults with resected pancreatic cancer: RR 0.66 (95% CI 0.31-1.4).

Low quality evidence from 2 RCTs (n=1465) showed that there is a clinically important difference favouring any other type of adjuvant chemotherapy on the number of people who experience grade 3 or 4 neutrophils toxicities compared to adjuvant gemcitabine in adults with resected pancreatic cancer: RR 1.91 (95% CI 1.59-2.31).

- High quality evidence from 1 RCT (n=377) showed there is a clinically important difference favouring adjuvant S-1 on the number of people who experience grade 3 or 4 neutrophils toxicities compared to adjuvant gemcitabine in adults with resected pancreatic cancer: RR 9.05 (95% CI 5.53-14.83).
- Moderate quality evidence from 1 RCT (n=1088) showed no clinically important difference between adjuvant gemcitabine and adjuvant fluororacil and folinic acid on the number of people who experience grade 3 or 4 neutrophils toxicities in adults with resected pancreatic cancer: RR 1.01 (95% CI 0.81-1.26).

Moderate quality evidence from 4 RCTs (n=2289) showed there is a clinically important difference favouring any other type of adjuvant chemotherapy on the number of people who experience a grade 3 or 4 platelet toxicity compared to adjuvant gemcitabine in adults with resected pancreatic cancer: RR 2.04 (95% CI 1.17-3.53).

- Moderate quality evidence from 1 RCT (n=377) showed no clinically important difference between adjuvant gemcitabine and adjuvant S-1 on the number of people who experience grade 3 or 4 platelet toxicity in adults with resected pancreatic cancer: RR 1.97 (95% CI 0.91-4.27).
- Moderate quality evidence from 1 RCT (n=377) showed there is a clinically important difference favouring adjuvant fluororacil combined with folinic acid on the number of people who experience a grade 3 or 4 platelet toxicity compared to adjuvant gemcitabine in adults with resected pancreatic cancer: RR 17.44 (95% CI 1.01-301.45).
- Low quality evidence from 1 RCT (n=99) showed no clinically important difference between adjuvant gemcitabine only and adjuvant gemcitabine and UFT on the number of people who experience grade 3 or 4 platelet toxicity in adults with resected pancreatic cancer: RR 7.14 (95% CI 0.38-134.71).
- Very low quality evidence from 1 RCT (n=725) showed no clinically important difference between adjuvant gemcitabine only and adjuvant gemcitabine combined with capecitabine on the number of people who experience a grade 3 or 4 platelet toxicity in adults with resected pancreatic cancer: RR 0.86 (95% CI 0.31-2.34).

High quality evidence from 2 RCTs (n=1465) showed there is a clinically important difference favouring adjuvant gemcitabine leads to a clinically significant decrease in the number of people who experience grade 3 or 4 stomatitis compared to any other type of adjuvant chemotherapy in adults with resected pancreatic cancer: RR 0.03 (95% CI 0.01-0.13).

- Low quality evidence from 1 RCT (n=377) showed no clinically important difference between adjuvant gemcitabine and adjuvant S-1 on the number of people who experience grade 3 or 4 stomatitis in adults with resected pancreatic cancer: RR 0.09 (95% CI 0-1.61).
- High quality evidence from 1 RCT (n=1088) showed there is a clinically important difference favouring adjuvant gemcitabine on the number of people who experience grade 3 or 4 stomatitis compared to adjuvant fluororacil and folinic acid in adults with resected pancreatic cancer: RR 0.02 (95% CI 0-0.14).

Very low quality evidence from 4 RCTs (n=2289) showed no clinically important difference between adjuvant gemcitabine and any other type of adjuvant chemotherapy on the number

of people who experience a grade 3 or 4 white blood cell count toxicity in adults with resected pancreatic cancer: RR 1.65 (95% CI 0.75-3.63) [random effects analysis].

- High quality evidence from 1 RCT (n=377) showed there is a clinically important difference favouring adjuvant S-1 leads to a clinically significant increase in the number of people who experience a grade 3 or 4 white blood cell count toxicity compared to adjuvant gemcitabine in adults with resected pancreatic cancer: RR 4.55 (95% CI 2.76-7.51) [fixed effects analysis].
- Moderate quality evidence from 1 RCT (n=377) showed there is a clinically important difference favouring adjuvant fluororacil and folinic acid on the number of people who experience a grade 3 or 4 white blood cell count toxicity compared to adjuvant gemcitabine in adults with resected pancreatic cancer: RR 1.7 (95% CI 1.11-2.59) [fixed effects analysis].
- Low quality evidence from 1 RCT (n=99) showed no clinically important difference between adjuvant gemcitabine only and adjuvant gemcitabine combined with UFT on the number of people who experience grade 3 or 4 white blood cell toxicity in adults with resected pancreatic cancer: RR 1.25 (95% CI 0.57-2.74) [fixed effects analysis].
- Low quality evidence from 1 RCT (n=725) showed no clinically important difference between adjuvant gemcitabine only and adjuvant gemcitabine combined with capecitabine on the number of people who experience grade 3 or 4 white blood cell toxicity in adults with resected pancreatic cancer: RR 0.74 (95% CI 0.46-1.19) [fixed effects analysis].

Low quality of evidence from 1 RCT (n=99) showed no clinically important difference between adjuvant gemcitabine and adjuvant gemcitabine combined with UFT on the number of people who experience grade 3 or 4 glucose intolerance (RR 0.34 [95% CI 0.01 to 8.15]), haemoglobin toxicity (RR 2.04 [95% CI 0.39 to 10.64]), leukocytes (RR 1.25 [95% CI 0.57 to 2.74]) in adults with resected pancreatic cancer.

Health-related quality of life

Very low quality evidence from 1 RCT (n=311) showed no clinically important difference between adjuvant gemcitabine and adjuvant S-1 on EQ-5D quality of life scores 3 months (n=311; SMD 0.15 [95% CI -0.08 to 0.37) and 6 months (n=291; SMD 0.14 [95% CI -0.09 to 0.37]) after randomisation in adults with resected pancreatic cancer.

Very low quality evidence from 1 RCT showed no clinically important differences between adjuvant gemcitabine and adjuvant S-1 on EQ-5D quality of life scores at 12 months (n=255; SMD 0.4 [95% CI 0.15-0.65]) and 24 months (n=171; SMD 0.42 [95% CI 0.11-0.72]) after randomisation in adults with resected pancreatic cancer.

Low quality evidence from 1 RCT (n=565) showed no clinically important difference between adjuvant gemcitabine and adjuvant fluororacil combined with folinic acid on global quality of life in adults with resected pancreatic cancer: SMD 0.15 (95% CI -0.01 to 0.32).

Patient experience

No evidence was identified to inform this outcome.

PROMS

No evidence was identified to inform this outcome.

10.3.6.3 Adjuvant chemotherapy versus adjuvant chemoradiotherapy

Disease-free survival

Very low quality evidence from 1 RCT (n=90) showed no clinically important difference between adjuvant chemotherapy (gemcitabine) and adjuvant chemoradiotherapy on disease-free survival in adults with resected pancreatic cancer: HR 0.97 (95% CI 0.62-1.52).

Relapse-free survival

No evidence was identified to inform this outcome.

Overall survival

Very low quality evidence from 2 RCTs (n=238) showed no clinically important difference between adjuvant chemotherapy (fluororacil and folinic acid; gemcitabine) and adjuvant chemoradiotherapy on overall survival in adults with resected pancreatic cancer: HR 0.79 (95% CI 0.59-1.07).

- Very low quality evidence from 1 RCT (n=148) showed no clinically important difference between adjuvant fluororacil combined with folinic acid and adjuvant chemoradiotherapy on overall survival in adults with resected pancreatic cancer: HR 0.7 (95% CI 0.49-1.01).
- Very low quality evidence from 1 RCT (n=90) showed no clinically important difference between adjuvant gemcitabine and adjuvant chemoradiotherapy on overall survival in adults with resected pancreatic cancer: HR 1.02 (95% CI 0.61-1.72).

Adverse events

Very low quality evidence from 1 RCT (n=148) showed no clinically important difference between adjuvant fluororacil combined with folinic acid and adjuvant chemoradiotherapy on the number of people who experience any grade 3 or 4 haematological (RR 4.87 [95% CI 0.24-99.7]) or non-haematological (RR 4.38 [95% CI 0.98-19.59]) toxicity in adults with resected pancreatic cancer.

Very low quality evidence from 1 RCT (n=85) showed no clinically important difference between adjuvant gemcitabine and adjuvant chemoradiotherapy on the number of people who experience grade 3 or 4 anorexia (RR 0.2 [95% CI 0.01-4.14]), fatigue (RR 0.68 [95% CI 0.12-3.88]), fever (RR 0.15 [95% CI 0.01-2.75]), gastritis (RR 0.2 [95% CI 0.01 to 4.14]), haemoglobin (RR 0.15 [95% CI 0.01-2.75]), haemorrhage (RR 1.02 [95% CI 0.07- 15.84]), nausea (RR 0.34 [95% CI 0.01- 8.14]), neutrophils (RR 1.32 [95% CI 0.76- 2.29]), other gastrointestinal toxicities (RR 0.34 [95% CI 0.01- 8.14]), platelets (RR 0.34 [95% CI 0.01-8.14]), serum glutamicpyruvic transaminase (RR 1.02 [95% CI 0.32-3.28]), stomatitis (RR 8.76 [95% CI 0.48-159.93]), vomiting (RR 0.34 [95% CI 0.01- 8.14]), weight loss (RR 0.34 [95% CI 0.01- 8.14]), white blood cell count (RR 0.88 [95% CI 0.32-2.4]) in adults with resected pancreatic cancer.

Very low quality evidence from 2 RCTs (n=233) showed no clinically important difference between adjuvant chemotherapy and adjuvant chemoradiotherapy on the number of people who experience grade 3 or 4 diarrhoea in adults with resected pancreatic cancer: RR 1.49 (95% CI 0.25-8.95).

Very low quality evidence from 1 RCT (n=85) showed no clinically important difference between adjuvant gemcitabine and adjuvant chemoradiotherapy on the number of people who experience grade 3 or 4 diarrhoea in adults with resected pancreatic cancer: RR 0.31 (95% CI 0.01-8.14).

Very low quality evidence from 1 RCT (n=148) showed no clinically important difference between adjuvant fluororacil combined with folinic acid and adjuvant chemoradiotherapy on

the number of people who experience grade 3 or 4 diarrhoea in adults with resected pancreatic cancer: RR 4.87 (95% CI 0.24-99.7).

Health-related quality of life

No evidence was identified to inform this outcome.

Patient experience

No evidence was identified to inform this outcome.

PROMS

No evidence was identified to inform this outcome.

10.3.6.4 Adjuvant chemotherapy versus adjuvant chemoimmunotherapy

Disease-free survival

Very low quality evidence from 1 RCT (n=88) showed there is a clinically important difference favouring adjuvant chemoimmunotherapy (interleukin-2) on disease-free survival compared to combined adjuvant chemotherapy (gemcitabine, carboplatin, mitomycin C, fluororacil, and folinic acid) in adults with resected pancreatic cancer: HR 1.99 (95% CI 1.07-3.7).

Relapse-free survival

No evidence was identified to inform this outcome.

Overall survival

Very low quality evidence from 1 RCT (n=88) showed there is a clinically important difference favouring adjuvant chemoimmunotherapy (interleukin-2) on overall survival compared to combined adjuvant chemotherapy (gemcitabine, carboplatin, mitomycin C, fluororacil, and folinic acid) in adults with resected pancreatic cancer: HR 2.05 (95% CI 1.12-3.76).

Adverse events

Very low quality evidence from 1 RCT (n=88) showed no clinically important difference between combined adjuvant chemotherapy (gemcitabine, carboplatin, mitomycin C, fluororacil, and folinic acid) and adjuvant chemoimmunotherapy on the number of people who experience grade 3 or 4 nausea (RR 2.87 [95% CI 0.12-68.58]) or vomiting (RR 0.19 [95% CI 0.01-3.87]) in adults with resected pancreatic cancer.

Health-related quality of life

No evidence was identified to inform this outcome.

Patient experience

No evidence was identified to inform this outcome.

PROMS

No evidence was identified to inform this outcome.

10.3.6.5 Adjuvant chemotherapy versus adjuvant chemoradioimmunotherapy

Disease-free survival

Very low quality evidence from 1 RCT (n=132) showed no clinically important difference between adjuvant fluororacil and adjuvant chemoradioimmunotherapy (fluororacil, cisplatin and interferon α-2b) on disease-free survival in adults with resected pancreatic cancer: HR 1.02 (95% CI 0.64-1.65).

Relapse-free survival

No evidence was identified to inform this outcome.

Overall survival

Very low quality evidence from 1 RCT (n=132) showed no clinically important difference between adjuvant fluororacil and adjuvant chemoradioimmunotherapy (fluororacil, cisplatin and interferon α-2b) on overall survival in adults with resected pancreatic cancer: HR 0.96 (95% CI 0.63-1.48).

Adverse events

Very low quality evidence from 1 RCT (n=110) showed that there is a clinically important difference favouring adjuvant fluororacil on the number of people who experience any grade 3 or 4 toxicity compared to adjuvant chemoradioimmunotherapy (fluororacil, cisplatin and interferon α-2b) in adults with resected pancreatic cancer: RR 0.22 (95% CI 0.12-0.4).

Health-related quality of life

Very low quality evidence from 1 RCT (n=85/86) showed that there is a clinically important difference favouring adjuvant fluororacil on EORTC QLQ-C30 global health status (MD 7.3 [95% CI 0.41-13.59]), and the nausea/vomiting (MD 7.7 [95% CI 1.67-13.73]), role functioning (MD 13.9 [95% CI -4.16 to 23.64]) and social functioning subscales (MD 10 [95% CI 0.75-19.25]) compared to adjuvant chemoradioimmunotherapy (fluororacil, cisplatin and interferon α-2b) in adults with resected pancreatic cancer.

Patient experience

No evidence was identified to inform this outcome.

PROMS

No evidence was identified to inform this outcome.

10.3.6.6 Adjuvant chemoradiotherapy followed by chemotherapy versus no adjuvant therapy

10.3.6.7 Disease-free survival

No evidence was identified to inform this outcome.

Relapse-free survival

No evidence was identified to inform this outcome.

Overall survival

No evidence was identified to inform this outcome.

Adverse events

Very low quality evidence from 1 RCT (n=141) showed no clinically important difference between adjuvant chemoradiotherapy followed by chemotherapy (fluororacil and folinic acid) and no adjuvant therapy on the number of people who experience any grade 3 or 4 haematological toxicity (RR 10.55 [95% CI 0.59-187.23]), stomatitis (RR 8.29 [95% CI 0.45-151.2]) and diarrhoea (RR 4.61 [95% CI 0.22-94.27]) in adults with resected pancreatic cancer.

Very low quality evidence from 1 RCT (n=144) showed that there is a clinically important difference favouring no adjuvant therapy on the number of people who experience a grade 3 or 4 non-haematological toxicity compared to adjuvant chemoradiotherapy followed by chemotherapy (fluororacil and folinic acid) in adults with resected pancreatic cancer: RR 22.05 (95% CI 1.32-367.2).

Health-related quality of life

No evidence was identified to inform this outcome.

Patient experience

No evidence was identified to inform this outcome.

PROMS

No evidence was identified to inform this outcome.

10.3.6.8 Adjuvant chemoradiotherapy followed by chemotherapy versus adjuvant chemotherapy

Disease-free survival

No evidence was identified to inform this outcome.

Relapse-free survival

No evidence was identified to inform this outcome.

Overall survival

Very low quality evidence from 1 RCT (n=147) showed no clinically important difference between adjuvant chemoradiotherapy followed by chemotherapy (fluororacil and folinic acid) and adjuvant chemotherapy (fluororacil and folinic acid) on overall survival in adults with resected pancreatic cancer: HR 1.32 (95% CI 0.9-1.92).

Adverse events

Very low quality evidence from 1 RCT showed no clinically important difference between adjuvant chemoradiotherapy followed by chemotherapy (fluororacil and folinic acid) and adjuvant chemotherapy (fluororacil and folinic acid) on the number of people who experience any grade 3 or 4 haematological toxicity (n=147; RR 2.6 [95% CI 0.52 to 13]), non-haematological toxicity (n=147; RR 1.27 [95% CI 0.56-2.89]), stomatitis (n=144; RR 8.29 [95% CI 0.45-151.2]), and diarrhoea (n=150; RR 5 [95% CI 0.24-102.42]) in adults with resected pancreatic cancer.

Health-related quality of life

No evidence was identified to inform this outcome.

Patient experience

No evidence was identified to inform this outcome.

PROMS

No evidence was identified to inform this outcome.

10.3.6.9 Adjuvant chemoradiotherapy followed by chemotherapy versus adjuvant chemoradiotherapy

Disease-free survival

No evidence was identified to inform this outcome.

Relapse-free survival

No evidence was identified to inform this outcome.

Overall survival

Low quality evidence from 1 RCT (n=145) showed a clinically important difference favouring adjuvant chemoradiotherapy followed by chemotherapy (fluororacil and folinic acid) on overall survival compared to adjuvant chemoradiotherapy only in adults with resected pancreatic cancer: HR 0.67 (95% CI 0.47-0.96).

Adverse events

Very low quality evidence from 1 RCT (n=147) showed no clinically important difference between adjuvant chemoradiotherapy followed by chemotherapy (fluororacil and folinic acid) and adjuvant chemoradiotherapy only on the number of people who experience any grade 3 or 4 haematological toxicity (n=145; RR 11.15 [95% CI 0.63-198.04]), stomatitis (n=148; RR 8.76 [95% CI 0.48-159.93]) and diarrhoea (n=144; RR 4.61 [95% CI 0.22-94.27]) in adults with resected pancreatic cancer.

Very low quality evidence from 1 RCT (n=145) showed that there is a clinically important difference favouring adjuvant chemoradiotherapy only on the number of people who experience any grade 3 or 4 non-haematological toxicities compared to chemoradiotherapy followed by chemotherapy (fluororacil and folinic acid) in adults with resected pancreatic cancer: RR 5.58 (95% CI 1.28-24.28).

Health-related quality of life

No evidence was identified to inform this outcome.

Patient experience

No evidence was identified to inform this outcome.

PROMS

No evidence was identified to inform this outcome.

10.3.6.10 Adjuvant chemotherapy-1 (gemcitabine) followed by chemoradiotherapy versus adjuvant chemotherapy-2 (other) followed by chemoradiotherapy

Disease-free survival

Very low quality evidence from 1 RCT (n=100) showed no clinically important difference between adjuvant gemcitabine followed by chemoradiotherapy and adjuvant chemotherapy (PEFG) followed by chemoradiotherapy on prolonging disease-free survival in adults with resected pancreatic cancer: HR 1.33 (95% CI 0.86-2.06).

Relapse-free survival

No evidence was identified to inform this outcome.

Overall survival

Low quality evidence from 1 RCT (n=451) showed no clinically important difference between adjuvant gemcitabine followed by chemoradiotherapy and adjuvant chemotherapy (fluororacil) followed by chemoradiotherapy on overall survival in adults with resected pancreatic cancer: HR 0.93 (95% CI 0.76-1.15).

Adverse events

Low to moderate quality evidence from 1 RCT (n=451) showed that there is a clinically important difference favouring adjuvant chemotherapy (fluororacil) followed by chemoradiotherapy on the number of people who experience grade 4 toxicities (RR 11.1 [95% CI 3.45-35.73]), worst grade 3 or 4 haematological toxicities (RR 6.1 [95% CI 4.04-9.22]) and worst grade 3 or 4 overall toxicities (RR 1.27 [95% CI 1.13-1.44]) compared to adjuvant gemcitabine followed by chemoradiotherapy in adults with resected pancreatic cancer.

Low quality evidence from 1 RCT (n=451) showed no clinically important difference between adjuvant gemcitabine followed by chemoradiotherapy and adjuvant chemotherapy (fluororacil) followed by chemoradiotherapy on the number of people who experience grade 3 or 4 diarrhoea (RR 0.78 [95% CI 0.52-1.18]) or stomatitis (RR 0.65 [95% CI 0.4-1.08]), nor on the number of people who experience worst grade 3 or 4 non-haematological toxicities (RR 0.98 [95% CI 0.84-1.14]) in adults with resected pancreatic cancer.

Very low quality evidence from 1 RCT (n=102) showed that there is a clinically important difference favouring adjuvant gemcitabine followed by chemoradiotherapy on the number of people who experience a grade 3 or 4 neutropenic or thrombocytopenic toxicity compared to adjuvant chemotherapy (PEFG) followed by chemoradiotherapy in adults with resected pancreatic cancer: SMD -0.8 (95% CI -1.21 to -0.4) for both outcomes.

Health-related quality of life

No evidence was identified to inform this outcome.

Patient experience

No evidence was identified to inform this outcome.

PROMS

No evidence was identified to inform this outcome.

10.3.6.11 Immunotherapy versus no adjuvant therapy

Disease-free survival

No evidence was identified to inform this outcome.

Relapse-free survival

No evidence was identified to inform this outcome.

Overall survival

Very low quality evidence from 1 RCT (n=61) showed no clinically important difference between adjuvant immunotherapy (MoAb 494/32) and no adjuvant therapy on overall survival in adults with resected pancreatic cancer: HR 1.12 (95% CI 0.21-6.03).

Adverse events

Very low quality evidence from 1 RCT (n=61) showed no clinically important difference between adjuvant immunotherapy (MoAb 494/32) and no adjuvant therapy on the number of people who experience grade 3 or 4 abdominal pain in adults with resected pancreatic cancer: RR 3.3 (95% CI 0.14-77.95).

Health-related quality of life

No evidence was identified to inform this outcome.

Patient experience

No evidence was identified to inform this outcome.

PROMS

No evidence was identified to inform this outcome.

10.3.6.12 Chemoimmunotherapy versus no adjuvant therapy

Disease-free survival

Low quality evidence from 1 RCT (n=83) showed that there is a clinically important difference favouring adjuvant chemoimmunotherapy (interleukin-2) disease-free survival compared to no adjuvant therapy in adults with resected pancreatic cancer: HR 0.33 (95% CI 0.17-0.64).

Relapse-free survival

No evidence was identified to inform this outcome.

Overall survival

Low quality evidence from 1 RCT (n=83) showed that there is a clinically important difference favouring adjuvant chemoimmunotherapy (interleukin-2) on overall survival compared to no adjuvant therapy in adults with resected pancreatic cancer: HR 0.45 (95% CI 0.23-0.88).

Adverse events

Very low quality evidence from 1 RCT (n=83) showed no clinically important difference between chemoimmunotherapy (interleukin-2) and no adjuvant therapy on the number of

adults with resected pancreatic cancer who experience grade 3 or 4 vomiting: RR 4.66 (95% CI 0.23-94.18).

Health-related quality of life

No evidence was identified to inform this outcome.

Patient experience

No evidence was identified to inform this outcome.

PROMS

No evidence was identified to inform this outcome.

10.3.7 Recommendations

39. Give people time to recover from surgery before starting adjuvant therapy. Start adjuvant therapy as soon as they are well enough to tolerate all 6 cycles.

40. Offer adjuvant gemcitabine plus capecitabine[2] to people who have had sufficient time to recover after pancreatic cancer resection.

41. Consider adjuvant gemcitabine[3] for people who are not well enough to tolerate combination chemotherapy.

10.3.8 Evidence to recommendations

10.3.8.1 Relative value placed on the outcomes considered

Disease free survival, relapse free survival, overall survival, adverse events, health related quality of life, patient experience and patient reported outcome measures were considered to be the critical outcomes for this question.

Overall survival and adverse events were reported by all studies. Relapse free survival, disease free survival and health-related quality of life were reported only by some studies. No studies reported on patient experience or patient reported outcome measures.

10.3.8.2 Quality of evidence

The quality of the evidence was assessed by GRADE and the Cochrane risk of bias checklist.

The quality of the outcomes for the comparisons identified by this review were as follows:

- adjuvant gemcitabine versus other adjuvant chemotherapy - ranged from very low to high

[2] Although this use is common in UK clinical practice, at the time of consultation (July 2017) gemcitabine plus capecitabine did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[3] Although this use is common in UK clinical practice, at the time of consultation (July 2017) gemcitabine did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

- adjuvant gemcitabine followed by chemoradiotherapy versus other adjuvant chemotherapy followed by chemoradiotherapy - ranged from low to moderate.
- adjuvant chemotherapy with no adjuvant therapy - ranged from very low to moderate
- adjuvant chemoradiotherapy followed by chemotherapy versus adjuvant chemoradiotherapy - ranged from very low to low
- adjuvant chemoimmunotherapy versus no adjuvant therapy - ranged from very low to low
- adjuvant chemotherapy with adjuvant chemoradiotherapy – very low
- adjuvant chemotherapy with adjuvant chemoimmunotherapy – very low
- adjuvant chemotherapy with adjuvant chemoradioimmunotherapy – very low
- Adjuvant chemoradiotherapy followed by chemotherapy versus no adjuvant therapy – very low
- Adjuvant chemoradiotherapy followed by chemotherapy versus adjuvant chemotherapy – very low
- Adjuvant immunotherapy versus no adjuvant therapy – very low

The committee noted that the clinical evidence indicates adjuvant S1 is an effective adjuvant chemotherapy. However the committee also noted that the trial reporting this result recruited only in Japan. The committee considered, based on their knowledge and experience, that there are population differences between the Japanese and European populations which mean that these results may not be directly applicable to a western population. Consequently the committee agreed not to make a recommendation for clinical practice about S1. They considered making a recommendation for further research in this area but agreed it was unlikely to be feasible.

The committee also noted that the data for the use of adjuvant chemoradiotherapy was limited, of very low to low quality and only reported a restricted set of outcomes. Consequently the committee were not able to make any recommendations about this intervention. They agreed there were ongoing trials in this area and so they did not make a recommendation for further research.

The committee noted that only single studies had been found that examined immunotherapy, chemoimmunotherapy, or chemoradioimmunotherapy as adjuvant therapies. Because of the limited and low quality data on these interventions and the fact that none of these interventions are in regular use, the committee agreed not to make any recommendations for clinical practice. In the absence of any new agents with encouraging preliminary data, the committee recognised this was an unmet need but was not able to prioritise further randomised trials in this area at this time.

10.3.8.3 Consideration of clinical benefits and harms

The committee noted, based on directly relevant evidence, that adjuvant therapy with gemcitabine plus capecitabine had shown the most benefit to overall survival in people who have had pancreatic resection. The committee also noted that the evidence had shown adjuvant therapy was associated with toxicity. However the committee considered the benefits to overall survival outweighed the potential for increased toxicity and agreed to make a strong recommendation for this intervention.

Given that there would be people who may not tolerate the toxicity associated with combination therapy, the committee agreed it was important to make a recommendation for this group of people. The committee noted that adjuvant monotherapy with gemcitabine had also shown a benefit to overall survival, but not as much as the combination of gemcitabine and capecitabine. They therefore agreed to make a recommendation on adjuvant gemcitabine.

The committee also noted that Valle et al's analysis of ESPAC3 showed that overall survival favoured people receiving all 6 cycles of adjuvant therapy (compared with only 1-5 cycles). This study also demonstrated that delaying adjuvant therapy did not negatively affect outcomes. Therefore the committee agreed to recommend that commencement of adjuvant chemotherapy should be delayed until the person had fully recovered from surgery in order to maximize the chance of delivering all 6 cycles.

10.3.8.4 Consideration of economic benefits and harms

The committee noted that no relevant published economic evaluations had been identified and no additional economic analysis had been undertaken in this area.

The committee agreed that current practice is to use gemcitabine as adjuvant therapy. Therefore there are likely to be additional costs associated with the recommendation to offer gemcitabine in combination with capecitabine. However, since capecitabine is now generic and can be provided orally, rather than requiring daily injection, the committee thought that any increase in costs was unlikely to be significant. In addition, the proportion of people with pancreatic cancer who have resection and therefore are able to receive adjuvant therapy is small. The committee also considered that there were likely to be cost savings as a result of the recommendations because provision of adjuvant therapy would reduce the number of people who relapse, hence saving the costs of investigations for relapse and second line therapies.

10.3.9 References

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10.4 Follow-up for people with resected pancreatic cancer

Review question: What is the optimal follow-up protocol for people with resected pancreatic adenocarcinoma?

10.4.1 Introduction

Pancreatic surgery is both technically challenging and highly specialist in terms of pre and post-operative care. Previous UK guidelines specified that pancreatic cancer surgery should be performed in specialised units covering a geographical population of over 2 million people, but they did not stipulate optimal follow-up after surgery. Surgical resection followed by adjuvant chemotherapy is the only hope of cure for pancreatic cancer patients. Post-surgery, for those people with suitable performance status, a 6 month course of adjuvant chemotherapy is recognised as the gold standard treatment.

The question of how best to follow up people thereafter varies regionally, nationally and internationally, not least due to lack of a high quality evidence base.

There are 3 main reasons to follow-up people after they have had their pancreatic cancer resected to:

4. manage post-surgical morbidity, including pain, change in bowel habit, pancreatic exocrine insufficiency, other nutrition requirements and diabetes;
5. diagnose disease recurrence with a view to expediting subsequent treatment and
6. support people and their families coping with a cancer diagnosis that is associated with one of the worst outcomes.

Most post-surgical morbidity is managed over the first 6 months but the ways in which this is done are variable.

There is also wide variation in how surveillance for disease recurrence is conducted across the UK. This ranges from intensive, 3 monthly clinic reviews involving surgeons, oncologists, specialist nurses and dieticians, to no formal clinic review at all. The latter approach may be justified because recurrence of pancreatic cancer is almost never resectable and the treatment options for unresectable disease remain very limited. There is also variation in what the surveillance involves (for example clinical examination, holistic needs assessment, monitoring of the serum CA19.9 tumour marker, cross sectional imaging such as CT, MRI or PET/CT), the intervals at which these are done or whether they are done at all.

Guidance is needed on the most effective follow-up protocol for people with resected pancreatic cancer.

10.4.1.1 Review protocol summary

The review protocol summary used for this question can be found in Table 147. Full details of the review protocol can be found in Appendix C.

Table 147: Clinical review protocol summary for the review of follow-up protocols

Population	Patients who have undergone surgical resection for pancreatic adenocarcinoma with curative intent
Intervention	• Gastro-intestinal or endocrine, psychological, oncological • Follow-up packages [including combinations of follow-up elements such as clinical assessment (including Holistic Needs Assessment (HNA) and clinical examination), imaging, blood tests including ca19.9, including the frequency of follow up]

Population	Patients who have undergone surgical resection for pancreatic adenocarcinoma with curative intent
Comparison	No active/scheduled follow-up or one of the interventions listed
Outcome	• Survival • Time to detection of recurrence • Proportion of asymptomatic recurrence (imaging) • Fitness for further intervention • Health Reported Quality of Life • Adverse events • Risk of increased radiation (following repeated imaging) • Patient Reported Outcome Measures • Patient acceptability

10.4.2 Description of clinical evidence

Two studies were included in this review (Reeder-Hayes et al. 2014; Vaccaro et al. 2010). A summary of the included studies is presented in Table 2. One study was an abstract (Vaccaro et al. 2010) and only a limited amount of data about this study could be extracted.

One study (n=4652) provided evidence on the overall mortality between various imaging approaches (PET, CT/MRI, and none) in pancreatic cancer (Reeder-Hayes et al. 2014). The other study (n=296) investigated the value of CT imaging compared to clinical symptoms and CA 19-9 levels in detecting cancer recurrence in pancreatic cancer (Vaccaro et al. 2010).

Further information about the search strategy can be found in Appendix D. See study selection flow chart in Appendix E, forest plots in Appendix H, GRADE tables in Appendix I, study evidence tables in Appendix F and list of excluded studies in Appendix G.

10.4.3 Summary of included studies

A summary of the studies that were included in this review is presented in Table 148.

Table 148: Summary of included studies

Study	Population	Intervention	Comparator	Outcomes
Reeder-Hayes, et al. (2014)	Individuals with a new, single primary cancer diagnosis of pancreatic malignancy (ICD-O-2 codes C250-C259) between 2003-2007. Included individuals were >66 years at diagnosis and continuously enrolled in Medicare part A and B for 1 year prior to diagnosis forward to death or end of the study period. Patients stratified into: Surgery, Borderline, Metastatic, and Unknown n= 6691; only n=4652 analysed	CT/MRI imaging No imaging follow-up	PET imaging	Mortality Survival beyond 180 days
Vaccaro, et al. (2010)	Pancreatic cancer patients who underwent potentially curative surgery n= 476; only n=296 analysed	CT imaging	Clinical symptoms and CA 19-9 blood levels	Cancer recurrence

10.4.4 Clinical evidence profile

The clinical evidence profiles for this review question are presented in Table 149 to Table 152.

10.4.4.1 CT/MRI versus PET

Table 149: Summary clinical evidence profile for CT/MRI versus PET on survival beyond 180 days

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	CT/MRI on Survival Beyond 180 days	PET				
Surgical Group Follow-up: 180 days	Study population		HR 0.8 (0.57 to 1.14)	372 (1 study)	⨁⊖⊖⊖ very low[1,2]	
	See comment[4]	See comment[4]				
	Moderate					
Borderline Group Follow-up: 180 days	Study population		HR 1.04 (0.82 to 1.33)	969 (1 study)	⨁⊖⊖⊖ very low[1,2,3]	
	See comment[4]	See comment[4]				
	Moderate					

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

CI: Confidence interval; HR: Hazard ratio;

1 Unclear if population confounders were accounted for in the analyses. High dropout rate 57%
2 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant.
3 Unclear if participants in the borderline population underwent resection
4Not calculable due to paucity of data

Table 150: Summary clinical evidence profile for CT/MRI versus PET on overall mortality

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	CT/MRI on Mortality (time-varying exposure model)	PET				
Mortality in Surgical Group Time-varying exposure model	Study population		HR 0.66 (0.52 to 0.83)	372 (1 study)	⨁⊖⊖⊖ very low[2,3]	
	See comment[1]	See comment[1]				

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Mortality in Borderline Group Time-varying exposure model	Study population		HR 0.95 (0.81 to 1.13)	969 (1 study)	⊕⊖⊖⊖ very low[2,3,4]	
	See comment[1]	See comment[1]				
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; HR: Hazard ratio;						
1 Not calculable due to paucity of data 2 Unclear if confounders between cohorts were accounted for in the analyses. 31% dropout in the analyses. 3 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant 4 Not clear if participants included in the borderline analyses have undergone surgical resection						

10.4.4.2 No imaging versus PET

Table 151: Summary clinical evidence profile for no follow-up imaging versus PET on survival beyond 180 days

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No follow-up on Survival Beyond 180 days	PET				
Surgical Group Follow-up: 180 days	Study population		HR 0.56 (0.37 to 0.85)	190 (1 study)	⊕⊖⊖⊖ very low[1]	
	See comment[4]	See comment[4]				
	Moderate					
Borderline group Follow-up: 180 days	Study population		HR 0.9 (0.69 to 1.19)	709 (1 study)	⊕⊖⊖⊖ very low[1,2,3]	
	See comment[4]	See comment[4]				
	Moderate					
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; HR: Hazard ratio;						
1 Unclear if confounders in the population were accounted for in the analyses. High dropout rate 57%. 2 Unclear if participants in the borderline population underwent resection 3 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant. 4 Not calculable due to paucity of data						

Table 152: Summary clinical evidence profile for no follow-up imaging versus PET on overall mortality

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No follow-up on mortality (time-varying exposure model)	PET				
Mortality in Surgical Group Time-varying exposure model	Study population		HR 0.17 (0.1 to 0.28)	190 (1 study)	⨁⊖⊖⊖ very low	
	See comment[1]	See comment[1]				
	Moderate					
Mortality in Borderline Group Time-varying exposure model	Study population		HR 1.02 (0.84 to 1.24)	709 (1 study)	⨁⊖⊖⊖ very low[2,3,4]	
	See comment[1]	See comment[1]				
	Moderate					

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

CI: Confidence interval; HR: Hazard ratio;

1 Not calculable due to paucity of data
2 Unclear if population confounders between cohorts were accounted for in the analyses. High dropout rate 31% in the analyses
3 Unclear if participants in the borderline analyses have undergone surgical resection
4 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant

10.4.5 Economic evidence

One study (Tzeng et al. 2013) was identified by the review of published economic evidence for this topic. The study compared different strategies of follow-up for people who had undergone surgical resection of the pancreas.

The study compared four follow-up strategies in total:

- 6 Monthly follow-up with CA 19-9 with routine CT Scan and chest x-ray (CT/CXR)
- 6 Monthly follow-up with CA 19-9 without routine CT/CXR
- 3 Monthly follow-up with CA 19-9 with routine CT/CXR
- 3 Monthly follow-up with CA 19-9 without routine CT/CXR

These were compared to a base case of no routine follow-up, with testing and imaging being initiated by patient symptoms. The study concluded that the most cost effective follow-up strategy was the least intensive (6 monthly follow-up with CA 19-9 without routine CT/CXR) with other strategies adding significant costs but only marginal survival advantage.

The study was deemed only partially applicable to the topic as it took a non-NHS +PSS perspective and potentially serious methodological issues were identified. For example, the survival parameters of the model were populated using retrospective, observational data

from one centre reporting survival following cancer recurrence identified through routine follow-up and that which was symptom initiated. The difference in survival (8 months) reported was included in the model unadjusted as the estimated survival difference between routine and symptom-led follow-up resulting in a potentially significant lead time bias. The study was also limited in its exploration of quality of life and sources of data were not adequately discussed or referenced.

References to all included studies and evidence tables for all economic evaluations included in the systematic literature review of the economic evidence are presented in Appendix L. Economic evidence profiles of these studies are presented in Appendix K.

10.4.6 Evidence statements

10.4.6.1 Follow-up imaging with CT/MRI versus PET Survival beyond 180 days

Very low quality evidence from 1 retrospective cohort study (n=372) showed no clinically important difference between follow-up imaging with CT/MRI and follow-up imaging with PET on survival beyond 180 days in a ‘surgical group’ of pancreatic cancer patients: HR=0.80 (95% CI 0.57-1.14)

Very low quality evidence from 1 retrospective cohort study (n=969) showed no clinically important difference between follow-up imaging with CT/MRI and follow-up imaging with PET on survival beyond 180 days in a ‘borderline group’ of pancreatic patients: HR=1.04 (95% CI 0.82-1.33)

Overall mortality

Very low quality evidence from 1 retrospective cohort study (n=372) showed that there was a clinically important difference favouring follow-up imaging with CT/MRI on mortality compared to follow-up imaging with PET in a ‘surgical group’ of pancreatic cancer patients: HR=0.66 (95% CI 0.52-0.83)

Very low quality evidence from 1 retrospective cohort study (n=969) showed there was no clinically important difference between follow-up imaging with CT/MRI and follow-up imaging with PET on mortality in a ‘borderline group’ of pancreatic cancer patients: HR=0.95 (95% CI 0.81-1.13)

Time to detection of recurrence

No evidence was identified to inform this outcome

Proportion of asymptomatic recurrence

No evidence was identified to inform this outcome

Fitness for further intervention

No evidence was identified to inform this outcome

Health related quality of life

No evidence was identified to inform this outcome

Adverse events

No evidence was identified to inform this outcome

Risk of increased radiation

No evidence was identified to inform this outcome

Patient reported outcome measures

No evidence was identified to inform this outcome

Patient acceptability

No evidence was identified to inform this outcome

10.4.6.2 No follow-up imaging versus PET

Survival beyond 180 days

Very low quality evidence from 1 retrospective cohort study (n=190) showed that there was a clinically important difference favouring no follow-up imaging on survival beyond 180 days compared to follow-up imaging with PET in a 'surgical group' of pancreatic cancer patients: HR=0.56 (95% CI 0.37-0.85)

Very low quality evidence from 1 retrospective cohort study (n=709) showed no clinically important difference between no follow-up imaging compared to follow-up imaging with PET on survival beyond 180 days in a 'borderline group' of pancreatic cancer patients: HR=0.90 (95% CI 0.69-1.19)

Overall mortality

Very low quality evidence from 1 retrospective cohort study (n=190) showed that there was a clinically important difference favouring no follow-up imaging on mortality compared to follow-up imaging with PET in a 'surgical group' of pancreatic cancer patients: HR=0.17 (95% CI 0.10-0.28)

Very low quality evidence from 1 retrospective cohort study (n=709) showed no clinically important difference between no follow-up imaging and follow-up imaging with PET on mortality in a 'borderline group' of pancreatic cancer patients: HR=1.02 (95% CI 0.84-1.24)

Time to detection of recurrence

No evidence was identified to inform this outcome

Proportion of asymptomatic recurrence

No evidence was identified to inform this outcome

Fitness for further intervention

No evidence was identified to inform this outcome

Health related quality of life

No evidence was identified to inform this outcome

Adverse events

No evidence was identified to inform this outcome

Risk of increased radiation

No evidence was identified to inform this outcome

Patient reported outcome measures

No evidence was identified to inform this outcome

Patient acceptability

No evidence was identified to inform this outcome

10.4.6.3 Follow-up imaging of CT versus symptoms and CA 19-9

Proportion of asymptomatic recurrence

Very low quality evidence from 1 abstract of a retrospective cohort study (n=296) showed that 15% of cancer recurrence was noted only on follow-up imaging of CT in the absence of symptoms or elevation of CA 19-9, however the uncertainty around this could not be calculated.

Survival

No evidence was identified to inform this outcome

Time to detection of recurrence

No evidence was identified to inform this outcome

Fitness for further intervention

No evidence was identified to inform this outcome

Health related quality of life

No evidence was identified to inform this outcome

Adverse events

No evidence was identified to inform this outcome

Risk of increased radiation

No evidence was identified to inform this outcome

Patient reported outcome measures

No evidence was identified to inform this outcome

Patient acceptability

No evidence was identified to inform this outcome

10.4.7 Recommendations

42. **For people who have had resection, offer ongoing specialist assessment and care to identify and manage any problems resulting from surgery.**

43. **For people who have new, unexplained or unresolved symptoms after treatment, provide access to specialist investigation and support services.**

10.4.8 Evidence to recommendations

10.4.8.1 Relative value placed on the outcomes considered

Survival, time to detection of recurrence, proportion of asymptomatic recurrence, fitness for further intervention, health-related quality of life, adverse events, risk of increased radiation, patient reported outcome measures and patient acceptability were considered to be the critical outcomes for this question. Evidence was only reported for the outcomes of survival, mortality and recurrence. No evidence was available for the other outcomes of interest.

10.4.8.2 Quality of evidence

Evidence was available for the comparisons of follow-up imaging with CT/MRI versus PET, no follow-up imaging versus PET and follow-up imaging with CT versus symptoms and CA19-9. The evidence for all comparisons was very low quality.

The committee noted that there were a variety of limitations with the evidence base. In the comparison of CT/MRI versus PET only 12% of people received PET, 97% of which included MRI/CT during follow-up. Most people followed-up with PET occurred late in their disease, with a median time of 197 days. PET imaging after an attempted curative resection may indicate an attempt to confirm recurrence with poor prognosis. It was not possible to distinguish between scans performed as routine surveillance and those obtained to confirm or monitor recurrence

Since the evidence base for this question was limited, of very low quality and only evaluated imaging and blood tests as potential investigations, it was not useful to the committee in identifying the optimal follow up protocol for people with resected pancreatic cancer. They, therefore, based the recommendations on their clinical knowledge and experience.

Given the limited evidence available, the committee noted that it would be useful to have more data on the effectiveness of follow up. However, they also noted that such a research study would take 10-15 years to complete, during which time the technologies used in follow up were likely to have moved on. This would mean the results of the study would then not be helpful in making recommendations for clinical practice. They, therefore, agreed not to make a recommendation for research in this area as it was unlikely to be practical. However, the committee noted that existing and new trials of interventions are likely to include collection of follow-up data which may help to resolve some of the uncertainty.

10.4.8.3 Consideration of clinical benefits and harms

The committee noted that there are 3 main reasons for following up people after resection of their pancreatic cancer – to manage any post-operative sequelae, to detect recurrence of the cancer and to provide psychological support. The patient perspective was that there are inevitably consequences resulting from resectional surgery and it is important that these are managed effectively. The committee unanimously agreed that specialist post-operative assessment was essential to achieving this. They agreed that, even though this recommendation was based on their experience and knowledge rather than high quality evidence, it should be a strong recommendation as it would be negligent not to offer assessment for the purpose of managing post-operative sequelae.

The committee noted the patient perspective following surgery was that new or persistent symptoms are often a source of concern for people. They, therefore, recommended that additional open access to specialist services should be available to provide information and support. The committee noted that this recommendation was in line with advice from NHS England enhanced recovery programmes.

There was no evidence to show whether detecting recurrence has any utility in terms of improving overall survival. The committee were, therefore, unable to make any

recommendations about what tests should be done to detect recurrence, the frequency of testing or the duration of follow-up.

The committee agreed that the benefits of the recommendations made would be a clearer route back to specialist teams. This clarity should lead to better management of post-operative sequelae and more timely, and accurate, identification of new or persistent symptoms. In turn, this would likely lead to avoidance of acute hospital admission and reduce primary care visits. The potential harms of the recommendations would be an increased number of visits. However, the committee agreed that the benefits in terms of better addressing the needs of people with pancreatic cancer and providing reassurance outweighed the potential harms.

10.4.8.4 Consideration of economic benefits and harms

The committee noted that the survival parameters of the model, in the one identified economic evaluation were populated using retrospective, observational data from one centre. This reported survival following cancer recurrence identified through routine follow-up and that which was symptom initiated. The study estimated an increase in survival of 8 months between recurrence identified by routine follow-up and that identified through changes in symptoms outside of routine follow-up. This was used as the survival difference between routine and symptom-led follow-up in the economic model. The committee noted that this value was likely to have significant lead time bias and that it was not supported by the clinical evidence review. As the survival difference in the model was a key driver of the results it was difficult to draw strong conclusions to support making recommendations. This uncertainty was reinforced by the non-NHS perspective of the economic evaluation as well as potentially serious methodological issues.

The committee did consider that any economic evaluation, including the one identified, would not pick up important justifications for follow-up such as a route back into secondary care and reduction in anxiety through routine imaging for recurrence. Therefore, despite there being no strong cost effectiveness evidence for routine follow-up, the committee still felt it was a worthwhile and efficient use of resources, especially as it was unlikely to result in any significant resource impact, as follow-up for the purposes of managing post-operative sequelae is already standard. The committee agreed that there may be some increased staffing costs associated with more people having specialist post-operative assessment. However, this is likely to be balanced by a reduction in costs associated with better management of post-operative sequelae leading to avoidance of emergency hospital admissions.

10.4.9 References

Reeder-Hayes KE, Freburger J, Feagnanes J et al. (2014) Comparative effectiveness of follow-up imaging approaches in pancreatic cancer. Journal of Comparative Effectiveness Research 3(5): 491-502

Tzeng CW, Abbott DE, Cantor SB et al. (2013) Frequency and intensity of postoperative surveillance after curative treatment of pancreatic cancer: a cost-effectiveness analysis.' Ann Surg Oncol 20(Suppl 3): 2197-203

Vaccaro V, Fleming JB, Wolff RA (2010) Role of surveillance CT scans in resected PC: Correlation with CA19-9 and symptoms. Journal of Clinical Oncology 28(15 - supplement): 4113

11 Management of unresectable pancreatic cancer

11.1 Management of locally advanced pancreatic cancer

Review question: What is the most effective treatment (chemotherapy, chemoradiotherapy, radiotherapy, combination of chemotherapy and chemoradiotherapy, biological therapies or other local therapies) for adults with newly diagnosed or recurrent unresectable locally advanced non-metastatic pancreatic cancer?

11.1.1 Introduction

Approximately 30-40% of the people present with locally advanced pancreatic cancer, which is unresectable, but without evidence of metastatic spread. Unlike people with borderline resectable disease, people with locally advanced pancreatic cancer can sometimes be downstaged to resectability with chemotherapy or chemoradiotherapy. They comprise a distinct subset of advanced disease, as the overall survival is significantly better than for people with metastatic disease (10-12 months versus 5-6 months).

Competing risks of locoregional progression versus systemic progression influence overall prognosis in this patient group. In addition to overall survival, management of local symptoms are an important consideration. Autopsy series suggest that about a third of these people die with local progression alone without evidence of metastatic spread. Both systemic therapy alone or in combination with loco-regional therapy (radiotherapy) has been widely used, but the optimal treatment strategy, particularly the role of radiation therapy, remains controversial.

Guidance is needed on what is the most effective treatment for people with locally advanced pancreatic cancer.

11.1.1.1 Review protocol summary

The review protocol summary used for this question can be found in Table 153. Full details of the review protocol can be found in Appendix C.

Table 153: Clinical review protocol summary for the review of most effective treatment of locally advanced, non-metastatic pancreatic cancer

Population	Patients with unresectable non-metastatic locally advanced pancreatic cancer	
Intervention/Comparison	• Chemotherapy	• CT • different types/regimens/combinations of chemotherapy • best supportive care
	• Radiotherapy/ SBRT +/- chemotherapy	
	• Immunotherapy	
	• Biological therapies	
	• Other local therapies (RFA, microwave	
	• CRT +/- CT (either sequence)	Chemoradiotherapy Best supportive care chemotherapy
Outcomes	• Objective Response (CR/PR/PD/SD/) • Resection rate	

	• Progression Free Survival (local, distant) • Overall Survival • Adverse Events • Health Related Quality of Life • Pain control • Patient experience • PROMS

11.1.2 Description of Clinical Evidence

Eighteen studies were included in the review: ten phase III RCTs (Cantore et al. 2005; Chauffert et al. 2008; Chung et al. 2004; Cohen et al. 2005; Hammel et al. 2016; Herman et al. 2013; Li et al. 2003; Loehrer et al. 2011; Shinchi et al. 2002; Sunamura et al. 2004), seven phase II RCTs including five studies (Heinemann et al. 2013; Hurt et al. 2015; Hurt et al. 2017; Khan et al. 2016; Mukherjee et al. 2013; Rich et al. 2012; Wilkowski et al. 2009) and one prospective cohort study (Cantore et al. 2012). A summary of the included studies is presented in Table 154.

Three RCTs (n=175) compared different chemoradiotherapy (CRT) regimens (gemcitabine based CRT versus paclitaxel-based CRT (Chung et al. 2004); gemcitabine-based CRT versus 5FU-based CRT (Li et al. 2003); gemcitabine/cisplatin-based CRT versus 5FU-based CRT (Wilkowski et al. 2009) in patients with locally advanced pancreatic cancer.

Two phase II RCTs (n=127) compared different CRT regimens after induction chemotherapy: gemcitabine-CRT versus capecitabine-CRT after induction chemotherapy (Mukherjee et al. 2013; Hurt et al. 2015); capecitabine-CRT + cetuximab versus capecitabine-CRT alone after induction chemotherapy (Khan et al. 2016) for patients with locally advanced pancreatic cancer.

One RCT (n=31) evaluated whether 5FU-based CRT affected the length and quality of survival in patients with locally advanced pancreatic cancer (Shinchi et al. 2002).

One RCT (n=95) compared gemcitabine/cisplatin-based CRT against the same CRT regimen followed by a sequential full-dose of gemcitabine and cisplatin in patients with locally advanced pancreatic cancer (Wilkowski et al. 2009).

One RCT (n=195) compared the effect of gemcitabine/paclitaxel-based CRT [low-dose gemcitabine plus paclitaxel and concurrent radiation] against the same CRT regimen followed by R115777 [a farnesyl transferase inhibitor] in patients with locally advanced pancreatic cancer (Rich et al. 2012).

One RCT (n=304) compared CRT + TNFerade with CRT alone in patients with locally advanced pancreatic cancer (Herman et al. 2013).

Two RCTs (n=182) compared CRT with chemotherapy in patients with locally advanced pancreatic cancer. One trial compared an intensified induction phase with CRT, followed by maintenance gemcitabine with gemcitabine alone (Chauffert et al. 2008); the other trial examined whether CRT improves survival or provides additional benefit compared with gemcitabine-based chemotherapy alone (Loehrer et al. 2011).

One phase III RCT (n=268) compared chemoradiotherapy with chemotherapy alone (after 4 months of gemcitabine-based induction chemotherapy in patients with locally advanced pancreatic cancer controlled (Hammel et al. 2016 - 2nd randomization).

One RCT (n=105) compared CRT (using 5FU and mytomycin C) against radiotherapy alone in patients with locally advanced pancreatic cancer (Cohen et al. 2005).

Two RCTs (n=617) compared the effect of different chemotherapy regimens in patients with locally advanced pancreatic cancer. One trial evaluated the FLEC regimen (5-fluoruracil + leucovorin + epirubicin + carboplatin) compared with the gold standard chemothreapy (Cantore et al. 2005); the other trial compared gemcitabine-based chemotherapy against gemcitabine+erlonitib based chemotherapy.

One RCT (n=95) compared the urokinase plasminogen activator (uPA) inhibitor upmostat in combination with gemcitabine-based chemotherapy against gemcitabine-based chemotherapy alone in locally advanced pancreatic cancer (Heinemann et al. 2013).

One RCT (n=48) compared radiotherapy plus a novel radiosensitiser (PR-350) against radiotherapy plus placebo in patients with locally advanced pancreatic cancer (Sunamura et al. 2004).

One observational study (n=107) compared giving radiofrequency ablation as a primary treatment against giving radiofrequency ablation after another primary treatment in patients with locally advanced pancreatic cancer (Cantore et al. 2012).

The Cochrane Collaboration's 'Risk of bias' tool was used for assessing risk of bias of randomised trials, the Newcastle-Ottawa Scale (NOS) was used for assessing the risk of bias of non-randomised studies (i.e. prospective cohort studies).

Further information about the search strategy can be found in Appendix D. See study selection flow chart in Appendix E, forest plots in Appendix H, GRADE tables in Appendix I, study evidence tables in Appendix F and list of excluded studies in Appendix G.

11.1.3 Summary of included studies

A summary of the studies that were included in this review is presented in Table 154.

Table 154: Summary of included studies

Study	Sample size	Intervention	Comparison	Outcomes	Study design & setting	Overall risk of bias
Cantore et al. 2005	N= 175 (138 randomised)	CT [FLEC -based] (n=71)	CT [GEM-based] (n=67)	Adverse Events	Design: Phase III RCT Setting: Italy Duration/follow-up: every 2 months until patients' death	Very serious
Cantore et al. 2012	N= 107	RFA as primary treatment (n=47)	RFA after other primary treatment (CT and/or CRT and/or IASC) (n=60)	Overall Survival	Design: Prospective cohort study. Setting: Italy Duration/follow-up: after 30 days and every 3 months – until 1 July 2011	Low
Chauffert et al. 2008	N= 111	CRT (n=59)	CT [GEM-based] (n=52)	Adverse Events	Design: Phase III RCT Setting: France Duration/follow-up: Median follow-up was 31 months in the CRT arm and 33 months in the GEM arm.	Very serious
Chung et al. 2004	N= 46	CRT [GEM-based] (n=22)	CRT [Paclitaxel-based] (n=24)	Objective Response Overall Survival Adverse Events	Design: Phase III RCT Setting: South Korea Duration/follow-up: every 3 months until patients death	Very serious
Cohen et al. 2005	N= 114	CRT (n=55)	Radiotherapy (n=49)	Adverse Events	Design: Open label Phase III RCT Setting: USA Duration/follow-up: unclear	Very serious
	N= 268	RANDOMISATION 1				Low

Study	Sample size	Intervention	Comparison	Outcomes	Study design & setting	Overall risk of bias
Hammel et al. 2016		CT [GEM-based] (n=223)	CT [GEM+ERLONITIB] (n=219)	Adverse Events	Design: Multicentre, open label, phase III RCT Setting: France Duration/follow-up: until patients' death	
		RANDOMISATION 2				
		CT [GEM+ERLONITIB] (n=135)	CRT (n=133)	Progression Free Survival Overall Survival Adverse Events		
Heinemann et al. 2013	N= 95	Gemcitabine + 200mg upmostat (n=31) Gemcitabine + 400mg upmostat (n=33)	CT [GEM-based] (n=31)	Adverse Events	Design: Open label, proof of concept, phase II RCT Setting: Germany Duration/follow-up: every 8 weeks until patients death	Serious
Herman et al. 2013	N= 304	CRT (standard of care) + TNFerade (n=187)	Standard of care (n=90)	Adverse Events	Design: Open label phase III RCT Setting: USA Duration/follow-up: "Median follow-up was 9.1 months"	Serious
Hurt et al. 2015	N= 114 (N=78 patients were randomly allocated)	CRT after induction CT [GEM-based] (n=38)	CRT after induction CT [Capecitabine-based] (n=36)	Health Related Quality of Life	Design: Multi-centre, open label, Phase II RCT Setting: UK Duration/follow-up: : "until progression, death, or 12-month follow-up assessment"	Serious
Khan et al. 2016	N= 13	CRT + cetuximab after induction CT (n=6)	CRT alone after induction CT (n=7)	Objective Response Overall Survival Adverse Events	Design: Phase II RCT Setting: UK Duration/follow-up: median follow-up of 61.2 months	Very serious
Li et al. 2003	N= 34	CRT [GEM-based] (n=16)	CRT [5FU-based] (n=18)	Adverse Events Pain control	Design: Open label phase III RCT Setting: Taiwan	Very serious

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Study	Sample size	Intervention	Comparison	Outcomes	Study design & setting	Overall risk of bias
				HQRL: Average monthly Karnofsky performance score	Duration/follow-up: until patients' death	
Loehrer et al. 2011	N= 71	CRT (n=34)	CT (n=37)	Adverse Events Health Related Quality of Life	Design: Phase III RCT Setting: USA Duration/follow-up: week 6, week 15/16 and 9 months post baseline	Very serious
Mukherjee et al. 2013	N= 114 (N=78 patients were randomly allocated)	CRT after induction CT [GEM-based] (n=38)	CRT after induction CT [Capecitabine-based] (n=36)	Objective Response Progression Free Survival Overall Survival Adverse Events	Design: Multi-centre, open label, Phase II RCT Setting: UK Duration/follow-up: : "until progression, death, or 12-month follow-up assessment"	Serious
Rich et al. 2012	N=195	CRT + R115777 (n=94)	CRT alone (n=91)	Overall Survival Adverse Events	Design: Phase II RCT Setting: USA Duration/follow-up: unclear	Serious
Shinchi et al. 2002	N=31	CRT (n=16)	BSC [no intervention] (n=15)	Health Related Quality of Life	Design: Phase III RCT Setting: Japan Duration/follow-up: monthly until patients' date	Very serious
Sunamura et al. 2004	N=48	PR-350 + radiotherapy (n=25)	Placebo + radiotherapy (n=22)	Objective Response Overall Survival Adverse Events	Design: Double-blind phase III RCT Setting: Japan Duration/follow-up: 6 months	Very serious
Wilkowski et al. 2009	N=95	CRT [GEM/Cisplatin] followed by Gemcitabine/Cisplatin-CT (n=31)	CRT [GEM/Cisplatin] (n=32) CRT [5-FU]	Adverse Events	Design: Multicentre phase II RCT Setting: Germany	Very serious

Study	Sample size	Intervention	Comparison	Outcomes	Study design & setting	Overall risk of bias
			(n=31)		Duration/follow-up: until patients' death	

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11.1.4 Clinical evidence profile

The clinical evidence profiles for this review question are presented in Table 155 to Table 172.

Table 155: Summary clinical evidence profile for gemcitabine-based chemoradiotherapy versus paclitaxel-based chemoradiotherapy in adults with unresectable non-metastatic locally advanced pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Paclitaxel-based CRT	GEM-based CRT				
Overall response rates (CR+PR) - 1 month follow-up	250 per 1000	138 per 1000 (38 to 480)	RR 0.55 (0.15 to 1.92)	46 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Overall response rates (CR+PR) - 1 year follow-up	167 per 1000	182 per 1000 (52 to 640)	RR 1.09 (0.31 to 3.84)	46 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Overall survival[4]	Median survival = 14 (95%CI 12.0-16.0) months	Median survival = 12 (95%CI 8.8-15.2) months	HR 0.98 (0.52 to 1.85)[4]	46 (1 study[1])	⊕⊖⊖⊖ very low[2,6]	
Adverse effects - Grade 3/4 toxicities - Haematological	208 per 1000	227 per 1000 (75 to 681)	RR 1.09 (0.36 to 3.27)	46 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Adverse effects - Grade 3/4 toxicities - Non-haematological	417 per 1000	817 per 1000 (492 to 1000)	RR 1.96 (1.18 to 3.28)	46 (1 study[1])	⊕⊕⊖⊖ low[2]	

CI: Confidence interval; RR: Risk ratio;

1 Chung et al. 2004
2 The quality of the evidence was downgraded because of the unclear risk of selection bias (no details given about the allocation method), the unclear risk of performance and detection bias (no details given in the text). Furthermore no research protocol was published for this trial
3 Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs
4 The median survival was 12 months in the gemcitabine group vs. 14 months in the paclitaxel group. There was no statistically significant difference in survival between the 2 groups (p= 0.951, log–rank test). Relative effect was calculated by the NGA staff by means of the Tieney et al. 2007 methods.
5 The quality of the evidence was downgraded by 2 because the unclear risk of selection bias (no details given about the randomisation and allocation methods). Furthermore no research protocol was published for this trial and no sample size calculations were provided.
6 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant

Table 156: Summary clinical evidence profile for gemcitabine-based chemoradiotherapy versus 5FU-based chemoradiotherapy in adults with unresectable non-metastatic locally advanced pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	5FU-based CRT	GEM-based CRT				
Overall pain control - follow-up not reported	62 per 1000	389 per 1000 (54 to 1000)	RR 6.22 (0.86 to 45.25)	34 (1 study[1])	⊕⊖⊖⊖ very low[1,2,3]	
Adverse effects - Grade 3/4 toxicities - Neutropenia	188 per 1000	334 per 1000 (99 to 1000)	RR 1.78 (0.53 to 5.97)	34 (1 study[1])	⊕⊖⊖⊖ very low[2,4]	
Adverse effects - Grade 3/4 toxicities - Thrombocytopenia	62 per 1000	19 per 1000 (1 to 428)	RR 0.3 (0.01 to 6.84)	34 (1 study[1])	⊕⊖⊖⊖ very low[2,4]	
Adverse effects - Grade 3/4 toxicities - Anaemia	188 per 1000	223 per 1000 (58 to 846)	RR 1.19 (0.31 to 4.51)	34 (1 study[1])	⊕⊖⊖⊖ very low[2,4]	
Adverse effects - Grade 3/4 toxicities - Anorexia	312 per 1000	334 per 1000 (125 to 884)	RR 1.07 (0.4 to 2.83)	34 (1 study[1])	⊕⊖⊖⊖ very low[2,4]	
Adverse effects - Grade 3/4 toxicities - Nausea	312 per 1000	334 per 1000 (125 to 884)	RR 1.07 (0.4 to 2.83)	34 (1 study[1])	⊕⊖⊖⊖ very low[2,4]	
Adverse effects - Grade 3/4 toxicities - Vomiting	188 per 1000	167 per 1000 (39 to 712)	RR 0.89 (0.21 to 3.8)	34 (1 study[1])	⊕⊕⊖⊖ low[4]	
Adverse effects - Grade 3/4 toxicities - GI bleeding	62 per 1000	56 per 1000 (4 to 817)	RR 0.89 (0.06 to 13.08)	34 (1 study[1])	⊕⊖⊖⊖ very low[1,4]	
HQRL: Average monthly Karnofsky performance score - follow-up not reported		The mean HQRL: average monthly Karnofsky performance score - follow-up not reported in the intervention groups was 9 higher		34 (1 study[1])	⊕⊕⊖⊖ low[2]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
		(6.98 to 11.02 higher)				

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio

1 Li et al. 2003
2 The quality of the evidence was downgraded because of the unclear risk of selection bias (no details given about the allocation method) , the unclear risk of performance and detection bias (no details given in the text). Furthermore no research protocol was published for this trial
3 Evidence was further downgraded by 1 due to serious imprecision as 95%CI crossed one default MID
4 Evidence was further downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs

Table 157: Summary clinical evidence profile for gemcitabine/Cisplatin-based chemoradiotherapy versus 5FU-based chemoradiotherapy in adults with unresectable non-metastatic locally advanced pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	5FU-based CRT	GEM/Cisplatin-based CRT				
Adverse effects - Grade 3/4 toxicities - Leukocytopenia	34 per 1000	516 per 1000 (73 to 1000)	RR 14.97 (2.12 to 105.82)	60 (1 study[1])	⊕⊕⊖⊖ low[2]	
Adverse effects - Grade 3/4 toxicities - Thrombocytopenia	34 per 1000	516 per 1000 (73 to 1000)	RR 14.97 (2.12 to 105.82)	60 (1 study[1])	⊕⊕⊖⊖ low[2]	
Adverse effects - Grade 3/4 toxicities - Anaemia	0 per 1000	0 per 1000 (0 to 0)	RR 4.69 (0.23 to 93.7)	60 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Adverse effects - Grade 3/4 toxicities - Lower GI tract	34 per 1000	97 per 1000 (11 to 879)	RR 2.81 (0.31 to 25.48)	60 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Adverse effects - Grade 3/4 toxicities - Upper GI tract	0 per 1000	0 per 1000 (0 to 0)	RR 12.19 (0.72 to 207.14)	60 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Adverse effects - Grade 3/4 toxicities - Non-haematological4	276 per 1000	356 per 1000 (166 to 756)	RR 1.29 (0.6 to 2.74)	60 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	

CI: Confidence interval; RR: Risk ratio;

1 Wilkowski et al. 2009
2 The quality of the evidence was downgraded because of the unclear risk of selection bias (no details given about the allocation method), the unclear risk of performance and detection bias (no details given in the text). Furthermore no research protocol was published for this trial and no sample size calculations were provided.
3 Evidence was further downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs
4 1- Fatigue; 2-Weight loss; 3- Diarrhoea; 4- Nausea; 5-Febrile neutropenia; 6-Infection without neutropenia.

Table 158: Summary clinical evidence profile for gemcitabine-chemoradiotherapy after induction chemotherapy versus capecitabine-chemoradiotherapy after induction chemotherapy in adults with unresectable non-metastatic locally advanced pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Capecitabine-CRT	GEM-CRT versus				
Overall response rates (CR+PR)[1]	229 per 1000	194 per 1000 (80 to 480)	RR 0.85 (0.35 to 2.1)	71 (1 study[2])	⊕⊖⊖⊖ very low[3,4]	
Progression Free Survival[5]	Median PFS = 12 (95%CI 10.2-14.2) months	Median PFS = 10.4 (95%CI 8.9-12.5) months	HR 0.6 (0.32 to 1.12)	72 (1 study[2])	⊕⊕⊕⊖ moderate[6]	
Overall Survival	1 year overall survival = 79·2% (95% CI 61.1–89.5)	1 year overall survival = 64·2% (95% CI 46.4–77.5)	HR 0.39 (0.18 to 0.85)	72 (1 study[2])	⊕⊕⊕⊕ high	
Adverse effects - Grade 3/4 toxicities - Haematological	0 per 1000	0 per 1000 (0 to 0)	RR 13.46 (0.8 to 227.22)	72 (1 study[2])	⊕⊕⊖⊖ low[3,7]	
Adverse effects - Grade 3/4 toxicities - Non-haematological	118 per 1000	264 per 1000 (91 to 762)	RR 2.24 (0.77 to 6.48)	72 (1 study[2])	⊕⊖⊖⊖ very low[3,4]	
Adverse effects - Grade 3/4 toxicities - Other	59 per 1000	79 per 1000 (14 to 445)	RR 1.34 (0.24 to 7.56)	72 (1 study[2])	⊕⊖⊖⊖ very low[2,8]	
HQRL - 23 -26 -39 - 52 weeks follow-up[9]	See comment	See comment	Not estimable[9]	48 (1 study[2])	⊕⊕⊖⊖ low[8]	

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;

1 GEM-CRT group: no complete responses; CAP-CRT group: 2 complete responses
2 Mukherjee et al. 2013
3 The quality of the evidence was downgraded of one point because the high risk of performance bias (no blinding of patients/ care providers delivering the interventions) and the high risk of detention bias (no masking of outcome assessors)
4 Evidence was further downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs
5 Median progression-free survival was 12·0 months (95% CI 10·2–14·6) in the capecitabine group and 10·4 months (95% CI 8·9–12·5) in the gemcitabine group
6 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. The quality of the evidence for this outcome was therefore downgraded for imprecision by one level as it was not statistically significant.
7 Evidence was further downgraded by 1 due to serious imprecision as 95%CI crossed one default MID
8 The quality of the evidence was downgraded of two points because the high risk of performance bias and the high risk of detention bias
9 Differences in changes in HQRL scores between trial arms rarely reached statistical significance; however, where they did, they favoured capecitabine therapy.

Table 159 Summary clinical evidence profile for capecitabine-chemoradiotherapy + cetuximab versus capecitabine-chemoradiotherapy alone after induction

chemotherapy in adults with unresectable non-metastatic locally advanced pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Capecitabine-CRT alone	Capecitabine-CRT + cetuximab				
Objective response rate	333 per 1000	167 per 1000 (13 to 757)	RR 0.5 (0.06 to 4.15)	12 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Overall survival[4]	See comment	See comment	Not estimable [4]	12 (1 study[1])	⊕⊕⊖⊖ low[5]	
Adverse effects - Grade 3/4 toxicities - Hyponatraemia6	167 per 1000	55 per 1000 (3 to 1000)	RR 0.33 (0.02 to 6.86)	12 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Adverse effects - Grade 3/4 toxicities - Fatigue6	167 per 1000	55 per 1000 (3 to 1000)	RR 0.33 (0.02 to 6.86)	12 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Adverse effects - Grade 3/4 toxicities - Abdominal pain6	167 per 1000	55 per 1000 (3 to 1000)	RR 0.33 (0.02 to 6.86)	12 (1 study[1])	⊕⊕⊖⊖ low[3]	

CI: Confidence interval; RR: Risk ratio;

1 Khan et al. 2016

2 The quality of the evidence was downgraded because of the unclear risk of selection bias (no details given about the allocation method), the unclear risk of performance and detection bias (no details given in the text). Furthermore sample size not achieved as the trial was closed pre-maturely -following emergent data from LAP-07

3 Evidence was further downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs

4 median OS was 15.8 months and 22.0 months in arms capecitabine-CRT alone and capecitabine-CRT + cetuximab respectively (p > 0.05)

5 The quality of the evidence was downgraded because of the unclear risk of selection bias. Furthermore sample size not achieved as the trial was closed pre-maturely -following emergent data from LAP-07

6 no grade 3-4 toxicity was registered

Table 160 Summary clinical evidence profile for chemoradiotherapy versus best supportive care in adults with unresectable non-metastatic locally advanced pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Best supportive care	CRT				
Average of monthly Karnofsky scores		The mean average of monthly Karnofsky score in the intervention groups		31 (1 study[1])	⊕⊕⊖⊖ low[2]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
		was 11.6 higher (6.61 to 16.59 higher)				

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval;

1 Shinchi et al. 2002
2 The quality of the evidence was downgraded because of the unclear risk of selection bias (no details given about the allocation method), the unclear risk of performance and detection bias (no details given in the text). Furthermore no research protocol was published for this trial and no sample size calculations were provided.

Table 161 Summary clinical evidence profile for chemoradiotherapy followed by chemotherapy versus chemoradiotherapy alone in adults with unresectable non-metastatic locally advanced pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	CRT	CRT followed by CT				
Adverse effects - Grade 3/4 toxicities - Leukocytopenia	34 per 1000	630 per 1000 (90 to 1000)	RR 18.26 (2.6 to 128.02)	56 (1 study[1])	⊕⊕⊖⊖ low[2]	
Adverse effects - Grade 3/4 toxicities - Thrombocytopenia	34 per 1000	370 per 1000 (51 to 1000)	RR 10.74 (1.47 to 78.39)	56 (1 study[1])	⊕⊖⊖⊖ very low[2]	
Adverse effects - Grade 3/4 toxicities - Anaemia	0 per 1000	0 per 1000 (0 to 0)	RR 3.21 (0.14 to 75.68)	56 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Adverse effects - Grade 3/4 toxicities - Upper GI tract	0 per 1000	0 per 1000 (0 to 0)	RR 5.36 (0.27 to 106.78)	56 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Adverse effects - Grade 3/4 toxicities - Lower GI tract	34 per 1000	12 per 1000 (1 to 290)	RR 0.36 (0.02 to 8.41)	56 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Adverse effects - Grade 3/4 toxicities - Non-haematological[4]	276 per 1000	74 per 1000 (17 to 317)	RR 0.27 (0.06	56 (1 study[1])	⊕⊖⊖⊖ very low[2,5]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
			to 1.15)			

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio;

1 Wilkowski et al. 2009
2 The quality of the evidence was downgraded because of the unclear risk of selection bias (no details given about the allocation method), the unclear risk of performance and detection bias (no details given in the text). Furthermore no research protocol was published for this trial and no sample size calculations were provided.
3 Evidence was further downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs
4 1- Fatigue; 2-Weight loss; 3- Diarrhoea; 4- Nausea; 5-Febrile neutropenia; 6-Infection without neutropenia.
5 Evidence was further downgraded by 1 due to serious imprecision as 95%CI crossed one default MID

Table 162 Summary clinical evidence profile for chemoradiotherapy + R115777 versus chemoradiotherapy alone in adults with unresectable non-metastatic locally advanced pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	CRT	CRT + R115777				
Overall survival[1]	1-year overall survival = 46.2% (95%CI 35.7%-43.6%) months	1-year overall survival = 34.0% (95%CI 24.7%-43.6%) months	Not estimable [1]	185 (1 study[2])	⊕⊕⊕⊖ moderate [3]	
Adverse effects - Grade 3/4 toxicities - Allergy/immunology[4]	33 per 1000	21 per 1000 (4 to 124)	RR 0.65 (0.11 to 3.77)	185 (1 study[2])	⊕⊖⊖⊖ very low[5,6]	
Adverse effects - Grade 3/4 toxicities - Blood/bone marrow[4]	330 per 1000	458 per 1000 (316 to 659)	RR 1.39 (0.96 to 2)	185 (1 study[2])	⊕⊕⊖⊖ low[5,7]	
Adverse effects - Grade 3/4 toxicities - Cardiovascular (general)4	33 per 1000	75 per 1000 (20 to 279)	RR 2.26 (0.6 to 8.47)	185 (1 study[2])	⊕⊖⊖⊖ very low[3,6]	
Adverse effects - Grade 3/4 toxicities - Coagulation[4]	11 per 1000	4 per 1000 (0 to 86)	RR 0.32 (0.01 to 7.82)	185 (1 study[2])	⊕⊖⊖⊖ very low[5,6]	
Adverse effects - Grade 3/4 toxicities - Constitutional symptoms[4]	88 per 1000	149 per 1000 (66 to 338)	RR 1.69 (0.75 to 3.84)	185 (1 study[2])	⊕⊖⊖⊖ very low[5,6]	
Adverse effects - Grade 3/4 toxicities - Endocrine[4]	11 per 1000	4 per 1000 (0 to 86)	RR 0.32 (0.01 to 7.82)	185 (1 study[2])	⊕⊖⊖⊖ very low[5,6]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Adverse effects - Grade 3/4 toxicities - Haemorrhage	330 per 1000	20 per 1000 (7 to 86)	RR 0.06 (0.02 to 0.26)	185 (1 study[2,4])	⊕⊖⊖⊖ very low[5,6]	
Adverse effects - Grade 3/4 toxicities - Gastrointestinal	352 per 1000	394 per 1000 (271 to 573)	RR 1.12 (0.77 to 1.63)	185 (1 study[2,6])	⊕⊖⊖⊖ very low[5,6]	

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio;

1 All patients included in this analysis have died, the median survival time was 11.5 months (95% CI: 8.2–12.6) for the CXRT arm and 8.9 months (95% CI: 7.3–10.4) for the CXRT+R115777 arm (non-significant difference: p value not reported)
2 Rich et al. 2012
3 The quality of the evidence was downgraded of one point because of the unclear risk of selection bias (no details given about the randomisation and allocation methods)
4 No 3-4 grade toxicities were reported for the following outcomes in both intervention groups: Auditory/hearing; Cardiovascular (arrhythmia); Dermatology/skin; Ocular/visual/ renal/genitourinary
5 The quality of the evidence was downgraded of one point because of the unclear risk of selection bias (no details given about the randomisation and allocation methods), the unclear risk of performance and detection bias (no details given in the text)
6 Evidence was further downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs
7 Evidence was further downgraded by 1 due to serious imprecision as 95%CI crossed one default MID

Table 163 Summary clinical evidence profile for chemoradiotherapy + TNFerade versus chemoradiotherapy alone in adults with unresectable non-metastatic locally advanced pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	CRT	CRT + TNFerade				
Adverse effects - Grade 3/4 toxicities - Gatrointestinal[1]	111 per 1000	182 per 1000 (94 to 351)	RR 1.64 (0.85 to 3.16)	277 (1 study[2])	⊕⊕⊖⊖ low[3,4]	
Adverse effects - Grade 3/4 toxicities - Haematological[5]	356 per 1000	320 per 1000 (228 to 455)	RR 0.9 (0.64 to 1.28)	277 (1 study[2])	⊕⊖⊖⊖ very low[3,5]	
Adverse effects - Grade 3/4 toxicities - Non-gastrointestinal/non-haematologic[6]	78 per 1000	117 per 1000 (52 to 265)	RR 1.51 (0.67 to 3.41)	277 (1 study[2])	⊕⊖⊖⊖ very low[3,5]	

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio;

1 In descending order of frequency, the most commonly occurring GI toxicities were nausea/vomiting, abdominal pain, and anorexia in the SOC TNFerade arm versus nausea/vomiting, diarrhoea, and anorexia in the SOC arm.
2 Herman et al. 2013
3 The quality of the evidence was downgraded of one point because of the unclear risk of selection bias (no

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
details given about the randomisation and allocation methods) and the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions) *4 Evidence was further downgraded by 1 due to serious imprecision as 95%CI crossed one default MID* *5 Evidence was further downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs* *6 In both arms, the majority of hematologic toxicities (85%) took place during gemcitabine-based maintenance therapy following chemoradiotherapy.* *7 In descending order of frequency, the most commonly occurring non-GI/ nonhematologic toxicities were fatigue, chills/rigors/sweats, pyrexia, and dehydration in the SOC TNFerade arm versus fatigue, dehydration, dermatitis, and hypokalaemia in the SOC arm.*						

Table 164 Summary clinical evidence profile for chemoradiotherapy versus chemotherapy in adults with unresectable non-metastatic locally advanced pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	CT	CRT				
Adverse effects - Grade 3/4 toxicities - Haemoglobin	57 per 1000	177 per 1000 (38 to 814)	RR 3.09 (0.67 to 14.25)	69 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Adverse effects - Grade 3/4 toxicities - Leukocytes	143 per 1000	323 per 1000 (126 to 833)	RR 2.26 (0.88 to 5.83)	69 (1 study[1])	⊕⊖⊖⊖ very low[2,4]	
Adverse effects - Grade 3/4 toxicities - Neutrophils	343 per 1000	384 per 1000 (206 to 717)	RR 1.12 (0.6 to 2.09)	69 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Adverse effects - Grade 3/4 toxicities - Nausea	86 per 1000	294 per 1000 (88 to 977)	RR 3.43 (1.03 to 11.4)	69 (1 study[1])	⊕⊖⊖⊖ very low[2,4]	
Adverse effects - Grade 3/4 toxicities - Vomiting	86 per 1000	265 per 1000 (78 to 895)	RR 3.09 (0.91 to 10.44)	69 (1 study[1])	⊕⊖⊖⊖ very low[2,4]	
Adverse effects - Grade 3/4 toxicities - Hypokalaemia	57 per 1000	118 per 1000 (23 to 601)	RR 2.06 (0.4 to 10.51)	69 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Adverse effects - Grade 3/4 toxicities - Fatigue	57 per 1000	323 per 1000 (77 to 1000)	RR 5.66 (1.35	69 (1 study[1])	⊕⊕⊖⊖ low[2]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
			to 23.68)			
Adverse effects - Grade 3/4 toxicities - Anorexia	29 per 1000	177 per 1000 (22 to 1000)	RR 6.18 (0.78 to 48.64)	69 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
HQRL - Trial outcome index [mean difference of change from baseline] - Change at week 6		The mean HQRL - trial outcome index [mean difference of change from baseline] - change at week 6 in the intervention groups was 12.2 lower (17.98 to 6.42 lower)		71 (1 study[1])	⊕⊕⊖⊖ low[2,5]	
HQRL - Trial outcome index [mean difference of change from baseline] - Change at week 15/16		The mean HQRL - trial outcome index [mean difference of change from baseline] - change at week 15/16 in the intervention groups was 3.3 lower (9.08 lower to 2.48 higher)		71 (1 study[1])	⊕⊖⊖⊖ very low[2,4,5]	
HQRL - Trial outcome index [mean difference of change from baseline] - Change at 9 months		The mean HQRL - trial outcome index [mean difference of change from baseline] - change at 9 months in the intervention groups was 2.7 higher (3.08 lower to 8.48 higher)		71 (1 study[1])	⊕⊖⊖⊖ very low[2,4,5]	

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio;

1 Loehrer et al. 2011
2 The quality of the evidence was downgraded of two points point because the high risk of bias: 1)Sample size calculation required a sample size of 316 patients however recruitment was stopped early due to poor accrual rates; 2) 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; and 3) Comparison of progression was compromised as precise tumour measurement was difficult in many patients due to margins being obscured by local inflammatory processes. Additionally quality of the evidence was downgraded because of the unclear risk of selection bias (no details given about the allocation method), the unclear risk of performance and detection bias (no details given in the text).
3 Evidence was further downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs
4 Evidence was further downgraded by 1 due to serious imprecision as 95%CI crossed one default MID
5 Quality of life data should be taken with caution due to high rate of attrition from baseline (high risk of attrition bias)

Table 165 Summary clinical evidence profile chemoradiotherapy versus chemotherapy followed by maintenance chemotherapy in adults with unresectable non-metastatic locally advanced pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	CT followed by maintenance CT	CRT followed by maintenance CT				
Adverse effects - Grade 3/4 haematological toxicities - Induction phase	250 per 1000	288 per 1000 (160 to 522)	RR 1.15 (0.64 to 2.09)	119 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Adverse effects - Grade 3/4 haematological toxicities - Maintenance phase	200 per 1000	492 per 1000 (278 to 868)	RR 2.46 (1.39 to 4.34)	119 (1 study[1])	⊕⊕⊖⊖ low[2]	
Adverse effects - Grade 3/4 non-haematological toxicities - Induction phase	167 per 1000	407 per 1000 (213 to 775)	RR 2.44 (1.28 to 4.65)	119 (1 study[1])	⊕⊕⊖⊖ low[2]	
Adverse effects - Grade 3/4 non-haematological toxicities - Maintenance phase	183 per 1000	204 per 1000 (97 to 424)	RR 1.11 (0.53 to 2.31)	119 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio;

1 Chauffert et al. 2008
2 The quality of the evidence was downgraded because of the unclear risk of performance bias (no blinding of patients/ care providers delivering the interventions), the potential risk of detection bias (no details about the blinding of outcome assessors) and unclear risk of selection bias (no details given about the concealment allocation methods). Furthermore no research protocol was published for this trial, no sample size calculations were provided. and the trial was stopped before completion of recruitment
3 Evidence was further downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs

Table 166 Summary clinical evidence profile for chemoradiotherapy versus chemotherapy after chemotherapy induction therapy in adults with unresectable non-metastatic locally advanced pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	CT after CT	CRT after CT induction therapy				

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95 % CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	induction therapy					
Overall survival[1]	Median overall survival = 16.5 (95% CI, 14.5-18.5) months	Median overall survival = 15.2 (95% CI, 13.9-17.3) months	HR 1.03 (0.79 to 1.14)	269 (1 study[2])	⊕⊕⊕⊖ moderate[3]	
Progression-free survival[4]	Median PFS = 8.4 (95%CI 7.8-9.4) months	PFS = 9.9 (95%CI 8.8-10.4) months	HR 0.78 (0.61 to 1)	269 (1 study[2])	⊕⊕⊕⊖ moderate[3]	
Adverse effects - Grade 3/4 toxicities - Hematological[5]	30 per 1000	88 per 1000 (29 to 267)	RR 2.93 (0.97 to 8.87)	269 (1 study[2])	⊕⊕⊖⊖ low[6,7]	
Adverse effects - Grade 3/4 toxicities - Non-hematological[8]	180 per 1000	170 per 1000 (101 to 285)	RR 0.94 (0.56 to 1.58)	269 (1 study[2])	⊕⊖⊖⊖ very low[6,9]	

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;

1 no difference in survival with median overall survival from the date of the first randomization of 15.2months (95%CI, 13.9-17.3months) in the CRT group vs 16.5 months (95%CI, 14.5-18.5 months) in the CT group
2 Hammel et al. 2016 -2nd randomisation
3 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. The quality of the evidence for this outcome was therefore downgraded for imprecision by one level as it was not statistically significant.
4 no difference in progression-free survival from the date of the first randomization between CT group (median, 8.4 months; 95% CI, 7.8-9.4 months) and the CRT group (median, 9.9months; 95%CI, 8.8-10.4months)
5 Including neutrophils, platelets, haemoglobin, and febrile neutropenia
6 The quality of the evidence was downgraded of one point because the high risk of performance bias (no blinding of patients/ care providers delivering the interventions) and the high risk of detention bias (no masking of outcome assessors)
7 Evidence was further downgraded by 1 due to serious imprecision as 95%CI crossed one default MID
8 Including Nausea, vomiting, diarrhoea , mucositis, acne, rash, dyspnoea, allergic reaction, fever, aspartate transaminase, bilirubin, and γ-glutamyl transpeptidase and creatinine. Nausea 3-4 grade toxicity differed : N/n= 133/6; N/n=136/0; p=0.008
9 Evidence was further downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs

Table 167 Summary clinical evidence profile for chemoradiotherapy versus radiotherapy in adults with unresectable non-metastatic locally advanced pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Radiotherapy	CRT				
Adverse effects - Grade 3/4 toxicities - Gastrointestinal	19 per 1000	6 per 1000 (0 to 146)	RR 0.32 (0.01 to 7.72)	108 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Adverse effects - Grade 3/4 toxicities - Vomiting	75 per 1000	54 per 1000 (13 to 232)	RR 0.72 (0.17 to 3.08)	108 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Adverse effects - Grade 3/4 toxicities - Diarrhoea	See comment	See comment	Not estimable	108 (1 study[1])	⊕⊖⊖⊖ very low[2,4]	
Adverse effects - Grade 3/4 toxicities - Infection	0 per 1000	0 per 1000 (0 to 0)	RR 2.89 (0.12 to 69.47)	108 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Adverse effects - Grade 3/4 toxicities - Haemorrhage	See comment	See comment	Not estimable	108 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Adverse effects - Grade 3/4 toxicities - Skin, mucous membrane	0 per 1000	0 per 1000 (0 to 0)	RR 4.82 (0.24 to 98.13)	108 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Adverse effects - Grade 3/4 toxicities - Neurologic	19 per 1000	73 per 1000 (8 to 630)	RR 3.85 (0.45 to 33.38)	108 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Adverse effects - Grade 3/4 toxicities - Respiratory	See comment	See comment	Not estimable	108 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Adverse effects - Grade 3/4 toxicities - Genitourinary	19 per 1000	18 per 1000 (1 to 283)	RR 0.96 (0.06 to 15.01)	108 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Adverse effects - Grade 3/4 toxicities - Hematologic	94 per 1000	255 per 1000 (98 to 658)	RR 2.7 (1.04 to 6.97)	108 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Adverse effects - Grade 3/4 toxicities - Liver	94 per 1000	37 per 1000 (8 to 179)	RR 0.39 (0.08 to 1.9)	108 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Adverse effects - Grade 3/4 toxicities - Other[4]	19 per 1000	36 per 1000 (3 to 389)	RR 1.93 (0.18 to 20.63)	108 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). *CI: Confidence interval; RR: Risk ratio;*						
1 Cohen et al. 2005 *2 The quality of the evidence was downgraded two points because of the unclear risk of selection bias (no sufficient details given about the randomisation method), the high of performance and detection bias (no blinding of patients/ care providers delivering the interventions; and no masking of outcome assessors). Furthermore no research protocol was published for this trial and no sample size calculations were provided.* *3 Evidence was further downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs* *4 Includes constipation, cardiac, fever.*						

Table 168 Summary clinical evidence profile for gemcitabine+erlonitib-based chemotherapy versus gemcitabine-based chemotherapy in adults with unresectable non-metastatic locally advanced pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	GEM-based CT	GEM+erloniti b-based CT				
Adverse effects - Grade 3/4 toxicities - haematological1	332 per 1000	388 per 1000 (302 to 498)	RR 1.17 (0.91 to 1.5)	442 (1 study[2])	⊕⊕⊖⊖ low[3,4]	
Adverse effects - Grade 3/4 toxicities - Non-haematological1	395 per 1000	399 per 1000 (316 to 501)	RR 1.01 (0.8 to 1.27)	442 (1 study[2])	⊕⊖⊖⊖ very low[3,5]	
The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). *CI: Confidence interval; RR: Risk ratio;*						
1 Including neutrophils, platelets, haemoglobin, and febrile neutropenia *2 Hammel et al. 2016 -1st randomisation* *3 The quality of the evidence was downgraded of one point because the high risk of performance bias (no blinding of patients/ care providers delivering the interventions) and the high risk of detention bias (no masking of outcome assessors)* *5 Evidence was further downgraded by 1 due to serious imprecision as 95%CI crossed one default MID* *5 Evidence was further downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs*						

Table 169 Summary clinical evidence profile for FLEC-based chemotherapy versus gemcitabine-based chemotherapy in adults with unresectable non-metastatic locally advanced pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	GEM-based CT	FLEC-based CT				
Adverse effects - Grade 3/4 toxicities[1]	224 per 1000	479 per 1000 (289 to 795)	RR 2.14 (1.29 to 3.55)	138 (1 study[2])	⊕⊕⊖⊖ low[3]	

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

1 Any 3-4 grade toxicity including: leukopenia, vomiting, diarrhoea , anaemia, thrombocytopenia, fever, mucositis, and gastrointestinal bleeding.
2 Cantore et al. 2005
3 The quality of the evidence was downgraded because of the unclear risk of selection bias (no details given about the allocation method), the unclear risk of performance and detection bias (no details given in the text). Furthermore no research protocol was published for this trial and the required sample size (103 patients per) was not achieved

Table 170: Summary clinical evidence profile for gemcitabine-based chemotherapy + upmostat versus gemcitabine-based chemotherapy alone in adults with unresectable non-metastatic locally advanced pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	GEM-based CT	GEM-based CT + upmostat				
Adverse effects - Grade 3/4 toxicities - Patients with any grade 3/4 toxicity - GEM + 200mg upmostat	433 per 1000	568 per 1000 (338 to 949)	RR 1.31 (0.78 to 2.19)	60 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Adverse effects - Grade 3/4 toxicities - Patients with any grade 3/4 toxicity - GEM + 400mg upmostat	433 per 1000	667 per 1000 (416 to 1000)	RR 1.54 (0.96 to 2.47)	63 (1 study[1])	⊕⊕⊖⊖ low[2,4]	

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio;

1 Heinemann et al. 2013
2 The quality of the evidence was downgraded because of the high risk of performance bias (no blinding of patients/ care providers delivering the interventions) and the high risk of detention bias (no masking of outcome assessors)
3 Evidence was further downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs
4 Evidence was further downgraded by 1 due to serious imprecision as 95%CI crossed one default MID

Table 171: Summary clinical evidence profile for radiotherapy + PR-350 radiosensitiser versus radiotherapy + placebo in adults with unresectable non-metastatic locally advanced pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Radiotherapy + Placebo	Radiotherapy + PR-350 Radiosensitiser				
Objective Response - Effective response	217 per 1000	474 per 1000 (191 to 1000)	RR 2.18 (0.88 to 5.41)	42 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Overall survival[4]	See comment	See comment	Not estimable[4]	47 (1 study[1])	⊕⊕⊖⊖ low[5]	
Adverse effects - Grade 3/4 toxicities[6]	40 per 1000	15 per 1000 (1 to 352)	RR 0.38 (0.02 to 8.8)	47 (1 study[1])	⊕⊖⊖⊖ very low[2,7]	

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio;

1 Sunamura et al. 2004
2 The quality of the evidence was downgraded of two points because the potential risk of performance bias (no details about blinding of patients/ care providers delivering the interventions), the unclear risk of detention bias (no information provided in the text) and the unclear risk of selection bias (no details given about the randomisation and allocation methods). Furthermore no research protocol was published for this trial and no sample size calculations were provided.
3 Evidence was further downgraded by 1 due to serious imprecision as 95%CI crossed one default MID
4 The median survival period of the PR-350 group was 318.5 days and that of control group was 303.0 days (no difference between the 2 groups, p value not reported)
5 The quality of the evidence was downgraded of one because the unclear risk of selection bias (no details given about the randomisation and allocation methods). Furthermore no research protocol was published for this trial and no sample size calculations were provided.
6 All patients, except 1 from the control group, were determined to be negative for toxicity, and the PR-350 compound was considered to be safe
7 Evidence was further downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs

Table 172 Summary clinical evidence profile for radiofrequency ablation as primary treatment versus radiofrequency ablation after other primary treatments in adults with unresectable non-metastatic locally advanced pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	RFA after other primary treatments	RFA as primary treatment				
Overall Survival1	See comment	See comment	Not estimable[1]	107 (1 study[2])	⊕⊕⊖⊖ low	

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval;

1 Median overall survival was shorter in the primary RFA group than in control group -RFA following any other primary treatment (14·7 versus 25·6 months; P = 0·004)
2 Cantore et al. 2012

11.1.5 Economic evidence

11.1.5.1 Systematic literature review

A literature review of published cost effectiveness analyses did not identify any relevant studies for this topic.

11.1.5.2 Economic modelling

As there were potential implications for resource use associated with making recommendations in this area and it was deemed a high economic priority by the committee a network meta-analysis (NMA) and economic model was developed to aid in making recommendations in this area. The full methods and results of the NMA and economic model can be found in Chapter 13.

11.1.5.3 Overview of methods

A NMA was developed to consider the effectiveness of treatments for unresectable locally advanced non-metastatic pancreatic cancer (LAPC). The NMA includes all studies, identified by the accompanying clinical evidence review, which are phase II or phase III randomised comparative trials that compared treatments which fit into the broad groups of:

- chemotherapy,
- chemoradiotherapy,
- combination of chemotherapy and chemoradiotherapy,
- radiotherapy
- biological therapies

with another treatment or to placebo, best supportive care or no treatment. Only studies published in the year 2000 or later were included in the NMA. Studies were excluded from the NMA if they included cancers other than pancreatic cancer or included populations that had both locally advanced and metastatic disease and the locally advanced group were not analysed and reported separately. Studies which considered a previously treated patient group with responding or stable disease were also excluded from the NMA, unless they were randomised before receiving treatment.

The systematic review identified 9 trials involving 1294 patients considering 12 different treatments which were eligible for inclusion in the NMA. From the evidence reported it was decided that one primary NMA considering overall survival (OS) could be created as this outcome was reported by or could be derived from all trials. Two secondary NMAs were created looking at progression-free survival and objective response. As these outcomes were not reported by all trials not all studies could be included in these secondary NMAs. All three NMAs had gemcitabine as the reference treatment. Outcomes were reported in terms of a hazard ratio for overall survival and progression-free survival and in absolute terms and odds ratio for objective response.

Results from the NMAs were used to inform an economic model again comparing the cost effectiveness of treatments for unresectable LAPC. The model was a partitioned survival analysis considering three states ‘alive and not progressed’, ‘alive and progressed’ and ‘death’. The economic evaluation considered all treatments included in the primary NMA apart from best supportive care, TNFerade and Upamostat. FOLFIRINOX was also added as part of a secondary economic analysis despite no evidence being identified which matched the inclusion criteria for it to be included in any of the NMAs or the clinical evidence review. The clinical inputs for this intervention were informed by one systematic review and patient level meta-analysis. The study identified 13 studies of 653 patients, 355 of which had LAPC. A secondary analysis was included in the economic model to compare a change in treatment for disease which had not progressed. Three interventions were considered for this economic

model. This covered all interventions that were investigated in studies which were solely excluded from the NMA on account of being in people with responding or stable disease. The model was configured so that change in treatment happened 12 weeks into the model.

The main outcome of the economic model was incremental cost per QALY compared to the base case strategy. A NHS and PSS perspective was taken. The model had a time horizon of three years which was deemed sufficient to capture the lifetime of the vast majority of the cohort. All health outcomes were discounted at a rate of 3.5% per annum in line with the NICE guidelines manual.

All chemotherapy and radiotherapy were costed in line with the trial protocols identified in the accompanying clinical evidence review. All patients in the cohort were assumed to complete the regimens as per the trial protocols. Given the relatively low life expectancy of the model cohort, the high probability of progression and the potential for serious adverse events this assumption was likely to be an unrealistic assumption. However it was likely to bias against interventions with the lower adverse events and higher overall survival and progression-free survival i.e. the more clinically effective interventions.

The cost of chemotherapy drugs were taken from the Drugs and Pharmaceutical Electronic Market Information Tool (eMIT). Where the cost of the chemotherapy regimens were not available on eMIT the drugs were costed using the BNF (BNF 72). The costs of drug procurement and administration were based on NHS reference costs. Radiotherapy and surgery were also costed using NHS reference costs. For radiotherapy, the model cohort were assumed to complete the regimen specified in the trial protocols. The cost of surgery was estimated assuming a probability of complications of 39.6%.

No UK costs were identified for the specific adverse events considered by the economic model. In the absence of this evidence it was assumed that the adverse events could be treated during one face-to-face consultant follow-up meeting and was costed as such using NHS reference costs. Only one cost was assumed for any combination of the four considered adverse events. Again this assumption was likely to bias against the more effective treatments.

Each of these health states were given a quality of life weighting based on those reported in a previous economic evaluation of LAPC. This study used expert opinion to estimate a utility weight of 0.68 for patients without progressed disease. Based on a review of the literature a detriment of 0.12 was estimated for disease progression. This gave an estimate of 0.56 for patients with progressed disease. These estimates were considered low quality and were therefore given a wide range during PSA. In the base case analysis no quality of life detriment was assigned to adverse events as these were considered to be straight forward to treat and would only occur for a short period.

11.1.5.4 Results of the NMA and economic model

The studies included in the NMA had a serious risk of bias and the quality of inputs for the model ranged from very low to good quality across all outcomes and comparisons, with most of the evidence being of low quality. The NMAs for progression-free survival and objective response had very wide credible intervals and all crossed the line of no effect therefore it was difficult to conclude anything based solely on these. In all three analyses only one treatment, chemoradiotherapy with gemcitabine, reported a hazard ratio or odds ratio, which had a 95% credible interval that did not pass the line of no effect. This effect would have been completely driven by one trial, Loehrer et al. 2012. The estimated hazard ratios and credible intervals compared to gemcitabine for the treatments in the overall survival NMA are reported in Table 173. Results of all other NMAs are reported in Chapter 13

Table 173: Estimated Hazard Ratios and Credible Intervals for overall survival compared to gemcitabine

Treatment		median (HR)	2.5%CrI	97.5%CrI	sd
Chemorad (GEM)		0.58	0.37	0.92	0.14
Chemorad (Gem) + Cisplatin		0.62	0.26	1.50	0.33
Chemorad (Gem) +CisplatinX2		0.63	0.26	1.56	0.34
Chemorad(5-fu)+TNFerade		0.69	0.30	1.59	0.34
Gem+400 Upamostat		0.75	0.49	1.15	0.17
FLEC		0.75	0.55	1.02	0.12
Chemorad(5-fu)		0.77	0.36	1.67	0.34
Gem+ 200 Upamostat		0.90	0.61	1.32	0.18
Best Supportive Care		0.99	0.29	3.41	0.84
Gemcitabine		1	Reference		
Gemcitabine + Erlotinib		1.19	0.98	1.45	0.12
Chemorad(5-fu) + Cisplatin		1.45	0.88	2.39	0.39

For the economic model in the primary base case analysis, considering only interventions included in the NMA, chemoradiotherapy with gemcitabine came out as the preferred option with an incremental net monetary benefit (INMB) of £786 when a £20,000 per QALY willingness to pay was assumed. Full results of the primary base case analysis are shown in Table 174.

Table 174: Primary Base Case Analysis Results

	Total Cost	Total QALY	Incremental Cost	Incremental QALYs	INMB £20k per QALY	INMB £50k per QALY
Gemcitabine	£3,157	0.80	Reference	Reference	Reference	Reference
Chemorad (Gem)	£6,713	1.01	£3,556	0.22	£786	£7,299
Chemorad (Gem) + Cisplatin	£6,397	0.98	£3,240	0.18	£374	£5,794
Chemorad (Gem) +CisplatinX2	£6,554	0.98	£3,397	0.18	£251	£5,724
Chemorad(5-fu)	£6,336	0.88	£3,179	0.08	-£1,601	£767
Chemorad(5-fu) + Cisplatin	£6,651	0.63	£3,494	-0.17	-£6,875	-£11,946
FLEC	£6,310	0.92	£3,152	0.12	-£753	£2,846
Gemcitabine + Erlotinib	£10,373	0.71	£7,216	-0.08	-£8,861	-£11,330

Considerable uncertainty around this conclusion was identified during probabilistic sensitivity analysis with only a 14% probability of chemoradiotherapy with gemcitabine being the most cost effective therapy at a £20,000 per QALY willingness to pay. Chemoradiotherapy with gemcitabine and cisplatin becomes the preferred treatment option at the £20,000 per QALY threshold with a 24% chance of being the preferred option. Chemoradiotherapy with gemcitabine, the preferred choice in the deterministic analysis now has a 16% probability of being the most cost effective option. Gemcitabine alone had a 17% probability of being the preferred option in this scenario. As the only monotherapy in the analysis this corresponds to an 83% probability that some form of combination therapy is the most cost effective option. Again the plateauing lines for all interventions suggests there is significant uncertainty around the clinical inputs for the model. This suggests that interventions were likely to be cost effective if the regimens were effective at NICE's conventional thresholds. It was also

acknowledged that there may be scope to consider a higher £50,000 per QALY threshold given the potential benefits and short life expectancy of the interventions and population. The use of either a £20,000 or £50,000 threshold did not alter the conclusions of the model.

When FOLFIRINOX was considered this regimen came out as the preferred option with an INMB of £5,992 compared to gemcitabine alone at a willingness to pay of £20,000 per QALY. During probabilistic sensitivity analysis FOLFIRINOX had a >40% chance of being the preferred option compared to all other regimens for all willingness to pay per QALY above £15,000. During this analysis gemcitabine alone has a 3% and zero probability of being cost effective for a willingness to pay per QALY of £20,000 and £50,000 respectively. Again, this strongly suggests that a combination therapy approach is almost certainly the most cost effective treatment option.

The secondary analysis around the use of chemoradiotherapy in stable and responding patients predicted that the use of chemoradiotherapy with capecitabine in this patient population would be cost effective. Again this result was robust to sensitivity analysis.

11.1.5.5 Conclusions

Of the interventions considered in the NMA, chemoradiotherapy with gemcitabine was the preferred option in the deterministic results but chemoradiotherapy with gemcitabine and cisplatin was the preferred option in the largest number of iterations in the PSA. However, it never had a greater than 25% probability compared to all other interventions at a willingness to pay per QALY values of £20,000 and £50,000 respectively. It was therefore again difficult to strongly conclude for any intervention to be the preferred option from this group. The economic model suggested that gemcitabine alone was unlikely to be the preferred option for any conventionally used willingness to pay threshold suggesting that a form combination therapy

FOLFIRINOX was the preferred option in the when included in the analysis and in over 40% of the iterations of the probabilistic sensitivity analysis. However, despite its prevalent usage for treatment of LAPC across England no direct, randomised comparative evidence was identified for this intervention. The comparability of FOLFIRINOX to other interventions considered in the NMA and economic model is not strong. Whilst FOLFIRINOX was robust to the probabilistic sensitivity analysis, as the overall survival and progression-free survival for FOLFIRINOX were reduced closer to those of other interventions in the NMA, the strength of this conclusion was largely reduced. Comparative randomised evidence comparing FOLFIRINOX with other interventions in the NMA, would increase the comparability of this intervention and the strength of any conclusions drawn. Additional randomised clinical trials which would strengthen and increase the power of the NMA would likely reduce this uncertainty and increase the strength of any recommendations made from the model.

It is difficult to draw comparisons between the NMA and economic model above with the economic model used in TA25. The cost effectiveness evidence for TA25 compared 5-FU chemotherapy with gemcitabine chemotherapy. The two economic evaluations for this technology assessment were largely based around one RCT (Burris et al. 1997) comparing gemcitabine monotherapy to 5-FU monotherapy in patients with either locally advanced or metastatic pancreatic cancer. The models submitted estimated a cost per QALY for gemcitabine compared to 5-FU of between £7,200 and £18,700. Given that 5-FU monotherapy was not a comparison considered in the NMA and economic model above, due to an absence of identified trials, direct comparisons of results could not be made. The costs of gemcitabine are also now likely to be much reduced compared to those considered in TA25 given that the treatment is now ‘off patent’ for this condition.

Despite the TA25 models not being strictly comparable to the economic model above the most pertinent difference is that gemcitabine monotherapy is now very unlikely to be the preferred option with the PSA estimating an almost 0% probability of being cost effective. This however is compared to regimens that were not considered by TA25. However,

interventions that have a component of gemcitabine, in particular chemoradiation with gemcitabine, perform favourably in the economic model.

11.1.6 Evidence Statements for pair-wise comparisons

11.1.6.1 Different chemoradiotherapy regimens

Objective Response

Very low quality evidence from 1 Phase III RCT (n=46) showed no clinically important difference between gemcitabine-based chemoradiotherapy (CRT) and paclitaxel-based chemoradiotherapy about the relative probability of objective response rate (CR + PR) in adults with unresectable non-metastatic locally advanced pancreatic cancer: RR 0.55 (95% CI 0.15-1.92), where RR higher than 1 favours the gemcitabine-based CRT group.

Resection rate

No evidence was identified to inform this outcome

Progression Free Survival

No evidence was identified to inform this outcome

Overall Survival

Very low quality evidence from one Phase III RCT (n=46) showed no clinically important difference between gemcitabine-based CRT and paclitaxel-based CRT on survival rates in adults with unresectable non-metastatic locally advanced pancreatic cancer: HR=0.98 (95% CI 0.52-1.85), where RR higher than 1 favours the GEM-based CRT group.

Adverse Events

Very low and low quality evidence from one Phase III RCT (n=46) showed no clinically important difference between gemcitabine-based CRT and paclitaxel-based CRT about the relative risk of grade 3/4 toxicities (including haematological and non-haematological) in adults with unresectable non-metastatic locally advanced pancreatic cancer: RR 1.09 (95% CI 0.36-3.27) and RR 1.96 (95% CI 1.18-3.28) respectively, where RR higher than 1 favours the paclitaxel-based CRT group.

Very low and low quality evidence from one open label phase III RCT (n=34) showed no clinically important difference between gemcitabine-based CRT and 5FU-based CRT about the relative risk of grade 3/4 toxicities (including nausea, vomiting, anorexia, anaemia, neutropenia, thrombocytopenia and GI bleeding) in adults with unresectable non-metastatic locally advanced pancreatic cancer (relative effect not estimable).

Low quality evidence from 1 multicentre phase II RCT (n=60) showed a clinical important difference favouring 5FU-based CRT in drug-related grade 3/4 toxicities (leukocytopenia and thrombocytopenia) compared to gemcitabine/cisplatin-based CRT in adults with unresectable non-metastatic locally advanced pancreatic cancer: RR 14.97 (95% CI 2.12-105.82) and RR 14.97 (95% CI 2.12-105.82) respectively.

Very low quality evidence from 1 multicentre phase II RCT (n=60) showed no clinically important difference between 5FU-CRT and gemcitabine/cisplatin-CRT about the relative risk of grade 3/4 toxicities (including non-haematological, lower GI tract, upper GI tract, anaemia) in adults with unresectable non-metastatic locally advanced pancreatic cancer (relative effect not estimable).

Health Related Quality of Life

Low quality evidence from one open label phase III RCT (n=34) showed a clinically important difference favouring gemcitabine-based CRT on global quality of life scores compared to 5FU-based CRT in adults with unresectable non-metastatic locally advanced pancreatic cancer: MD = 9.00 (95% CI 6.98-11.03).

Pain control

Very low quality evidence from one open label phase III RCT (n=34) showed a clinically important difference favouring gemcitabine-based CRT on pain control compared to 5FU-based CRT in adults with unresectable non-metastatic locally advanced pancreatic cancer: RR 6.22 (95% CI 0.86-45.25).

Patient experience and PROMS

No evidence was identified to inform this outcome

11.1.6.2 Different chemoradiotherapy regimens after induction chemotherapy

Objective Response

Very low quality evidence from one open label phase II RCT (n=71) showed no clinically important difference between gemcitabine-CRT and capecitabine-CRT after induction chemotherapy on the relative probability of objective response rate (CR + PR) in adults with unresectable non-metastatic locally advanced pancreatic cancer: RR 0.85 (95% CI 0.35-2.10), where RR higher than 1 favours the GEM-CRT group.

Very low quality evidence from one Phase II RCT (n=13) showed no clinically important difference between CRT + cetuximab and CRT alone after induction chemotherapy on the relative probability of objective response rate (CR + PR) in adults with unresectable non-metastatic locally advanced pancreatic cancer: RR 0.50 (95% CI 0.06-4.15), where RR higher than 1 favours the CRT + cetuximab group.

Resection rate

No evidence was identified to inform this outcome

Progression Free Survival

Moderate quality evidence from one open label phase II RCT (n=72) showed no clinically important difference between gemcitabine-CRT and capecitabine-CRT after induction chemotherapy on time to progression rates in adults with unresectable non-metastatic locally advanced pancreatic cancer: HR=0.60 (95% CI 0.32-1.12), where HR higher than 1 favours the gemcitabine-CRT arm.

Overall Survival

Moderate quality evidence from one open label phase II RCT (n=72) indicates that capecitabine-CRT after induction chemotherapy is associated with a clinically important difference in overall survival compared to gemcitabine-CRT after induction chemotherapy in adults with unresectable non-metastatic locally advanced pancreatic cancer: HR=0.39 (95% CI 0.18-0.85)

Low quality evidence from one Phase II RCT (n=13) showed no clinically important difference between CRT + cetuximab and CRT alone after induction chemotherapy on survival rates in adults with unresectable non-metastatic locally advanced pancreatic cancer (relative effect not estimable).

Adverse Events

Very low and low quality evidence from one open label phase II RCT (n=72) showed no clinically important difference between gemcitabine-CRT and capecitabine-CRT after induction chemotherapy on the relative risk of grade 3/4 toxicities (including haematological and non-haematological toxicities) in adults with unresectable non-metastatic locally advanced pancreatic cancer: RR 13.46 (95% CI 0.8-227.22) and 2.24 (95% CI 0.77-6.48) respectively, where RR less than 1 favours the gemcitabine-CRT arm.

Very low and low quality evidence from one Phase II RCT (n=13) showed no clinically important difference between CRT + cetuximab and CRT alone after induction chemotherapy on relative risk of grade 3/4 toxicities (including hyponatremia, fatigue and abdominal pain) in adults with unresectable non-metastatic locally advanced pancreatic cancer: RR 0.33 (95% CI 0.02-6.86) for all outcomes, where RR less than 1 favours the CRT + cetuximab group.

Health Related Quality of Life

Low quality evidence from one open label phase II RCT (n=48) showed no clinically important difference between gemcitabine-CRT and capecitabine-CRT after induction chemotherapy on the improvement of quality of life (measured as mean of the EORTC QLQ-C30) in adults with unresectable non-metastatic locally advanced pancreatic cancer (relative effect not estimable).

Pain control

No evidence was identified to inform this outcome

Patient experience and PROMS

No evidence was identified to inform this outcome

11.1.6.3 Chemoradiotherapy versus best supportive care

Objective Response

No evidence was identified to inform this outcome

Resection rate

No evidence was identified to inform this outcome

Progression Free Survival

No evidence was identified to inform this outcome

Overall Survival

No evidence was identified to inform this outcome

Adverse Events

No evidence was identified to inform this outcome

Health Related Quality of Life

Low quality evidence from one phase III RCT (n=31) indicates a clinically important difference favouring CRT on global quality of life scores (measured as mean of the Karnofsky

performance status) compared to best supportive care [no CRT] in adults with unresectable non-metastatic locally advanced pancreatic cancer: MD = 11.60 (95% CI 6.61-15.69).

Pain control

No evidence was identified to inform this outcome

Patient experience and PROMS

No evidence was identified to inform this outcome

11.1.6.4 Chemoradiotherapy versus chemoradiotherapy followed by chemotherapy

Objective Response

No evidence was identified to inform this outcome

Resection rate

No evidence was identified to inform this outcome

Progression Free Survival

No evidence was identified to inform this outcome

Overall Survival

No evidence was identified to inform this outcome

Adverse Events

Low quality evidence from one multicentre phase II RCT (n=56) showed a clinically important difference favouring CRT [5FU-CRT] on the relative risk of drug-related grade 3/4 toxicities (leukocytopenia and thrombocytopenia) compared to CRT followed by chemotherapy [gemcitabine/cisplatin-CRT followed by gemcitabine chemotherapy] in adults with unresectable non-metastatic locally advanced pancreatic cancer: RR 18.26 (95% CI 2.60-128.02) and 10.74 (95% CI 1.47-78.39) respectively, where RR less than 1 favours the CRT followed by chemotherapy arm.

Very low quality evidence from one multicentre phase II RCT (n=56) showed no clinically important difference between CRT [5FU-CRT] and CRT followed by chemotherapy [gemcitabine/cisplatin-CRT followed by gemcitabine chemotherapy] on the relative risk of grade 3/4 toxicities (including non-haematological, lower GI tract, upper GI tract, anaemia) in adults with unresectable non-metastatic locally advanced pancreatic cancer.

Health Related Quality of Life

No evidence was identified to inform this outcome

Pain control

No evidence was identified to inform this outcome

Patient experience and PROMS

No evidence was identified to inform this outcome

.

11.1.6.5 Chemoradiotherapy + R115777 versus chemoradiotherapy alone

Objective Response

No evidence was identified to inform this outcome

Resection rate

No evidence was identified to inform this outcome

Progression Free Survival

No evidence was identified to inform this outcome

Overall Survival

Moderate quality evidence from one phase II RCT (n=185) showed no clinically important difference between CRT+R115777 and CRT alone in survival rates after induction chemotherapy in adults with unresectable non-metastatic locally advanced pancreatic cancer (relative effect not estimable).

Adverse Events

Very low and low quality evidence from one phase II RCT (n=185) showed no clinically important difference between CRT+R115777 and CRT alone on the relative risk of grade 3/4 toxicities (including allergy/immunology, blood/bone marrow, cardiovascular, coagulation, constitutional, endocrine, and gastrointestinal) in adults with unresectable non-metastatic locally advanced pancreatic cancer: RR 0.65 (95% CI 0.11-3.77); RR 1.39 (95% CI 0.96-2.0); RR 2.26 (95% CI 0.6-8.47); RR 0.32 (95% CI 0.01-7.82); RR 1.69 (95% CI 0.75-3.84); RR 0.32 (95% CI 0.01-7.82); and RR 1.12 (95% CI 0.77-1.63) respectively, where RR less than 1 favours the CRT+R115777 arm.

No grade 3/4 toxicities were reported for the following outcomes in both intervention groups: auditory/hearing, cardiovascular (arrhythmia), dermatology/skin, and ocular/visual/ renal/genitourinary.

Moderate quality evidence from one phase II RCT (n=185) suggests a clinically important difference favouring CRT+R115777 on the relative risk of drug-related grade 3/4 toxicities (haemorrhage) compared to CRT alone: RR 0.06 (95% CI 0.02-0.26).

Health Related Quality of Life

No evidence was identified to inform this outcome

Pain control

No evidence was identified to inform this outcome

Patient experience and PROMS

No evidence was identified to inform this outcome

11.1.6.6 Chemoradiotherapy + TNFerade versus chemoradiotherapy alone

Objective Response

No evidence was identified to inform this outcome

.

Resection rate

No evidence was identified to inform this outcome

Progression Free Survival

No evidence was identified to inform this outcome

Overall Survival

No evidence was identified to inform this outcome

Adverse Events

Very low quality evidence from one open label phase III RCT (n=304) showed no clinically important difference between CRT + TNFerade and CRT alone on the relative risk of grade 3/4 toxicities (including gastrointestinal, haematological, and non-gastrointestinal/haematological) in adults with unresectable non-metastatic locally advanced pancreatic cancer: RR 1.64 (95% CI 0.85-3.16); RR 0.90 (95% CI 0.64-1.28); and RR 1.51 (95% CI 0.67-3.41) respectively, where RR less than 1 favours the CRT + TNFerade arm.

Health Related Quality of Life

No evidence was identified to inform this outcome

Pain control

No evidence was identified to inform this outcome

Patient experience and PROMS

No evidence was identified to inform this outcome

11.1.6.7 Chemoradiotherapy versus chemotherapy

Objective Response

No evidence was identified to inform this outcome

Resection rate

No evidence was identified to inform this outcome

Progression Free Survival

No evidence was identified to inform this outcome

Overall Survival

No evidence was identified to inform this outcome

Adverse Events

Low quality evidence from one phase III RCT (n=71) showed a clinically important difference favouring CRT on the relative risk of drug-related grade 3/4 toxicities (fatigue) compared to chemotherapy in adults with unresectable non-metastatic locally advanced pancreatic cancer: RR 5.66 (95% CI 1.35-33.68)

Very low quality evidence from one phase III RCT (n=71) showed no clinically important difference between CRT and chemotherapy on the relative risk of grade 3/4 toxicities (including haemoglobin, leukocytes, neutrophils, nausea, vomiting, hypokalaemia, and anorexia) in adults with unresectable non-metastatic locally advanced pancreatic cancer: RR 3.09 (95% CI 0.67-14.25); RR 2.26 (95% CI 0.88-5.83); RR 1.12 (95% CI 0.60-2.09); RR 3.43 (95% CI 1.03-11.40); RR 3.09 (95% CI 0.91-10.44); RR 2.06 (95% CI 0.40-10.51); and RR 6.18 (95% CI 0.78-48.64) respectively, where RR less than 1 favours the CRT arm.

Health Related Quality of Life

Low and very low quality evidence from one phase III RCT (n=71) showed a clinically important difference favouring CRT on the improvement of global quality of life scores compared to chemotherapy at 6 weeks follow-up in adults with unresectable non-metastatic locally advanced pancreatic cancer: MD = -12.20 (95% CI -17.98 to -6.42, measured as mean difference of changes from baseline).

The same study showed no clinically important difference between CRT and chemotherapy on the improvement in global quality of life scores (measured as mean difference of changes from baseline) at 16 week and 9 month follow-up in adults with unresectable non-metastatic locally advanced pancreatic cancer: MD = -3.30 (95% CI -9.08 to 2.48) and 2.70 (95% CI -3.08 to 8.48), where MD less than 1 favours the GEM-CRT arm.

Patient experience and PROMS

No evidence was identified to inform this outcome

11.1.6.8 Chemotherapy versus chemoradiotherapy after induction chemotherapy

Objective Response

No evidence was identified to inform this outcome

Resection rate

No evidence was identified to inform this outcome

Progression Free Survival

Moderate quality evidence from one open label phase III RCT (n=368) showed no clinically important difference between chemotherapy and CRT after induction chemotherapy on time to progression rates in adults with unresectable non-metastatic locally advanced pancreatic cancer: HR=0.78 (95% CI 0.61-1.00), where HR higher than 1 favours the CT arm.

Overall Survival

Moderate quality evidence from one open label phase III RCT (n=368) showed no clinically important difference between chemotherapy and CRT after induction chemotherapy on overall survival rates in adults with unresectable non-metastatic locally advanced pancreatic cancer: HR=1.03 (95% CI 0.79-1.14), where HR higher than 1 favours the CT arm.

Adverse Events

Very low and low quality evidence from one open label phase III RCT (n=368) showed no clinically important difference between chemotherapy and CRT after induction chemotherapy on the relative risk of grade 3/4 toxicities (including haematological and non-haematological) in adults with unresectable non-metastatic locally advanced pancreatic cancer: RR = 2.93

(95% CI 0.97-8.87) and 0.94 (95% CI 0.56-1.58), where RR less than 1 favours the CRT arm.

Health Related Quality of Life

No evidence was identified to inform this outcome

Pain control

No evidence was identified to inform this outcome

Patient experience and PROMS

No evidence was identified to inform this outcome

11.1.6.9 Chemoradiotherapy versus radiotherapy

Objective Response

No evidence was identified to inform this outcome

Resection rate

No evidence was identified to inform this outcome

Progression Free Survival

No evidence was identified to inform this outcome

Overall Survival

No evidence was identified to inform this outcome

Adverse Events

Very low quality evidence from one open label Phase III RCT (n=114) showed no clinically important difference between CRT and radiotherapy on the relative risk of grade 3/4 toxicities (including gastrointestinal, vomiting, infection, skin, mucous, neurologic, genitourinary, hematologic, liver, constipation, cardiac, and fever) in adults with unresectable non-metastatic locally advanced pancreatic cancer: RR 0.32 (95% CI 0.01-7.72); RR 0.72 (95% CI 0.17-3.08); RR 2.89 (95% CI 0.12-69.47); RR 4.82 (95% CI 0.24-98.13); RR 3.85 (95% CI 0.45-33.38); RR 0.96 (95% CI 0.06-15.01); RR 2.70 (95% CI 1.04-6.97); RR 0.39 (95% CI 0.08-1.90) and RR 1.93 (95% CI 0.18-20.63) respectively, where RR less than 1 favours the CRT arm.

No grade 3/4 toxicities were reported for the following outcomes in both intervention groups: diarrhoea, haemorrhage, and respiratory system.

Health Related Quality of Life

No evidence was identified to inform this outcome

Pain control

No evidence was identified to inform this outcome

Patient experience and PROMS

No evidence was identified to inform this outcome

11.1.6.10 Different chemotherapy regimens

Objective Response

No evidence was identified to inform this outcome

Resection rate

No evidence was identified to inform this outcome

Progression Free Survival

No evidence was identified to inform this outcome

Overall Survival

No evidence was identified to inform this outcome

Adverse Events

Very low quality evidence from one open label phase III RCT (n=443) showed no clinically important difference between the gemcitabine chemotherapy and gemcitabine/erlotinib chemotherapy on the relative risk of grade 3/4 toxicities (including haematological and non-haematological) in adults with unresectable non-metastatic locally advanced pancreatic cancer: RR = 1.17 (95% CI 0.91-1.5) and 1.01 (95% CI 0.8-1.27) respectively, where RR less than 1 favours the gemcitabine/erlotinib chemotherapy arm.

Low quality evidence from one Phase III RCT (n=138) showed a clinically important difference favouring gemcitabine chemotherapy on drug-related grade 3/4 toxicities (including leukopenia, vomiting, diarrhoea, anaemia, thrombocytopenia, fever, microsites, and gastrointestinal bleeding) compared to FLEC chemotherapy in adults with unresectable non-metastatic locally advanced pancreatic cancer: RR = 2.14 (95% CI 1.29-3.55).

Health Related Quality of Life

No evidence was identified to inform this outcome

Pain control

No evidence was identified to inform this outcome

Patient experience and PROMS

No evidence was identified to inform this outcome

11.1.6.11 Gemcitabine- based chemotherapy + upmostat versus gemcitabine-based chemotherapy alone

Objective Response

No evidence was identified to inform this outcome

Resection rate

No evidence was identified to inform this outcome

Progression Free Survival

No evidence was identified to inform this outcome

Overall Survival

No evidence was identified to inform this outcome

Adverse Events

Very low and low quality evidence from one open label phase II RCT (n=95) showed no clinically important difference between gemcitabine-based chemotherapy and gemcitabine-based chemotherapy + upmostat on the relative risk of grade 3/4 toxicities (any type) in adults with unresectable non-metastatic locally advanced pancreatic cancer: RR = 1.31 (95% CI 0.78-2.19)- 200mg upmostat and RR 1.54 (95% CI 0.96-2.74)- 400mg upmostat, where RR less than 1 favours the gemcitabine-based chemotherapy + upmostat arm.

Health Related Quality of Life

No evidence was identified to inform this outcome

Pain control

No evidence was identified to inform this outcome

Patient experience and PROMS

No evidence was identified to inform this outcome

11.1.6.12 Radiotherapy + PR-350 Radiosensitiser versus Radiotherapy + Placebo

Objective Response

Very low quality evidence from one double-blind phase III RCT (n=48) showed no clinically important difference between radiotherapy + PR-350 and radiotherapy + placebo on the relative probability of objective response rate (CR + PR) in adults with unresectable non-metastatic locally advanced pancreatic cancer: RR 2.18 (95% CI 0.88-5.41), where RR higher than 1 favours the radiotherapy + PR-350 group.

Resection rate

No evidence was identified to inform this outcome

Progression Free Survival

No evidence was identified to inform this outcome

Overall Survival

Low quality evidence from one double-blind phase III RCT (n=48) showed no clinically important difference between radiotherapy + PR-350 and radiotherapy + placebo on survival rates in adults with unresectable non-metastatic locally advanced pancreatic cancer (relative effect not estimable).

Adverse Events

Very low quality evidence from 1 double-blind phase III RCT (n=48) showed no clinically important difference between radiotherapy + PR-350 and radiotherapy + placebo on the relative risk of grade 3/4 toxicities (including any type) in adults with unresectable non-metastatic locally advanced pancreatic cancer: RR 0.38 (95% CI 0.02-8.80), where RR higher than 1 favours the radiotherapy + PR-350 group.

Health Related Quality of Life

No evidence was identified to inform this outcome

Pain control

No evidence was identified to inform this outcome

Patient experience and PROMS

No evidence was identified to inform this outcome

11.1.6.13 Radiofrequency ablation (RFA) as primary treatment versus RFA after other primary treatments.

Objective Response

No evidence was identified to inform this outcome

Resection rate

No evidence was identified to inform this outcome

Progression Free Survival

No evidence was identified to inform this outcome

Overall Survival

Low quality evidence from 1 prospective cohort study (n=107) indicates a clinical important difference favouring RFA as primary treatment on overall survival compared to RFA following any other primary treatment (relative effect not estimable).

Adverse Events

No evidence was identified to inform this outcome

Health Related Quality of Life

No evidence was identified to inform this outcome

Pain control

No evidence was identified to inform this outcome

Patient experience and PROMS

No evidence was identified to inform this outcome

11.1.7 Recommendations

44. Offer systemic combination chemotherapy to people with locally advanced pancreatic cancer who are well enough to tolerate it.

45. Consider gemcitabine for people with locally advanced pancreatic cancer who are not well enough to tolerate combination chemotherapy.

46. When using chemoradiotherapy, consider capecitabine as the radiosensitiser.

11.1.8 Evidence to recommendations

11.1.8.1 Relative value placed on the outcomes considered

Overall survival, progression free survival, objective response, resection rate, adverse events, health related quality of life, pain control, patient experience and PROMS were considered to be the critical outcomes for this question. Objective response was reported by eleven studies, progression free survival was reported by nine studies and overall survival was reported by sixteen studies.

11.1.8.2 Quality of evidence

Network meta-analysis (NMA)

Given the variation in practice for this topic and the potential for a significant resource impact from any recommendations, a network meta-analysis (NMA) was developed to help inform recommendations.

All identified phase III and phase II randomised clinical trials in pure locally advanced pancreatic cancer populations were considered in the network meta-analysis as long as the intervention in a given trial was also considered by another study and could therefore form part of the network. Studies where the patient group had received induction chemotherapy and were randomised only if they had responding or stable disease, were excluded. Three NMAs were built based on the outcomes of overall survival, progression free survival and objective response with gemcitabine monotherapy being used as the reference standard. The committee noted that most of the studies included in the NMA had a serious risk of bias and that the quality of inputs for the economic model ranged from very low to good quality across all outcomes and comparisons, with most of the evidence being of low quality.

The committee noted that the results of the NMA for progression free survival and objective response had very wide credible intervals and all crossed the line of no effect. They therefore agreed that no conclusions could be drawn from these outcomes.

The committee also noted that the results of the NMA for overall survival had one intervention, chemoradiotherapy with Gemcitabine, for which the 95% credible intervals did not pass the line of no effect (HR=1). They also noted that one RCT (Loehrer 2011) which was identified as having a serious risk of bias was independently driving the results of the NMA in this way. All other credible intervals crossed 1, although the credible intervals were much narrower than for the other NMAs. The committee agreed that the NMA considering overall survival would be somewhat useful for informing recommendations, but they noted great uncertainty and that caution in interpreting results was needed.

Usually this would mean making a weaker recommendation, but the committee agreed that because a very high proportion of people with locally advanced disease will go on to develop metastatic disease unless they have treatment, a stronger recommendation should be made.

The committee also noted that chemotherapy used in the identified studies would no longer be considered standard for either metastatic or locally advanced pancreatic cancer. There were no randomised clinical trials of FOLFIRINOX, which is frequently offered as standard of care, so it was not possible for this intervention to be included in the NMA. It was agreed that FOLFIRINOX should be investigated as a secondary economic analysis instead. The clinical data for FOLFIRINOX came from Suker 2016, which was a non-comparative patient level meta-analysis of 13 studies. The committee noted that this is a lower level of evidence than the RCT data on other interventions that went into the NMA, so used caution when interpreting the results. The committee noted that FOLFIRINOX is only suitable for fit patients.

Pairwise comparison

Pairwise comparisons were conducted for outcomes in the review question that were not covered by the NMA. Pairwise comparisons were also conducted for studies which did not meet the inclusion criteria for the NMA. The evidence for the pairwise comparisons ranged from very low to moderate quality across all outcomes and comparisons, with most of the evidence being either very low or low quality. The committee noted that the overall trend being reported by the evidence was that more chemotherapy (in the form of combination regimens) was associated with more adverse events.

Very little evidence was found on ablative therapies so the committee agreed not to make any recommendations for clinical practice about this intervention. They did not recommend further research on any of the ablative therapies investigated in this question as they did not think they were a priority for research funding.

11.1.8.3 Consideration of clinical benefits and harms

Based on the results of the NMA and economic analysis the committee agreed that combination chemotherapy was more clinically effective than monotherapy in terms of overall survival and the most cost effective option.

The health economic analysis showed FOLFIRINOX was cost effective but there was uncertainty about the clinical data used to inform the model. Therefore they agreed not to make a specific recommendation on FOLFIRINOX but noted that the offer of combination chemotherapy allowed FOLFIRINOX to be considered. Given the potential toxicity with combination chemotherapy and difficulty for less fit patients to tolerate it, the committee also recommended gemcitabine as an option for people who are unlikely to tolerate combination therapy.

The committee noted that consolidation chemoradiotherapy was relatively safe, improved local control and may be cost effective but that survival was not superior to chemotherapy alone. Therefore they agreed that they were unable to make a specific recommendation on the use of consolidation chemoradiotherapy. Based on data from pairwise comparisons that there was improved overall survival and less haematological toxicity with capecitabine-based chemoradiotherapy compared with gemcitabine-based chemoradiotherapy, the committee agreed to recommend capecitabine as the radiosensitiser for people in whom the decision to offer chemoradiotherapy has been made.

11.1.8.4 Consideration of economic benefits and harms

The estimates and distributions from the NMA were used to inform a bespoke economic model. The committee raised concerns that there were important elements for this topic not considered by the NMA, most notably the role of chemoradiotherapy in patients with stable and responding disease and the use of FOLFIRINOX (for which no randomised evidence was identified and thus was excluded from the NMA). Two secondary economic analyses were therefore performed to consider these.

In the primary base case analysis, considering only interventions included in the NMA, chemoradiotherapy with gemcitabine came out as the preferred option with an incremental net monetary benefit (INMB) of £786 when a £20,000 per QALY willingness to pay was assumed. However, considerable uncertainty around this conclusion was identified during probabilistic sensitivity analysis with only a 14% probability of being the most cost effective therapy at a £20,000 per QALY willingness to pay. Above a willingness to pay of £10,000 per QALY there was never more than a few percentage difference in being the preferred option between the top four therapies. It was therefore difficult for the committee to conclude which regimen was most cost effective.

When FOLFIRINOX was considered, this regimen came out as the preferred option with an INMB of £5,992 compared to gemcitabine alone. During probabilistic sensitivity analysis FOLFIRINOX had a >40% chance of being the preferred option compared to all other regimens for all willingness to pay per QALY above £15,000. The committee noted that this was based on observational data and that the likely associated biases would mean that inputs into the economic model would overestimate the true effectiveness of FOLFIRINOX. However, these results were robust to deterministic sensitivity analyses which reduced the effectiveness of FOLFIRINOX. The committee therefore agreed, based on the results of the economic model that whilst FOLFIRINOX appeared to be cost effective, the clinical data was very weak and therefore did not make a recommendation for this intervention.

The secondary analysis around the use of chemoradiotherapy in stable and responding patients predicted that the use of chemoradiotherapy with capecitabine in this patient population would be cost effective. Again this result was robust to sensitivity analysis. The committee noted that from the clinical evidence that whilst consolidation chemoradiotherapy appeared to be relatively safe and improve local control, that survival was not superior to chemotherapy alone. Therefore they agreed that they were unable to make a specific recommendation on the use of consolidation chemoradiotherapy.

It was also acknowledged by the committee that most of the uncertainty in the model was driven by clinical factors with the lines of the cost-effectiveness acceptability curve running almost horizontal for values above a willingness to pay of £15,000 per QALY. This suggested that interventions were likely to be cost effective if the regimens were effective at NICE's conventional thresholds. It was also acknowledged that there may be scope to consider a higher £50,000 per QALY threshold given the potential benefits and short life expectancy of the interventions and population. Whilst the use of either a £20,000 or £50,000 threshold did not alter the conclusions, it does strengthen the argument that the recommendations made around the model are cost effective.

The committee agreed that there was unlikely to be any significant resource impact as a result of the recommendations made since the interventions are already widely used as treatment in this patient group.

11.1.8.5 Other considerations

The committee noted that there was existing NICE Interventional Procedure guidance on the use of irreversible electroporation for treating pancreatic cancer (IPG579). It concluded that current evidence on its safety and efficacy is inadequate in quantity and quality, and therefore recommended that this procedure should only be used in the context of research. Consequently this intervention was not investigated by this guideline and the committee were not able to make any recommendations on it.

11.1.9 References

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11.2 Management of metastatic pancreatic cancer

Review question: What are the most effective interventions for adults with newly diagnosed or recurrent metastatic pancreatic cancer (Chemotherapy, surgery, radiotherapy)?

11.2.1 Introduction

At presentation, the majority of pancreatic cancer patients have locally advanced or metastatic disease. The prognosis of those with metastatic pancreatic cancer is measured in months, which may be extended, albeit to a limited extent by systemic chemotherapy. Pancreatic cancer frequently affects older people and metastatic disease is associated with multiple problems, including pain, weight loss, anorexia, cachexia, jaundice, nausea, vomiting, altered bowel habit, dyspepsia, mood disturbance and depression and increased risk of thromboembolic events.

Despite recent advances in chemotherapy, with interventions such as FOLFIRNOX and other combination regimes providing a prolonged median survival, the prognosis for people diagnosed with metastatic pancreatic cancer remains poor and any subsequent treatment is deemed palliative (for example not curative). People with metastatic pancreatic cancer may experience distressing symptoms that require ongoing and specialist support. In respect of this, it is important that people diagnosed with metastatic pancreatic cancer have their physical and psychological needs assessed at the time of diagnosis. General and specialist palliative care services have an important role in introducing the person with pancreatic cancer, and their family if applicable, to a range of services and support available to ease the burden of physical and psychological distress through the trajectory of their cancer diagnosis towards end of life. If a person presents with end stage metastatic disease with a poor performance status and no treatment can be offered to them, the support of specialist palliative care is essential.

Individuals with significant comorbidities or poor performance status due to advancing disease may not tolerate chemotherapy. For those people fit for treatment, various single agent and combination chemotherapy regimens are in routine use, few of which have undergone NICE technology appraisal. Those interventions where there is existing NICE technology appraisal guidance will not be reviewed here, nab-paclitaxel combined with gemcitabine (TA 360), and nano-liposomal irinotecan combined with 5fluororouracil and folinic acid (TA 440).

Metastatic disease results in a significant symptom burden for the individual which requires active management to achieve symptom control, with the intention of improving quality of life, patient and family experience. Radiotherapy with or without chemotherapy has been used to reduce local tumour volume (including at the coeliac plexus) with the intention of improving pain control. Pharmacological interventions including analgesia, antiemetics, pancreatic enzyme replacement, blood sugar management, corticosteroid and other hormonal agents as well as anticoagulants play a role in symptom management and may influence overall outcomes. An area of current uncertainty is whether isolated metastases can be effectively targeted by surgery or local ablative techniques.

While most randomised trials have focussed on evaluating first line chemotherapy, there is uncertainty regarding the role of second line chemotherapy in a subgroup of people who are sufficiently fit to receive it.

Guidance is needed on the most effective interventions for people with metastatic pancreatic cancer.

11.2.1.1 Review protocol summary

The review protocol summary used for this question can be found in Table 175. Full details of the review protocol can be found in Appendix C.

Table 175: Clinical review protocol summary for review of management of metastatic pancreatic cancer

Population	Patients with advanced and/or metastatic pancreatic cancer
Intervention	• Chemotherapy (1st line, 2nd line) • Surgery for metastatic disease +/- chemotherapy • Radiotherapy
Comparison	• Different Chemo types/regimens • Best supportive care • No surgery • Ablative techniques for metastases • Best supportive care • Best supportive care
Outcomes	• Response rate • Overall Survival • Progression Free Survival • Adverse Events • Health Related Quality of Life • Patient experience and PROMs • Symptom control

11.2.2 Description of Clinical Evidence

Thirty-nine phase II/III RCTs and 1 network-meta analysis of 23 RCTs (Gresham et al. 2014) were included in this review. A summary of the studies included in pairwise comparisons is presented in Table 176. A summary of the studies included in the NMA is presented in Table 177.

Two RCTs were found that compared chemotherapy with chemoimmunotherapy in adults with advanced/metastatic pancreatic cancer (Middleton et al. 2014; Wang et al. 2013). One of the studies assessed the efficacy and safety of sequential or simultaneous telomerase vaccination (GV1001) in combination with chemotherapy as first-line therapy in adults with advanced/metastatic pancreatic cancer (Middleton et al. 2014). The other study compared S-1 combined with cytokine-induced killer cells (CIK) with S-1 only in adults with advanced/metastatic pancreatic cancer who had previously received gemcitabine-based therapy (Wang et al. 2013).

A total of 15 RCTs (Bernhard et al. 2008; Burris et al. 1997; Chao et al. 2013; Deplanque et al. 2015; Eckhardt et al. 2009; Fuchs et al., 2015; Gourgou-Bourgade et al. 2013; Irigoyen et al. 2017; Lee et al. 2017; Kindler et al. 2010; Moinpour et al. 2010; Rougier et al. 2013; Sudo et al. 2014; Ueno et al. 2013; Yamaue et al. 2015) and 1 NMA (Gresham et al. 2014) of 23 RCTs (Abou-Alfa et al. 2006; Berlin et al. 2002; Bramhall et al. 2002; Colucci et al. 2010; Conroy et al. 2011; Cunningham et al. 2009; Gonçalves et al. 2012; Heinemann et al. 2006; Heinemann et al. 2012; Herrmann et al. 2007; Kindler et al. 2011; Louvet et al. 2005; Moore et al. 2007; Oettle et al. 2005; Philip et al. 2010; Poplin et al. 2006; Reni et al. 2005; Riess et al. 2005; Rocha Lima et al. 2004; Stathopoulos et al. 2006; Van-Cutsem et al. 2004; Van-Cutsem et al. 2009; Von-Hoff et al. 2013) were found that compared gemcitabine with other chemotherapy regimens. The majority of the studies were in a mixed population that included adults with either locally advanced or metastatic pancreatic cancer, whilst five of the studies were in adults with metastatic pancreatic cancer only (Chao et al. 2013; Fuchs et al. 2015; Gourgou-Bourgade et al. 2013; Irigoyen et al. 2017; Rougier et al. 2013). The majority of the studies in the NMA included adults with either locally advanced or metastatic pancreatic.

Data were extracted from the NMA for overall survival only. Data on response rate, progression-free survival, adverse events, and health-related quality of life were extracted from the original studies included in the NMA (pairwise evidence review). The NMA included a study (Von Hoff et al. 2013) that was part of a NICE TA evaluation (nab-Paclitaxel plus Gemcitabine). Therefore, this trial was considered in the NMA as a silent comparator (in order to foster the accuracy and the precision of the NMA), but it was excluded from the rest of the guideline decision-making (i.e. pairwise evidence review).

Three RCTs were found that compared gemcitabine with novel gemcitabine-based treatments in adults with locally advanced or metastatic pancreatic cancer (Middleton et al. 2017; Moore et al. 2003; Smith et al. 2003).

One RCT was identified that compared a low-dose gemctiabine infusion with a standard-dose gemcitabine infusion in adults with locally advanced or metastatic pancreatic cancer (Sakamoto et al. 2006).

Four RCTs were found that compared 5-FU with combination 5-FU in adults with metastatic pancreatic cancer (Cullinan et al. 1985; Cullinan et al. 1990; Ducreux et al. 2002; Maisey et al. 2002). Two of these studies were in adults with metastatic pancreatic cancer (Cullinan et al. 1985; Maisey et al. 2002), whilst two of them were in adults with locally advanced or metastatic pancreatic cancer (Cullinan et al. 1990; Ducreux et al. 2002).

Two RCTs, which were both in adults with locally advanced or metastatic pancreatic cancer, compared first-line combination 5-FU with other chemotherapy regimens (Bukowski et al. 1983; Oster et al. 1986). One of the studies compared FAM (a combination of 5-FU, Adriamycin [Doxorubicin], and Mitomycin) with FSM (a combination of 5-FU, Streptozotocin,

and Mitomycin) (Oster et al. 1986); whilst the other study compared FSM with MF (a combination of Mitomycin C and 5-FU) (Bukowski et al. 1983).

Three RCTs were found that compared regional intra-arterial chemotherapy (RIAC) with systemic chemotherapy in adults with locally advanced or metastatic pancreatic cancer (Aigner et al. 1998; Cantore et al. 2004; Ji et al. 2003).

Two RCTs were found that compared a combination of chemotherapy and a prophylactic anticoagulant with chemotherapy only in adults with locally advanced or metastatic pancreatic cancer. One study compared a combination of gemcitabine and weight-adjusted dalteparin (WAD) with gemcitabine only (Maraveyas et al. 2012), whilst one study compared a combination of first-line chemotherapy and prophylactic enoxaparin with chemotherapy only (Pelzer et al. 2015).

One RCT was found that compared second-line glufosfamide with best supportive care (BSC) in adults with metastatic pancreatic cancer (Ciuleanu et al. 2009).

Six RCTs were found that compared two types of second-line chemotherapy with one another in adults with locally advanced or metastatic pancreatic cancer who had previously received gemcitabine-based chemotherapy (Azmy et al. 2013; Dahan et al. 2010; Gill et al. 2016; Heinemann et al. 2012; Oettle et al. 2014; Ulrich-Pur et al. 2003).

The ISPOR checklist was used for the quality assessment of the NMA (Jansen et al. 2014), whilst the GRADE tool was used for assessing risk of bias and overall quality of the phase II/III RCTs.

Further information about the search strategy can be found in Appendix D. See study selection flow chart in Appendix E, forest plots in Appendix H, GRADE tables in Appendix I, study evidence tables in Appendix F and list of excluded studies in Appendix G.

11.2.3 Summary of included studies

A summary of the studies that were included in this review is presented in Table 176.

Table 176: Summary table of included studies

Study ID Country	Study design	Participants	Intervention	Comparison	Outcomes
Aigner et al. 1998 Germany	Multicentre Phase III RCT	14 patients with locally advanced/metastatic PC	Regional intra-arterial chemotherapy	Systemic chemotherapy	Overall response rate (CR + PR)
Azmy et al. 2013 Egypt	Phase III RCT	48 patients with locally advanced/metastatic PC	Second-line Oxaliplatin + 5-FU	Second-line bolus folinic acid + bolus 5-FU	Overall response rate (CR + PR) Progression Free Survival* Overall Survival* Adverse Events
Bernhard et al. 20081 Switzerland, Italy, Austria, Germany	Multicentre Phase III RCT	319 patients with locally advanced/metastatic PC	Gemcitabine + Capecitabine	Gemcitabine	Response rate Overall Survival Adverse Events Health-related quality of life
Bukowski et al. 1983 USA	Phase III RCT	181 patients with locally advanced/metastatic PC	First-line Streptozotocin, Mitomycin C + 5-FU	First-line Mitomycin C + 5-FU	Overall response rate (CR + PR) Overall Survival* Adverse Events Drug-related deaths
Burris et al. 1997 USA	Phase III RCT	160 patients with locally advanced/metastatic PC	5-FU	Gemcitabine	Response rate Overall Survival Adverse Events
Cantore et al. 2004	Phase III RCT	138 patients with locally	Regional Intra-Arterial Chemotherapy - FLEC	Gemcitabine single-agent	Overall response rate (CR + PR)

Study ID Country	Study design	Participants	Intervention	Comparison	Outcomes
Italy		advanced/metastatic PC			Overall Survival Adverse Events
Chao et al. 2013 Taiwan	RCT	46 patients with metastatic PC	Gemcitabine + Cisplatin	Gemcitabine	Response rate Progression-free Survival Overall Survival Adverse Events Health-related quality of life
Ciuleanu et al. 2009 Argentina, Brazil, Czech Republic, Hungary, India, Russia	Multicentre Phase III RCT	303 patients with metastatic PC	Second-line chemotherapy + best supportive care	Best supportive care	Progression-free Survival Overall Survival Adverse effects
Cullinan et al. 1990 USA	Phase III RCT	123 patients with metastatic PC	5-FU, Doxorubicin, + Cisplatin	5-FU	Overall response rate (CR + PR) Overall Survival Adverse Events
Cullinan et al. 1985 USA	Multicentre Phase III RCT	100 patients with metastatic PC	5-FU, Doxorubicin + Mitomycin	5-FU	Overall response rate (CR + PR) Overall Survival
Dahan et al. 2010 France	Multicentre Phase III RCT	202 patients with metastatic PC	5-FU, Folinic Acid + Cisplatin (LV5FU2-CDDP) then Gemcitabine after progression	Gemcitabine then LV5FU2-CDDP after progression	Overall response rate (CR + PR) Progression-free survival Overall Survival Adverse Events
Deplanque et al. 2015 France, Czech Republic, USA	Multicentre Phase III RCT	348 patients with locally advanced/metastatic PC	Gemcitabine + Masitinib	Gemcitabine + Placebo	Progression-free Survival Overall Survival Adverse Events
Ducreux et al. 2002	Phase III RCT	207 patients with metastatic PC	5-FU + Cisplatin	5-FU	Overall response rate (CR + PR)

Study ID Country	Study design	Participants	Intervention	Comparison	Outcomes
France					Progression-free survival Overall Survival Adverse Events
Eckhardt et al. 2009 Australia, Austria, France, Germany, Portugal, Spain, Sweden, UK, USA	Multicentre Phase III RCT	244 patients with locally advanced/metastatic PC (mixed population)	Gemcitabine + Tipifarnib	Gemcitabine + Placebo	Response rate Overall Survival Adverse Events
Fuchs et al. 2015 Australia, Canada, Japan, Brazil, Czech Republic, Poland, Spain, UK, US	Multicentre Phase III RCT	800 patients with metastatic PC	Gemcitabine + Ganitumab 12 mg/kg	Gemcitabine + Ganitumab 20 mg/kg Gemcitabine + Placebo	Response rate Progression-free Survival Overall Survival Adverse Events
Gill et al. 2016 Canada	Multicentre Phase III RCT	108 patients with locally advanced/metastatic PC	Second-line modified FOLFOX6 (infusional 5-FU, folinic acid + Oxaliplatin)	Second-line infusional 5-FU and folinic acid	Overall response rate (CR + PR) Progression-free Survival Overall Survival Adverse Events Health-related quality of life
Gourgou-Bourgade et al. 20132 France	Multicentre Phase III RCT	342 patients with metastatic PC	FOLFIRINOX (Oxaliplatin, Irinotecan, 5-FU + Leucovorin)	Gemcitabine	Health-related quality of life
Gresham et al. 2014	Network meta-analysis of 23 RCTs	23 RCTs with total of 9,989 patients with either metastatic PC or locally	FOLFIRINOX PEFG Gemcitabine with 5-FU	Capecitabine + Erlotinib Gemcitabine Gemcitabine + Erlotinib	Overall Survival

Study ID Country	Study design	Participants	Intervention	Comparison	Outcomes
		advanced/metastatic PC (see Table 177 for more details)	5-FU + Folinic Acid Axitinib Capecitabine Cetuximab Cisplatin Erlotinib Erlotinib + Bevacizumab Exatecan Irinotecan Marimastat Nab-Paclitaxel Oxaliplatin Pemetrexed Sorafenib Tipifarnib		
Irigoyen et al. 2017 Spain	Phase IIb RCT	120 patients with metastatic PC	Gemcitabine,Capecitabine + Erlotinib	GEM + Erlonitib	Overall response rate (CR + PR) Progression-free Survival Overall Survival Adverse Events
Ji et al. 2003 China	Multicentre Phase III RCT	29 patients with metastatic PC	Regional intra-arterial Chemotherapy	Systemic Chemotherapy	Overall response rate (CR + PR) Overall Survival*
Kindler et al. 2010 USA	Multicentre Phase III RCT	602 patients with locally advanced/metastatic PC	Gemcitabine + Bevacizumab	Gemcitabine + Placebo	Response rate Overall Survival Adverse Events
Lee et al. 2017 South Korea	Multicentre Phase III RCT	214 patients with locally advanced/metastatic PC	Gemcitabine + Capecitabine	Gemcitabine	Overall response rate (CR + PR) Progression-free Survival Overall Survival Adverse Events

Study ID Country	Study design	Participants	Intervention	Comparison	Outcomes
Maisey et al. 2002 UK	Phase III RCT	209 patients with locally advanced/metastatic PC	5-FU + Mitomycin	5-FU	Overall response rate (CR + PR) Progression free survival Overall Survival Adverse Events
Maraveyas et al. 2012 UK	Phase IIb RCT	123 patients with advanced/metastatic	Gemcitabine + weight-adjusted Dalteparin	Gemcitabine	Overall Survival* Adverse Events
Middleton et al. 2014 UK	Multicentre Phase III RCT	1062 patients with locally advanced/metastatic PC	Sequential ICT: Chemotherapy then GV1001 Concurrent ICT: Chemotherapy + GV1001	Chemotherapy	Overall response rate (CR + PR) at 8 weeks Time to progression Overall Survival Adverse Events Health-related quality of life
Middleton et al. 2017 UK	Multicentre Phase II RCT	142 patients with locally advanced/metastatic PC	Gemcitabine + Vandetanib	Gemcitabine + Placebo	Overall response rate (CR + PR) Progression-free Survival Overall Survival Adverse Events
Moinpour et al. 20104 Canada, USA	Multicentre Phase III RCT	720 patients with locally advanced/metastatic PC	Gemcitabine + Cetuximab	Gemcitabine	Health-related quality of life Patient experience and PROMs
Moore et al. 2003 Canada	Multicentre Phase III RCT	277 patients with locally advanced/metastatic PC	BAY 12-9566	Gemcitabine	Overall response rate (CR + PR) Progression-free Survival Overall Survival Adverse Events Health-related quality of life
Oettle et al. 2014	Multicentre Phase III RCT	160 patients with locally	Second-line Folinic Acid + 5-FU	Second-line Oxaliplatin + 5-FU	Progression-free Survival

Study ID Country	Study design	Participants	Intervention	Comparison	Outcomes
Germany		advanced/metastatic PC			Overall Survival Adverse Events
Oster et al. 1986 USA	Phase III RCT	184 patients with locally advanced/metastatic PC	5-FU, Adriamycin (Doxorubicin) + Mitomycin	5-FU, Streptozotocin, Mitomycin (n=94)	Overall response rate (CR + PR) Overall Survival* Adverse Events
Pelzer et al. 2015 Germany	Multicentre Phase III RCT	312 patients with locally advanced/metastatic PC	Chemotherapy + Prophylactic Enoxaparin	Chemotherapy	Progression-free Survival Overall Survival Adverse Events
Rougier et al. 2013 Belgium, France, Germany, Czech Republic, US	Multicentre Phase III RCT	546 patients with metastatic PC	Gemcitabine + Aflibercept	Gemcitabine + Placebo	Progression-free Survival Overall Survival Adverse Events
Sakamoto et al. 2006 Japan	Phase III RCT	21 patients with locally advanced/metastatic PC	Gemcitabine infusion at a low dose	Gemcitabine infusion at a standard dose	Overall response rate (CR + PR) until disease progression Overall Survival* Adverse Events
Smith et al. 2003 France, Germany, Sweden, Netherlands, Norway, UK	Multicentre Phase II/III RCT	55 patients with locally advanced/metastatic PC	ZD9331	Gemcitabine	Overall response rate (CR + PR) until disease progression Adverse Events
Sudo et al. 2014 Japan	Multicentre Phase III RCT	101 patients with locally advanced/metastatic PC	Gemcitabine + S-1	Gemcitabine	Response rate Progression-free Survival Overall Survival Adverse Events

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Study ID Country	Study design	Participants	Intervention	Comparison	Outcomes
Ueno et al. 2013 Japan, Taiwan	Multicentre Phase III RCT	834 patients with locally advanced/metastatic PC	Gemcitabine + S-1	Gemcitabine S-1	Response rate Progression-free Survival Overall Survival Adverse Events Health-related quality of life
Ulrich-Pur et al. 2003 Austria	RCT	38 patients with metastatic PC	Irinotecan + Raltitrexed	Raltitrexed	Objective/complete response Adverse Events
Wang et al. 2013 China	Multicentre Phase III RCT	58 patients with locally advanced/metastatic PC	Second-line S-1 + Cytokine-induced killer cells	Second-line S-1	Response rate Overall Survival* Adverse Events
Yamaue et al. 2015 Japan	Multicentre Phase III RCT	153 patients with locally advanced/metastatic PC	Gemcitabine + Elpamotide	Gemcitabine + Placebo	Progression-free Survival* Overall Survival Adverse Events

*Notes: *, indicates incompletely reported results*
1 See also Table 177, entry for Herrmann et al. 2007;
2 See also Table 177, entry for Conroy et al. 2011;
3 See also Table 177, entry for Philip et al., 2010.

Table 177: Summary of studies included in NMA

Study ID Country	Study design	Participants	Intervention	Comparison	Outcomes
Abou-Alfa et al. 2006 USA	Multicentre Phase III RCT	349 patients with locally advanced/metastatic PC	Gemcitabine + Exatecan	Gemcitabine	Response rate Progression-free Survival Adverse Events
Berlin et al. 2002 USA	Multicentre Phase III RCT	322 patients with locally advanced/metastatic PC	Gemcitabine + 5-FU	Gemcitabine	Response rate Progression-free Survival Adverse Events

Study ID Country	Study design	Participants	Intervention	Comparison	Outcomes
Bramhall et al. 2002 UK	Multicentre double-blind Phase III RCT	239 patients with locally advanced/metastatic PC	Gemcitabine + Marimastat	Gemcitabine	Response rate Progression-free Survival Adverse Events
Colucci et al. 2010 Italy	Multicentre Phase III RCT	400 patients with metastatic PC	Gemcitabine + Cisplatin	Gemcitabine	Response rate Progression-free Survival Adverse Events
Conroy et al. 2011 France	Multicentre Phase III RCT	342 patients with metastatic PC	FOLFIRINOX (Oxaliplatin, Irinotecan, 5-FU + Leucovorin)	Gemcitabine	Response rate Progression-free Survival Adverse Events Health-related quality of life1
Cunningham et al. 2009 UK, Switzerland, Austria	Multicentre non-blinded Phase III RCT	533 patients with locally advanced/metastatic PC	Gemcitabine + Capecitabine	Gemcitabine	Response rate Progression-free Survival Adverse Events
Gonçalves et al. 2012 France	Multicentre double-blind Phase III RCT	104 patients with locally advanced/metastatic PC	Gemcitabine + Sorafenib	Gemcitabine	Response rate Progression-free Survival Adverse Events
Heinemann et al. 2006 Germany	Multicentre non-blinded Phase III RCT	194 patients with locally advanced/metastatic PC	Gemcitabine + Cisplatin	Gemcitabine	Response rate Progression-free Survival Adverse Events Health-related quality of life
Heinemann et al. 2012 Germany	Multicentre non-blinded Phase III RCT	284 patients with locally advanced/metastatic PC	Gemcitabine + Erlotinib then Capecitabine	Capecitabine + Erlotinib then Gemcitabine	Response rate Adverse Events
Herrmann et al. 2007 Switzerland, Italy, Austria, Germany	Multicentre non-blinded Phase III RCT	319 patients with locally advanced/metastatic PC	Gemcitabine + Capecitabine	Gemcitabine	Response rate Progression-free Survival Adverse Events

Study ID Country	Study design	Participants	Intervention	Comparison	Outcomes
					Health-related quality of life2
Kindler et al. 2011 USA	Multicentre double-blind Phase III RCT	313 patients with locally advanced/metastatic PC	Gemcitabine + Axitinib	Gemcitabine	Response rate Progression-free Survival Adverse Events Health-related quality of life
Louvet et al. 2005 France, Italy	Multicentre Phase III RCT	313 patients with locally advanced/metastatic PC	Gemcitabine + Oxaliplatin	Gemcitabine	Response rate Progression-free Survival Adverse Events
Moore et al. 2007 Canada	Multicentre double-blind Phase III RCT	569 patients with locally advanced/metastatic PC	Gemcitabine + Erlotinib	Gemcitabine	Response rate Progression-free Survival Adverse Events
Oettle et al. 2005 Argentina, Australia, Austria, Belgium, France, Germany, Greece, Italy, The Netherlands, Peru, Portugal, Spain, Sweden, Taiwan, UK, US, Venezuela	Multicentre non-blinded Phase III RCT	565 patients with locally advanced/metastatic PC	Gemcitabine + Pemetrexed	Gemcitabine	Response rate Progression-free Survival Adverse Events
Philip et al. 2010 USA	Multicentre non-blinded Phase III RCT	741 patients with locally advanced/metastatic PC	Gemcitabine + Cetuximab	Gemcitabine	Response rate Progression-free Survival Adverse Events Health-related quality of life3
Poplin et al. 2006 (2009) USA	Multicentre Phase III RCT	547 patients with locally	Gemcitabine + oxaliplatin	Gemcitabine	Response rate Progression-free Survival Adverse Events

Study ID Country	Study design	Participants	Intervention	Comparison	Outcomes
		advanced/metastatic PC			
Reni et al. 2005 Italy	Multicentre non-blinded Phase III RCT	99 patients with locally advanced/metastatic PC	PEFG	Gemcitabine	Response rate Progression-free Survival Health-related quality of life4
Riess et al. 2005 Germany	Multicentre Phase III RCT	463 patients with locally advanced/metastatic PC	Gemcitabine, 5-FU + Folinic Acid	Gemcitabine	Unclear (coinference abstract)
Rocha Lima et al. 2004 New Zealand, USA	Multicentre Phase III RCT	360 patients with locally advanced/metastatic PC	Gemcitabine + Irinotecan	Gemcitabine	Response rate Progression-free Survival Health-related quality of life
Stathopoulos et al. 2006 Greece	Multicentre Phase III RCT	130 patients with locally advanced/metastatic PC	Gemcitabine + Irinotecan	Gemcitabine	Response rate Progression-free Survival Adverse Events
Van-Cutsem et al. 2004 Belgium, Germany, Czech Republic, Netherlands Poland, USA	Multicentre double-blind Phase III RCT	688 patients with locally advanced/metastatic PC	Gemcitabine + Tipifarnib	Gemcitabine	Response rate Progression-free Survival Adverse Events Health-related quality of life
Van-Cutsem et al. 2009 Australia, Austria, Belgium, Canada, China, Czech Republic, France, Germany, Italy, Netherlands, Peru, Poland, Singapore,	Multicentre double-blind Phase III RCT	607 patients with metastatic PC	Gemcitabine + Erlotinib	Gemcitabine, Erlotinib + Bevacizumab	Response rate Progression-free Survival Adverse Events

Study ID Country	Study design	Participants	Intervention	Comparison	Outcomes
Sweden, Taiwan, UK					
Von-Hoff et al. 2013 Australia, Austria, Belgium, Canada, Czech Republic, France, Germany, , Italy, Poland, Russia, Spain, Ukraine, USA	Multicentre non-blinded Phase III RCT	871 patients with metastatic PC	Gemcitabine + Nab-paclitaxel	Gemcitabine	Response rate Progression-free Survival Adverse Events

Notes: 1 See Table 176, data from Gourgou-Bourgade et al. 2013;
2 See Table 176, data from Bernhard et al. 2008;
3 See Table 176, data from Moinpour et al. 2010;

11.2.4 Clinical evidence profile

The clinical evidence profiles for this review question are presented in Table 178 to Table 210.

11.2.4.1 Chemotherapy versus chemoimmunotherapy

11.2.4.1.1 First-line chemotherapy with sequential or concurrent immunotherapy versus chemotherapy

Table 178: Summary clinical evidence profile for first-line chemotherapy with sequential or concurrent immunotherapy versus chemotherapy in adults with locally advanced or metastatic pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Chemotherapy alone	1st-line chemotherapy + sequential/concurrent immunotherapy				
Overall response rate (CR + PR) at 8 weeks - Sequential ICT	73 per 1000	71 per 1000 (42 to 121)	RR 0.98 (0.58 to 1.67)	708 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Overall response rate (CR + PR) at 8 weeks - Concurrent ICT	73 per 1000	82 per 1000 (49 to 137)	RR 1.13 (0.68 to 1.88)	712 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Time to progression - Sequential ICT	Median time: 6.4 (4.8 to 7.1) months	Median time: 4.5 (4.3 to 4.6) months	HR 1.5 (1.26 to 1.79)	708 (1 study[1])	⊕⊕⊕⊖ moderate[2]	
Time to progression - Concurrent ICT	Median time: 6.4 (4.8 to 7.1) months	Median time: 4.5 (4.3 to 4.6) months	HR 1 (0.84 to 1.19)	712 (1 study[1])	⊕⊕⊖⊖ low[2,4]	
Overall Survival - Sequential ICT	Median time: 7.9 (7.1 to 8.8) months	Median time: 6.9 (6.4 to 7.6) months	HR 1.19 (0.97 to 1.48)	708 (1 study[1])	⊕⊕⊖⊖ low[2,4]	
Overall Survival - Concurrent ICT	Median time: 7.9 (7.1 to 8.8) months	Median time: 6.6 (5.0 to 7.3) months	HR 1.05 (0.85 to 1.29)	712 (1 study[1])	⊕⊕⊖⊖ low[2,4]	
Grade 3/4/5 toxicities: Nausea - Sequential ICT	36 per 1000	43 per 1000 (21 to 89)	RR 1.18 (0.57	708 (1 study[1])	⊕⊖⊖⊖	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
			to 2.44)		very low[2,3]	
Grade 3/4/5 toxicities: Nausea - Concurrent ICT	36 per 1000	57 per 1000 (29 to 112)	RR 1.56 (0.79 to 3.08)	712 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Grade 3/4/5 toxicities: Vomiting - Sequential ICT	47 per 1000	51 per 1000 (27 to 98)	RR 1.08 (0.57 to 2.07)	708 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Grade 3/4/5 toxicities: Vomiting - Concurrent ICT	47 per 1000	62 per 1000 (34 to 115)	RR 1.31 (0.71 to 2.42)	712 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Grade 3/4/5 toxicities: Diarrhoea - Sequential ICT	47 per 1000	31 per 1000 (15 to 66)	RR 0.66 (0.31 to 1.39)	708 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Grade 3/4/5 toxicities: Diarrhoea - Concurrent ICT	47 per 1000	31 per 1000 (15 to 66)	RR 0.65 (0.31 to 1.38)	712 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Grade 3/4/5 toxicities: Fatigue - Sequential ICT	75 per 1000	103 per 1000 (64 to 166)	RR 1.36 (0.85 to 2.2)	708 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Grade 3/4/5 toxicities: Fatigue - Concurrent ICT	75 per 1000	124 per 1000 (78 to 196)	RR 1.65 (1.04 to 2.6)	712 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Grade 3/4/5 toxicities: Neutropenia - Sequential ICT	190 per 1000	165 per 1000 (120 to 228)	RR 0.87 (0.63 to 1.2)	708 (1 study[1])	⊕⊕⊖⊖ low[2,3]	
Grade 3/4/5 toxicities: Neutropenia - Concurrent ICT	190 per 1000	222 per 1000 (167 to 298)	RR 1.17 (0.88 to 1.57)	712 (1 study[1])	⊕⊕⊖⊖ low[2,5]	
Grade 3/4/5 toxicities: Pain - Sequential ICT	95 per 1000	111 per 1000 (72 to 172)	RR 1.17 (0.76 to 1.81)	708 (1 study[1])	⊕⊕⊖⊖ low[2,5]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Grade 3/4/5 toxicities: Pain - Concurrent ICT	95 per 1000	119 per 1000 (77 to 182)	RR 1.25 (0.81 to 1.92)	712 (1 study[1])	⊕⊕⊖⊖ low[2,5]	
Health Related Quality of Life at 20 weeks (EORTC QLQ-C30) - Sequential ICT		The mean health related quality of life at 20 weeks (EORTC QLQ-C30) - sequential ICT in the intervention groups was 11.1 lower (24.28 lower to 2.08 higher)		708 (1 study[1])	⊕⊕⊖⊖ low[2,5]	
Health Related Quality of Life at 20 weeks (EORTC QLQ-C30) - Concurrent ICT		The mean health related quality of life at 20 weeks (EORTC QLQ-C30) - concurrent ICT in the intervention groups was 1.7 higher (10.46 lower to 13.86 higher)		704 (1 study[1])	⊕⊕⊖⊖ low[2,5]	

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;

1 Middleton et al., 2014
2 The quality of the evidence was downgraded because of the high risk of performance bias (no blinding of patients/ care providers delivering the interventions)
3 Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs
4 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. The quality of the evidence for this outcome was therefore downgraded for imprecision by one level as it was not statistically significant.
5 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID

11.2.4.1.2 Second-line chemoimmunotherapy versus chemotherapy

Table 179: Summary clinical evidence profile for second-line chemoimmunotherapy versus chemotherapy in adults with locally advanced or metastatic pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Chemotherapy alone	2nd-line chemotherapy + concurrent immunotherapy				

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Overall response rate (CR + PR) - unclear follow-up	67 per 1000	71 per 1000 (11 to 473)	RR 1.07 (0.16 to 7.1)	58 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Progression Free Survival	-	-	Not estimable [4]	58 (1 study[1])	⊕⊕⊖⊖ low[5]	
Overall Survival	-	-	Not estimable [4]	58 (1 study[1])	⊕⊕⊖⊖ low[2]	
Grade 3/4 toxicities - Neutropenia	33 per 1000	36 per 1000 (2 to 544)	RR 1.07 (0.07 to 16.32)	58 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Grade 3/4 toxicities - Nausea/vomiting	33 per 1000	12 per 1000 (1 to 280)	RR 0.36 (0.02 to 8.4)	58 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Grade 3/4 toxicities - Diarrhoea	67 per 1000	71 per 1000 (11 to 473)	RR 1.07 (0.16 to 7.1)	58 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Grade 3/4 toxicities - Fatigue	33 per 1000	12 per 1000 (1 to 280)	RR 0.36 (0.02 to 8.4)	58 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;

1 Wang et al., 2013
2 The quality of the evidence was downgraded of two points because of the unclear risk of selection bias, the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions) and the unclear risk of detention bias (no masking of outcome assessors)
3 The quality of the evidence was further downgraded from low to very low due to serious imprecision as 95%CI crossed two default MIDs
4 The median time to progression was 2.5 (95 % CI 2.3–2.8) and 2.9 (95 % CI 2.6–3.2) months (p = 0.037) for CT group and ICT group, respectively. The median overall survival was 6.1 (95 % CI 5.7–6.5) and 6.6 (95 % CI 6.1–7.1) months (p = 0.09) for CT group and ICT group, respectively.
5 The quality of the evidence was downgraded because of the unclear risk of selection bias and the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions). Furthermore, for this outcome the findings were reported only narratively (potential bias due to selective reporting)

11.2.4.2 Gemcitabine versus other chemotherapy

11.2.4.2.1 Adults with metastatic pancreatic cancer

Table 180: Summary clinical evidence profile for gemcitabine versus other chemotherapy (Response rate, overall survival and progression-free survival)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Exp. Chemotherapy	GEM alone				
Overall response rate (CR + PR) - FOLFIRINOX	94 per 1000	316 per 1000 (188 to 529)	RR 3.38 (2.01 to 5.65)	342 (1 study[1])	⊕⊕⊕⊕ high	
Overall response rate (CR + PR) - GEM + Cisplatin	98 per 1000	122 per 1000 (71 to 207)	RR 1.25 (0.73 to 2.12)	445 (2 studies[2,3])	⊕⊖⊖⊖ very low[4,5]	
Overall response rate (CR + PR) - GEM + Ganitumab 12 mg/kg	102 per 1000	161 per 1000 (106 to 244)	RR 1.58 (1.04 to 2.39)	619 (1 study6)	⊕⊕⊕⊖ moderate[7]	
Overall response rate (CR + PR) - GEM + Ganitumab 20 mg/kg	102 per 1000	147 per 1000 (89 to 244)	RR 1.44 (0.87 to 2.39)	464 (1 study6)	⊕⊕⊕⊖ moderate[7]	
Progression Free Survival - FOLFIRINOX	Median time: 6.4 (n.r) months	Median time: 3.3(n.r) months	HR 0.47 (0.32 to 0.69)	342 (1 study[1])	⊕⊕⊕⊕ high	
Progression Free Survival - GEM + Aflibercept	Median time: 3.7(n.r) months	Median time: 3.7(n.r) months	HR 1.02 (0.83 to 1.25)	546 (1 study[8])	⊕⊕⊕⊖ moderate [9]	
Progression Free Survival - GEM + Cisplatin	Median time: 3.8 (n.r) months	Median time: 3.9(n.r) months	HR 0.97 (0.8 to 1.18)	400 (1 study[3])	⊕⊕⊖⊖ low [9,10]	
Progression Free Survival - GEM + Ganitumab - 12 mg/kg	Median time: 3.7 (3.6 to 4.4) months	Median time: 3.6 (3.4 to 3.8) months	HR 1 (0.84 to 1.19)	650 (1 study[6])	⊕⊕⊕⊖ moderate [9]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Progression Free Survival - GEM + Ganitumab - 20 mg/kg	Median time: 3.7 (3.6 to 4.4) months	Median time: 3.7 (3.2 to 5.0) months	HR 0.97 (0.77 to 1.22)	482 (1 study[6])	⊕⊕⊕⊖ moderate [9]	
Overall Survival - GEM + Aflibercept	Median time: 6.5 (5.6 to 7.9) months	Median time: 7.8 (6.8 to 8.6) months	HR 1.17 (0.92 to 1.49)	546 (1 study[8])	⊕⊕⊕⊖ moderate [9]	
Overall Survival - GEM + Cisplatin	-	-	HR 0.92 (0.76 to 1.11)	400 (2 studies[2,3])	⊕⊕⊖⊖ low [9,10]	
Overall Survival - GEM + Ganitumab - 12 mg/kg	Median time: 7.0 (6.2 to 8.5) months	Median time: 7.2 (6.3 to 8.2) months	HR 1 (0.82 to 1.22)	650 (1 study[6])	⊕⊕⊕⊖ moderate [9]	
Overall Survival - GEM + Ganitumab - 20 mg/kg	Median time: 7.1 (6.3 to 8.5) months	Median time: 7.2 (6.3 to 8.2) months	HR 0.97 (0.76 to 1.24)	482 (1 study[6])	⊕⊕⊕⊖ moderate [9]	

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;

1 Conroy et al., 2011
2 Chao et al., 2013
3 Colucci et al., 2010
4 The quality of the evidence was downgraded because of the unclear risk of selection bias (no details provided in the text) in one study (Chao et al., 2013), besides the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions), and detection bias in both pooled studies
5 Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs
6 Fuchs et al., 2015
7 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID
8 Rougier et al., 2013
9 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant
10 The quality of the evidence was downgraded because of the unclear risk of performance bias (no blinding of patients/ care providers delivering the interventions) and the potential risk of detection bias (no details about the blinding of outcome assessors)

Table 181: Summary clinical evidence profile for gemcitabine versus other chemotherapy (Adverse events)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Exp. Chemotherapy	GEM alone				

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Grade 3/4 toxicities: Diarrhoea - FOLFIRINOX	18 per 1000	127 per 1000 (39 to 419)	RR 7.17 (2.18 to 23.58)	334 (1 study[1])	⊕⊕⊕⊕ high	
Grade 3/4 toxicities: Diarrhoea - GEM + Aflibercept	11 per 1000	11 per 1000 (2 to 55)	RR 1 (0.2 to 4.93)	541 (1 study[2])	⊕⊕⊖⊖ low[3]	
Grade 3/4 toxicities: Diarrhoea - GEM + Cisplatin	14 per 1000	5 per 1000 (1 to 45)	RR 0.34 (0.04 to 3.23)	421 (2 studies[4,5])	⊕⊖⊖⊖ very low[3,6]	
Grade 3/4 toxicities: Diarrhoea - GEM + Ganitumab 12 mg/kg	3 per 1000	10 per 1000 (1 to 91)	RR 3.02 (0.32 to 28.87)	632 (1 study[7])	⊕⊕⊖⊖ low[3]	
Grade 3/4 toxicities: Diarrhoea - GEM + Ganitumab 20 mg/kg	3 per 1000	12 per 1000 (1 to 137)	RR 3.96 (0.36 to 43.37)	477 (1 study[7])	⊕⊕⊖⊖ low[3]	
Grade 3/4 toxicities: Fatigue - FOLFIRINOX	178 per 1000	236 per 1000 (154 to 362)	RR 1.33 (0.87 to 2.04)	334 (1 study[1])	⊕⊕⊕⊖ moderate[8]	
Grade 3/4 toxicities: Fatigue - GEM + Cisplatin	32 per 1000	54 per 1000 (20 to 145)	RR 1.69 (0.63 to 4.57)	375 (1 study[5])	⊕⊖⊖⊖ very low[3,9]	
Grade 3/4 toxicities: Fatigue - GEM + Ganitumab 12 mg/kg	38 per 1000	60 per 1000 (30 to 122)	RR 1.59 (0.79 to 3.23)	632 (1 study[7])	⊕⊕⊖⊖ low[3]	
Grade 3/4 toxicities: Fatigue - GEM + Ganitumab 20 mg/kg	38 per 1000	50 per 1000 (21 to 120)	RR 1.32 (0.55 to 3.17)	477 (1 study[7])	⊕⊕⊖⊖ low[3]	
Grade 3/4 toxicities: Neutropenia - FOLFIRINOX	210 per 1000	457 per 1000 (327 to 641)	RR 2.18 (1.56 to 3.06)	331 (1 study[1])	⊕⊕⊕⊕ high	
Grade 3/4 toxicities: Neutropenia - GEM + Aflibercept	240 per 1000	305 per 1000 (230 to 401)	RR 1.27 (0.96	541 (1 study[2])	⊕⊕⊕⊖ moderate[8]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
			to 1.67)			
Grade 3/4 toxicities: Neutropenia - GEM + Cisplatin	131 per 1000	241 per 1000 (158 to 366)	RR 1.84 (1.21 to 2.8)	421 (2 studies[4,5])	⊕⊕⊖⊖ low[6,8]	
Grade 3/4 toxicities: Neutropenia - GEM + Ganitumab 20 mg/kg	205 per 1000	463 per 1000 (353 to 609)	RR 2.26 (1.72 to 2.97)	477 (1 study[7])	⊕⊕⊕⊕ high	
Grade 3/4 toxicities: Neutropenia - GEM + Ganitumab 12 mg/kg	205 per 1000	98 per 1000 (66 to 146)	RR 0.48 (0.32 to 0.71)	632 (1 study[7])	⊕⊕⊕⊕ high	
Grade 3/4 toxicities: Nausea/Vomiting - FOLFIRINOX	83 per 1000	145 per 1000 (78 to 270)	RR 1.75 (0.94 to 3.26)	335 (1 study[1])	⊕⊕⊕⊖ moderate[8]	
Grade 3/4 toxicities: Nausea/Vomiting - GEM + Aflibercept	37 per 1000	78 per 1000 (37 to 162)	RR 2.11 (1.01 to 4.39)	541 (1 study[2])	⊕⊕⊕⊖ moderate[8]	
Grade 3/4 toxicities: Nausea/Vomiting - GEM + Cisplatin	19 per 1000	34 per 1000 (10 to 116)	RR 1.83 (0.54 to 6.2)	421 (2 studies[4,5])	⊕⊖⊖⊖ very low[3,6]	
Grade 3/4 toxicities: Nausea/Vomiting - GEM + Ganitumab 12 mg/kg	63 per 1000	61 per 1000 (33 to 111)	RR 0.96 (0.52 to 1.76)	632 (1 study7)	⊕⊕⊖⊖ low[3]	
Grade 3/4 toxicities: Nausea/Vomiting - GEM + Ganitumab 20 mg/kg	63 per 1000	32 per 1000 (12 to 82)	RR 0.5 (0.19 to 1.3)	477 (1 study[7])	⊕⊕⊖⊖ low[3]	
Grade 3/4 toxicities: Thrombocytopenia - FOLFIRINOX	36 per 1000	91 per 1000 (36 to 229)	RR 2.55 (1.01 to 6.4)	333 (1 study[1])	⊕⊕⊕⊖ moderate[8]	
Grade 3/4 toxicities: Thrombocytopenia - GEM + Aflibercept	63 per 1000	111 per 1000 (63 to 196)	RR 1.77 (1 to 3.13)	541 (1 study[2])	⊕⊕⊕⊖ moderate[8]	
Grade 3/4 toxicities:	51 per 1000	164 per 1000 (86 to 316)	RR 3.2 (1.67	421 (2 studies[4,5])	⊕⊕⊕⊖ moderate[6]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Thrombocytopenia - GEM + Cisplatin			to 6.14)			
Grade 3/4 toxicities: Thrombocytopenia - GEM + Ganitumab 12 mg/kg	66 per 1000	85 per 1000 (50 to 148)	RR 1.29 (0.75 to 2.24)	632 (1 study[7])	⊕⊕⊖⊖ low[3]	
Grade 3/4 toxicities: Thrombocytopenia - GEM + Ganitumab 20 mg/kg	66 per 1000	75 per 1000 (38 to 148)	RR 1.13 (0.57 to 2.24)	477 (1 study[7])	⊕⊕⊖⊖ low[3]	
Grade 3/4 toxicities: Leucopoenia - GEM + Cisplatin	47 per 1000	88 per 1000 (42 to 186)	RR 1.89 (0.9 to 3.98)	421 (2 studies[4,5])	⊕⊕⊖⊖ low[6,8]	
Grade 3/4 toxicities: Leucopoenia - GEM + Ganitumab 12 mg/kg	28 per 1000	48 per 1000 (21 to 107)	RR 1.68 (0.74 to 3.78)	632 (1 study[7])	⊕⊕⊖⊖ low[3]	
Grade 3/4 toxicities: Leucopoenia - GEM + Ganitumab 20 mg/kg	28 per 1000	25 per 1000 (8 to 80)	RR 0.88 (0.28 to 2.82)	477 (1 study[7])	⊕⊕⊖⊖ low[3]	
The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). *CI: Confidence interval; RR: Risk ratio;*						
1 Conroy et al., 2011 *2 Rougier et al., 2013* *3 Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs* *4 Chao et al., 2013* *5 Colucci et al., 2010* *6 The quality of the evidence was downgraded because of the unclear risk of selection bias (no details provided in the text) in one study (Chao et al., 2013), besides the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions), and detection bias in both pooled studies* *7 Fuchs et al., 2015* *8 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID* *9 The quality of the evidence was downgraded because of the unclear risk of performance bias (no blinding of patients/ care providers delivering the interventions) and the potential risk of detection bias (no details about the blinding of outcome assessors)*						

Table 182: Summary clinical evidence profile for gemcitabine versus other chemotherapy (Health-related quality of life)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Exp. Chemotherapy	GEM alone				

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
HRQL - Number of patients with a clinically significant (10 point) deterioration QLQ-C30 - Global health status	204 per 1000	79 per 1000 (43 to 147)	RR 0.39 (0.21 to 0.72)	320 (1 study[1])	⊕⊕⊕⊕ high	
HRQL - Number of patients with a clinically significant (10 point) deterioration QLQ-C30 - Physical functioning	236 per 1000	165 per 1000 (106 to 259)	RR 0.7 (0.45 to 1.1)	320 (1 study[1])	⊕⊕⊕⊖ moderate[2]	
HRQL - Number of patients with a clinically significant (10 point) deterioration QLQ-C30 - Role functioning	274 per 1000	164 per 1000 (107 to 255)	RR 0.6 (0.39 to 0.93)	320 (1 study[1])	⊕⊕⊕⊖ moderate[2]	
HRQL - Number of patients with a clinically significant (10 point) deterioration QLQ-C30 - Emotional functioning	89 per 1000	86 per 1000 (42 to 174)	RR 0.96 (0.47 to 1.95)	320 (1 study[1])	⊕⊕⊖⊖ low[3]	
HRQL - Number of patients with a clinically significant (10 point) deterioration QLQ-C30 - Cognitive functioning	102 per 1000	67 per 1000 (33 to 141)	RR 0.66 (0.32 to 1.38)	320 (1 study[1])	⊕⊕⊖⊖ low[3]	
HRQL - Number of patients with a clinically significant (10 point) deterioration QLQ-C30 - Social functioning	255 per 1000	140 per 1000 (89 to 224)	RR 0.55 (0.35 to 0.88)	320 (1 study[1])	⊕⊕⊕⊕ high	
HRQL - Number of patients with a clinically significant (10 point) deterioration QLQ-C30 - Fatigue	312 per 1000	222 per 1000 (153 to 318)	RR 0.71 (0.49 to 1.02)	320 (1 study[1])	⊕⊕⊕⊖ moderate[2]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
HRQL - Number of patients with a clinically significant (10 point) deterioration QLQ-C30 - Nausea/vomiting	191 per 1000	117 per 1000 (69 to 199)	RR 0.61 (0.36 to 1.04)	320 (1 study[1])	⊕⊕⊕⊖ moderate [2]	
HRQL - Number of patients with a clinically significant (10 point) deterioration QLQ-C30 - Pain	140 per 1000	74 per 1000 (38 to 144)	RR 0.53 (0.27 to 1.03)	320 (1 study[1])	⊕⊕⊕⊖ moderate [2]	
HRQL - Number of patients with a clinically significant (10 point) deterioration QLQ-C30 - Dyspnea	242 per 1000	196 per 1000 (131 to 298)	RR 0.81 (0.54 to 1.23)	320 (1 study[1])	⊕⊕⊕⊖ moderate [2]	
HRQL - Number of patients with a clinically significant (10 point) deterioration QLQ-C30 - Insomnia	96 per 1000	122 per 1000 (65 to 231)	RR 1.28 (0.68 to 2.42)	320 (1 study[1])	⊕⊕⊖⊖ low[3]	
HRQL - Number of patients with a clinically significant (10 point) deterioration QLQ-C30 - Loss of appetite	178 per 1000	148 per 1000 (89 to 243)	RR 0.83 (0.5 to 1.36)	320 (1 study[1])	⊕⊕⊖⊖ low[3]	
HRQL - Number of patients with a clinically significant (10 point) deterioration QLQ-C30 - Constipation	134 per 1000	111 per 1000 (62 to 199)	RR 0.83 (0.46 to 1.49)	320 (1 study[1])	⊕⊕⊖⊖ low[3]	
HRQL - Number of patients with a clinically significant (10 point) deterioration QLQ-C30 - Diarrhoea	204 per 1000	226 per 1000 (149 to 344)	RR 1.11 (0.73 to 1.69)	320 (1 study[1])	⊕⊕⊖⊖ low[3]	
HRQL - Number of patients with a clinically significant (10 point) deterioration QLQ-C30 -	51 per 1000	135 per 1000 (62 to 294)	RR 2.65 (1.22 to 5.77)	320 (1 study[1])	⊕⊕⊖⊖ low[3]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Financial difficulties Follow-up: - between baseline and the end of treatment (6 months).3						
The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). *CI: Confidence interval; RR: Risk ratio;*						
1 Gourgou-Bourgade et al., 2013 *2 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID* *3 Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs* *4 between baseline and the end of treatment (6 months)*						

Table 183: Summary clinical evidence profile for gemcitabine and erlotinib versus gemcitabine, erlotinib and capecitabine

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	GEM + erlotinib + capecitabine	GEM + erlotinib				
Overall response rate (CR + PR)	183 per 1000	216 per 1000 (106 to 446)	RR 1.18 (0.58 to 2.43)	120 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Progression Free Survival	Median time: 4.3 (n.r.) months	Median time: 3.8 (n.r.) months	HR 0.88 (0.58 to 1.34)	120 (1 study[1])	⊕⊕⊕⊖ moderate[4]	
Overall survival	Median time: 6.8 (n.r.) months	Median time: 7.7 (n.r.) months	HR 1.09 (0.72 to 1.65)	120 (1 study[1])	⊕⊕⊕⊖ moderate[4]	
Grade 3/4 toxicities: any[5]	567 per 1000	725 per 1000 (550 to 952)	RR 1.28 (0.97 to 1.68)	118 (1 study[1])	⊕⊕⊖⊖ low[2,4]	
**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).* *CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;*						
1 Irigoyen et al., 2017 *2 The quality of the evidence was downgraded because of the unclear risk of selection bias and potential risk of performance bias (open-label trial)* *3 Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs* *4 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. The quality of the evidence for this outcome was therefore downgraded for imprecision by one level as it was not statistically significant.* *5 including asthenia, diarrhoea, neutropenia, reduced appetite, thrombocytopenia, nausea, anaemia, rash, constipation, mucositis, vomiting, pyrexia, elevated GGT, hand - foot syndrome, and peripheral oedema)*						

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				

6 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID

11.2.4.2.2 Adults with locally advanced or metastatic pancreatic cancer

Table 184: Summary clinical evidence profile for gemcitabine versus other chemotherapy (Response rate)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Exp. Chemotherapy	Corresponding risk GEM alone				
Overall response rate (CR + PR) - 5-FU single-agent	48 per 1000	7 per 1000 (0 to 129)	RR 0.14 (0.01 to 2.71)	126 (1 study[1])	⊕⊕⊖⊖ low[2]	
Overall response rate (CR + PR) - S-1 single-agent	133 per 1000	210 per 1000 (141 to 313)	RR 1.58 (1.06 to 2.36)	489 (1 study[3])	⊕⊕⊕⊖ moderate[4]	
Overall response rate (CR + PR) - GEM + 5-FU	56 per 1000	69 per 1000 (29 to 162)	RR 1.24 (0.53 to 2.91)	322 (1 study[5])	⊕⊖⊖⊖ very low[2,6]	
Overall response rate (CR + PR) - GEM + Axitinib	13 per 1000	39 per 1000 (13 to 121)	RR 3.03 (0.99 to 9.29)	613 (1 study[7])	⊕⊕⊕⊖ moderate[4]	
Overall response rate (CR + PR) - GEM + Bevacizumab	100 per 1000	129 per 1000 (82 to 202)	RR 1.29 (0.82 to 2.02)	602 (1 study[8])	⊕⊕⊖⊖ low[2]	
Overall response rate (CR + PR) - GEM + Capecitabine	116 per 1000	198 per 1000 (148 to 264)	RR 1.70 (1.27 to 2.27)	1050 (3 studies[9,10,11])	⊕⊕⊕⊖ moderate[4]	
Overall response rate (CR + PR) - GEM + Cetuximab	69 per 1000	85 per 1000 (50 to 145)	RR 1.22 (0.72 to 2.08)	660 (1 study[12])	⊕⊖⊖⊖ very low[2,13]	
Overall response rate (CR +	82 per 1000	102 per 1000 (42 to 247)	RR 1.24	195 (1 study[14])	⊕⊖⊖⊖ very low[2,11]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
PR) - GEM + Cisplatin			(0.51 to 3)			
Overall response rate (CR + PR) - PEFG	85 per 1000	385 per 1000 (142 to 1000)	RR 4.52 (1.67 to 12.27)	99 (1 study[15])	⊕⊕⊕⊖ moderate[11]	
Overall response rate (CR + PR) - GEM + Exatecan	52 per 1000	69 per 1000 (29 to 159)	RR 1.33 (0.57 to 3.07)	349 (1 study)	⊕⊖⊖⊖ very low[2,6]	
Overall response rate (CR + PR) - GEM + Irinotecan	64 per 1000	160 per 1000 (92 to 281)	RR 2.5 (1.43 to 4.39)	490 (2 studies[16,17])	⊕⊕⊖⊖ low[11,18]	
Overall response rate (CR + PR) - GEM + Marimastat	118 per 1000	92 per 1000 (44 to 194)	RR 0.78 (0.37 to 1.65)	239 (1 study[19])	⊕⊕⊖⊖ low[19]	
Overall response rate (CR + PR) - GEM + Oxaliplatin	173 per 1000	268 per 1000 (175 to 412)	RR 1.55 (1.01 to 2.38)	313 (1 study)	⊕⊕⊖⊖ low[4,11]	
Overall response rate (CR + PR) - GEM + Pemetrexed	71 per 1000	148 per 1000 (89 to 246)	RR 2.09 (1.26 to 3.47)	565 (1 study[20])	⊕⊕⊕⊖ moderate[21]	
Overall response rate (CR + PR) - GEM + Sorafenib	231 per 1000	125 per 1000 (51 to 307)	RR 0.54 (0.22 to 1.33)	100 (1 study[22])	⊕⊕⊖⊖ low[2]	
Overall response rate (CR + PR) - GEM + Tipifarnib	81 per 1000	59 per 1000 (34 to 102)	RR 0.73 (0.42 to 1.26)	688 (1 study[23])	⊕⊕⊖⊖ low[2]	
Overall response rate (CR + PR) - GEM + S-1	120 per 1000	280 per 1000 (195 to 402)	RR 2.33 (1.62 to 3.34)	584 (2 studies[3,24])	⊕⊕⊕⊕ high	

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio;

1 Burris et al., 1997
2 Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs
3 Ueno et al., 2013
4 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				

5 Berlin et al., 2002
6 The quality of the evidence was downgraded because of the unclear risk of selection bias (no details provided in the text), the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions), besides the unclear risk of detection bias
7 Kindler et al., 2011
8 Kindler et al., 2010
9 Cunningham et al., 2009
10 Herrmann et al., 2007
11 The quality of the evidence was downgraded because of the unclear risk of performance bias (no blinding of patients/ care providers delivering the interventions) and detection bias
12 Philip et al., 2010
13 The quality of the evidence was downgraded because of the unclear risk of detection bias and the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions)
14 Heinemann et al., 2006
15 Reni et al., 2005
16 Rocha Lima et al., 2004
17 Stathopoulos et al., 2006
18 Serious heterogeneity. I-squared = 39%
19 Bramhall et al., 2002
20 Oettle et al., 2005
21 The quality of the evidence was downgraded because of the high risk of detection bias (no blinding of outcome assessors) and the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions)
22 Gonçalves et al., 2012
23 Van-Cutsem et al., 2004
24 Sudo et al., 2014
25 Lee et al., 2017

Table 185: Summary clinical evidence profile for gemcitabine versus other chemotherapy (Progression-free survival, overall survival)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Other Chemotherapy	GEM alone				
Progression Free Survival - S-1 single-agent	Median time: 4.1 (3.0 to 4.4) months	Median time: 3.8 (2.9 to 4.2) months	HR 1.09 (0.9 to 1.32)	834 (1 study[1])	⊕⊕⊕⊖ moderate[6]	
Progression Free Survival - GEM + 5-FU	Median time: 3.4 (n.r.) months	Median time: 2.2 (n.r) months	HR 0.77 (0.62 to 0.96)	322 (1 study[3])	⊕⊕⊕⊖ moderate[4]	
Progression Free Survival - GEM + Axitinib	Median time: 4.4 (4.0 to 5.6) months	Median time: 4.4 (3.7 to 5.2) months	HR 1.01 (0.78 to 1.3)	632 (1 study[5])	⊕⊕⊕⊖ moderate[6]	
Progression Free Survival -	-	-	HR 0.80 (0.72 to 0.90)	1050 (3	⊕⊕⊖⊖ low[4,11]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
GEM + Capecitabine				studies[7,8,29])		
Progression Free Survival - GEM + Bevacizumab	Median time: 3.8 (2.4 to 3.7) months	Median time: 2.9 (2.4 to 3.7) months	HR 0.96 (0.81 to 1.15)[9]	602 (1 study[27])	⊕⊕⊕⊖ moderate[6]	
Progression Free Survival - GEM + Cetuximab	Median time: 3.4 (n.r.) months	Median time: 3.0 (n.r.) months	HR 1.07 (0.93 to 1.23)	766 (1 study[10])	⊕⊕⊖⊖ low[6,11]	
Progression Free Survival - GEM + Cisplatin	Median time: 5.3 (n.r.) months	Median time: 3.1 (n.r.) months	HR 0.69 (0.5 to 0.95)	195 (1 study[12])	⊕⊕⊕⊖ moderate[11]	
Progression Free Survival - PEFG	Median time: 3.9 (IQR: 2.1-7.1) months	Median time: 3.8 (IQR: 2.7-8.2) months	HR 0.51 (0.33 to 0.78)	104 (1 study[13])	⊕⊕⊕⊖ moderate[11]	
Progression Free Survival - GEM + Elpamotide14	-	-	Not estimable[14]	153 (1 study[15])	⊕⊕⊕⊖ moderate[14,16,17]	
Progression Free Survival - GEM + Erlotinib	Median time: 3.75 (n.r.) months	Median time: 3.55 (n.r.) months	HR 0.77 (0.65 to 0.92)	569 (1 study[18])	⊕⊕⊕⊕ high[14]	
Progression Free Survival - GEM + Irinotecan	Median time: 3.5 (2.8 to 4.2) months	Median time: 3.0 (2.5 to 3.7) months	HR 0.98 (0.77 to 1.25)	180 (1 study[19])	⊕⊕⊕⊖ moderate[6]	
Progression Free Survival - GEM + Marimastat	Median Time: 92.5 (n.r.) days	Median time: 90.0 (n.r.) days	HR 0.95 (0.73 to 1.23)	239 (1 study[20])	⊕⊕⊕⊖ moderate[6]	
Progression Free Survival - GEM + Oxaliplatin	-	-	HR 0.83 (0.72 to 0.97)	1128 (2 studies[21,22])	⊕⊕⊕⊖ moderate[6]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Progression Free Survival - GEM + Sorafenib	Median time: 3.8 (3.1 to 6) months	Median time: 5.7 (3.7 to 7.5) months	HR 1.04 (0.7 to 1.55)	104 (1 study[23])	⊕⊕⊕⊖ moderate[2]	
Progression Free Survival - GEM + Tipifarnib	Median Time: 109 (n.r.) days	Median time: 112 (n.r.) days	HR 1.03 (0.87 to 1.22)	688 (1 study[24])	⊕⊕⊕⊖ moderate[6]	
Progression Free Survival - GEM + S-1	-	-	HR 0.65 (0.57 to 0.75)	658 (2 studies[1,25])	⊕⊕⊕⊕ high	
Overall Survival - 29	-	-30	See comment	9989 (23 studes[31])	⊕⊕⊕⊕ high	FOLFIRINOX, PEFG, GEM/erlotinib+/-bevacizumab, GEM/capecitabine, and GEM/oxaliplatin were associated with significant improvements in overall survival32
Overall Survival - 5-FU single-agent	-	-	HR1.75 (1.21-2.54)	126 (1 study[26])	⊕⊕⊕⊕ high	
Overall Survival - S-1 single-agent	Median time: 9.7 (7.6 to 10.8) months	Median time: 8.8 (8.0 to 9.7) months	HR 0.96 (0.71 to 1.3)	834 (1 study[1])	⊕⊕⊕⊖ moderate[6]	
Overall Survival - GEM + Bevacizumab	Median time: 5.0 (n.r.) months	Median time: 5.5 (n.r.) months	HR 0.96 (0.81 to 1.15)	602 (1 study[27])	⊕⊕⊕⊖ moderate[6]	
Overall Survival - GEM + Elpamotide	Median time: 8.4 (7.5 to 10.2) months	Median time: 8.5 (7.3 to 9.7) months	HR 0.87 (0.49 to 1.56)	153 (1 study[15])	⊕⊕⊕⊖ moderate[6]	
Overall Survival - GEM + Masitinib	Median time: 7.7 (6.1 to 10.6) months	Median time: 7.0 (6.1 to 10.6) months	HR 0.89 (0.7 to 1.13)	353 (1 study[28])	⊕⊕⊕⊖ moderate[6]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Overall Survival - GEM + S-1	-	-	HR 0.89 (0.74 to 1.08)	0 (2 studies[1,25])	⊕⊕⊕⊖ moderate[6]	

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; HR: Hazard ratio;

1 Ueno et al., 2013
3 Berlin et al., 2002
4 The quality of the evidence was downgraded because of the unclear risk of selection bias (no details given about the allocation method), besides the unclear risk of performance bias (no details given in the text)
5 Kindler et al., 2011
6 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. The quality of the evidence for this outcome was therefore downgraded for imprecision by one level as it was not statistically significant.
7 Cunningham et al., 2009
8 Herrmann et al., 2007
9 The median PFS was 3.8 months (95% CI, 3.4 to 4.0 months) and 2.9 months (95% CI, 2.4 to 3.7 months) for the bevacizumab and placebo arms, respectively (P .075).
10 Philip et al., 2010
11 The quality of the evidence was downgraded because of the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions) and detection bias (not masking of outcome assessors)
12 Heinemann et al., 2006
13 Reni et al., 2005
14 The quality of the evidence was downgraded because of the potential risk of selective findings reporting for this outcome.
15 Yamaue et al., 2015
16 The median PFS length was 3.71 months (95% CI, 2.10 – 3.98) in the Active group and3.75 months (95% CI, 2.27 – 5.59) in the Placebo group. There were no significant differences found between the two groups (log – rank P-value, 0.332).
17 From data provided by the authors about this outcome is not possible estimate the precision in the effect size estimates.
18 Moore et al., 2007
19 Rocha Lima et al., 2004
20 Bramhall et al., 2002
21 Louvet et al., 2005
22 Poplin et al., 2006 (2009)
23 Gonçalves et al., 2012
24 Van-Cutsem et al., 2004
25 Sudo et al., 2014
26 Burris et al., 1997
27 Kindler et al., 2010
28 Deplanque et al., 2015
29 FOLFIRINOX; Gemcitabine + 5-FU; Gemcitabine + Axitinib; Gemcitabine + Capecitabine; Gemcitabine + Capecitabine; Gemcitabine + Cetuximab; Gemcitabine + Cisplatin; Gemcitabine + Cisplatin; Gemcitabine + Erlotinib; Gemcitabine + Erlotinib; Gemcitabine + Erlotinib then Capecitabine; Gemcitabine + Exatecan; Gemcitabine + Irinotecan; Gemcitabine + Irinotecan; Gemcitabine + Marimastat; Gemcitabine + Nab-paclitaxel; Gemcitabine + Oxaliplatin; Gemcitabine + oxaliplatin; Gemcitabine + Pemetrexed; Gemcitabine + Sorafenib; Gemcitabine + Tipifarnib; Gemcitabine, 5-FU + Folinic Acid; and PEFG
30 The majority of the trials compared Gemcitabine single-agent to an experimental treatment.
31 Abou-Alfa et al. 2006; Berlin et al. 2002; Bramhall et al. 2002; Colucci et al. 2010; Conroy et al. 2011; Cunningham et al. 2009; Gonçalves et al. 2012; Heinemann et al. 2006; Heinemann et al. 2012; Herrmann et al. 2007; Kindler et al. 2011; Louvet et al. 2005; Moore et al. 2007; Oettle et al. 2005; Philip et al. 2010; Poplin et al. 2006 (2009) ; Reni et al. 2005; Riess et al. 2005; Rocha Lima et al. 2004; Stathopoulos et al. 2006; Van-Cutsem et al. 2004; Van-Cutsem et al. 2009; Von-Hoff et al. 2013
32 Please use the following hyperlinks for details on the findings:
http://media.springernature.com/full/springer-static/image/art%3A10.1186%2F1471-2407-14-471/MediaObjects/12885_2013_Article_4675_Fig2_HTML.jpg: Figure 2-Network of eligible trials where center node represents the reference comparator: Gemcitabine.
http://media.springernature.com/full/springer-static/image/art%3A10.1186%2F1471-2407-14-471/MediaObjects/12885_2013_Article_4675_Fig3_HTML.jpg: Figure 3-Indirect comparisons for overall survival: HRs and 95% CIs for various treatment comparisons.

Table 186: Summary clinical evidence profile for gemcitabine versus other chemotherapy (Adverse events - nausea/vomiting)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Exp. Chemotherapy	GEM alone				
Grade 3/4 toxicities: Nausea/Vomiting - 5-FU single-agent	127 per 1000	48 per 1000 (13 to 171)	RR 0.38 (0.1 to 1.35)	126 (1 study[1])	⊕⊕⊖⊖ low[2]	
Grade 3/4 toxicities: Nausea/Vomiting - S-1 single-agent	26 per 1000	33 per 1000 (13 to 88)	RR 1.29 (0.49 to 3.42)	545 (1 study[3])	⊕⊖⊖⊖ very low[2,4]	
Grade 3/4 toxicities: Nausea/Vomiting - GEM + 5-FU	120 per 1000	95 per 1000 (51 to 180)	RR 0.79 (0.42 to 1.5)	316 (1 study[5])	⊕⊖⊖⊖ very low[2,4]	
Grade 3/4 toxicities: Nausea/Vomiting - GEM + Axitinib	58 per 1000	82 per 1000 (46 to 147)	RR 1.4 (0.78 to 2.52)	613 (1 study[6])	⊕⊕⊖⊖ low[2]	
Grade 3/4 toxicities: Nausea/Vomiting - GEM + Capecitabine	89 per 1000	107 per 1000 (74 to 155)	RR 1.20 (0.83 to 1.74)	1017 (3 studies[7,8,29])	⊕⊖⊖⊖ very low[2,9]	
Grade 3/4 toxicities: Nausea/Vomiting - GEM + Cetuximab	54 per 1000	92 per 1000 (53 to 158)	RR 1.71 (0.99 to 2.95)	716 (1 study[10])	⊕⊕⊖⊖ low[9,11]	
Grade 3/4 toxicities: Nausea/Vomiting - GEM + Cisplatin	62 per 1000	225 per 1000 (95 to 529)	RR 3.63 (1.54 to 8.56)	195 (1 study[12])	⊕⊕⊕⊖ moderate[9]	
Grade 3/4 toxicities: Nausea/Vomiting - GEM + Elpamotide	38 per 1000	20 per 1000 (3 to 138)	RR 0.53 (0.08 to 3.66)	153 (1 study[15])	⊕⊕⊖⊖ low[11]	
Grade 3/4 toxicities: Nausea/Vomiting - GEM + Exatecan	57 per 1000	89 per 1000 (40 to 198)	RR 1.56 (0.7 to 3.46)	325 (1 study[16])	⊕⊖⊖⊖ very low[2,17]	
Grade 3/4 toxicities: Nausea/Vomitin	142 per 1000	228 per 1000 (155 to 331)	RR 1.6 (1.09	472 (2 studies[18,19])	⊕⊕⊖⊖ low[11,20]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
g - GEM + Irinotecan			to 2.33)			
Grade 3/4 toxicities: Nausea/Vomiting - GEM + Marimastat	218 per 1000	109 per 1000 (59 to 201)	RR 0.5 (0.27 to 0.92)	239 (1 study[21])	⊕⊕⊕⊖ moderate[11]	
Grade 3/4 toxicities: Nausea/Vomiting - GEM + Oxaliplatin	62 per 1000	171 per 1000 (112 to 263)	RR 2.77 (1.81 to 4.25)	840 (2 studies[22,23])	⊕⊕⊕⊖ moderate[20]	
Grade 3/4 toxicities: Nausea/Vomiting - GEM + Pemetrexed	66 per 1000	66 per 1000 (35 to 124)	RR 1 (0.53 to 1.88)	546 (1 study[24])	⊕⊖⊖⊖ very low[2,25]	
Grade 3/4 toxicities: Nausea/Vomiting - GEM + Tipifarnib	183 per 1000	137 per 1000 (100 to 184)	RR 0.75 (0.55 to 1.01)	915 (2 studies[26,27])	⊕⊕⊕⊖ moderate[11]	
Grade 3/4 toxicities: Nausea/Vomiting - GEM + S-1	31 per 1000	94 per 1000 (47 to 188)	RR 2.99 (1.49 to 5.99)	636 (2 studies[3,28])	⊕⊕⊕⊕ high	

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio;

1 Burris et al., 1997
2 Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs
3 Ueno et al., 2013
4 The quality of the evidence was downgraded because of the unclear risk of selection bias (no details given about the allocation method), besides the unclear risk of performance bias (no details given in the text)
5 Berlin et al., 2002
6 Kindler et al., 2011
7 Cunningham et al. 2009
8 Herrmann et al. 2007
9 The quality of the evidence was downgraded because of the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions) and detection bias (not masking of outcome assessors)
10 Philip et al. 2010
11 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID
12 Heinemann et al. 2006
14 The quality of the evidence was downgraded because of the potential risk of performance bias (no detail on blinding of patients/ care providers delivering the interventions) and the high detection bias (not masking of outcome assessors)
15 Yamaue et al. 2015
16 Abou-Alfa et al. 2006
17 The quality of the evidence was downgraded because of the unclear risk of selection bias (no details provided in the text), the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions), besides the unclear risk of detection bias
18 Rocha Lima et al. 2004
19 Stathopoulos et al. 2006
20 The quality of the evidence was downgraded because of the unclear risk of performance bias (no information on blinding of patients/ care providers delivering the interventions) and unclear risk of detection bias

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
21 Bramhall et al. 2002 *22 Louvet et al. 2005* *23 Poplin et al. 2006 (2009)* *24 Oettle et al. 2005* *25 The quality of the evidence was downgraded because of the unclear risk of performance bias (no information on blinding of patients/ care providers delivering the interventions) and high risk of detection bias* *26 Eckhardt et al. 2009* *27 Van-Cutsem et al. 2004* *28 Sudo et al. 2014* *29 Lee et al. 2017*						

Table 187: Summary clinical evidence profile for gemcitabine versus other chemotherapy (Adverse events - diarrhoea)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Exp. Chemotherapy	GEM alone				
Grade 3/4 toxicities: Diarrhoea - 5-FU single-agent	16 per 1000	48 per 1000 (5 to 446)	RR 3 (0.32 to 28.07)	126 (1 study[1])	⊕⊕⊖⊖ low[2]	
Grade 3/4 toxicities: Diarrhoea - S-1 single-agent	11 per 1000	55 per 1000 (16 to 188)	RR 5.02 (1.47 to 17.14)	545 (1 study[3])	⊕⊕⊕⊕ high	
Grade 3/4 toxicities: Diarrhoea - GEM + 5-FU	25 per 1000	63 per 1000 (20 to 197)	RR 2.5 (0.8 to 7.8)	316 (1 study[4])	⊕⊖⊖⊖ very low[2,5]	
Grade 3/4 toxicities: Diarrhoea - GEM + Axitinib	16 per 1000	13 per 1000 (4 to 48)	RR 0.81 (0.22 to 2.98)	613 (1 study[7])	⊕⊕⊖⊖ low[2]	
Grade 3/4 toxicities: Diarrhoea - GEM + Capecitabine	28 per 1000	42 per 1000 (22 to 81)	RR 1.53 (0.80 to 2.91)	1017 (3 studies[8])	⊕⊖⊖⊖ very low[2,9]	
Grade 3/4 toxicities: Diarrhoea - GEM + Cetuximab	25 per 1000	28 per 1000 (11 to 67)	RR 1.09 (0.45 to 2.66)	716 (1 study[10])	⊕⊖⊖⊖ very low[2]	
Grade 3/4 toxicities: Diarrhoea -	52 per 1000	30 per 1000 (8 to 125)	RR 0.59 (0.15	195 (1 study[11])	⊕⊖⊖⊖ very low[2,5]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
GEM + Cisplatin			to 2.42)			
Grade 3/4 toxicities: Diarrhoea - GEM + Erlotinib	7 per 1000	21 per 1000 (4 to 105)	RR 2.98 (0.61 to 14.63)	562 (1 study)	⊕⊕⊖⊖ low[2]	
Grade 3/4 toxicities: Diarrhoea - GEM + Exatecan	6 per 1000	12 per 1000 (1 to 130)	RR 1.87 (0.17 to 20.41)	325 (1 study13)	⊕⊖⊖⊖ very low[2,14]	
Grade 3/4 toxicities: Diarrhoea - GEM + Irinotecan	21 per 1000	145 per 1000 (57 to 370)	RR 6.92 (2.71 to 17.67)	472 (2 studies[15,16])	⊕⊕⊖⊖ low[17,18]	
Grade 3/4 toxicities: Diarrhoea - GEM + Oxaliplatin	24 per 1000	60 per 1000 (29 to 123)	RR 2.5 (1.22 to 5.15)	840 (2 studies[19,20])	⊕⊕⊖⊖ low[6,17]	
Grade 3/4 toxicities: Diarrhoea - GEM + Pemetrexed	7 per 1000	29 per 1000 (6 to 137)	RR 4 (0.86 to 18.67)	546 (1 study[21])	⊕⊕⊖⊖ low[6,17]	
Grade 3/4 toxicities: Diarrhoea - GEM + Sorafenib	58 per 1000	40 per 1000 (7 to 230)	RR 0.69 (0.12 to 3.98)	102 (1 study[22])	⊕⊕⊖⊖ low[2]	
Grade 3/4 toxicities: Diarrhoea - GEM + Tipifarnib	22 per 1000	29 per 1000 (13 to 66)	RR 1.34 (0.6 to 3.02)	915 (2 studies[23,24])	⊕⊕⊖⊖ low[2]	
Grade 3/4 toxicities: Diarrhoea - GEM + S-1	16 per 1000	41 per 1000 (15 to 112)	RR 2.59 (0.94 to 7.14)	636 (2 studies[3,25])	⊕⊕⊕⊖ moderate[6]	

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio;

1 Burris et al. 1997
2 Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs
3 Ueno et al. 2013
4 Berlin et al. 2002
5 The quality of the evidence was downgraded because of the unclear risk of selection bias (no details given about the allocation method), besides the unclear risk of performance bias (no details given in the text)
6 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID
7 Kindler et al. 2011
8 Herrmann et al. 2007, Cunningham et l., 2009 and Lee et al. 2017
9 The quality of the evidence was downgraded because of the potential risk of performance bias (no blinding of

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
patients/ care providers delivering the interventions) and detection bias (not masking of outcome assessors) *10 Philip et al. 2010* *11 Heinemann et al. 2006* *13 Abou-Alfa et al. 2006* *14 The quality of the evidence was downgraded because of the unclear risk of selection bias (no details provided in the text), the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions), besides the unclear risk of detection bias* *15 Rocha Lima et al. 2004* *16 Stathopoulos et al. 2006* *17 The quality of the evidence was downgraded because of the unclear risk of performance bias (no information on blinding of patients/ care providers delivering the interventions) and unclear risk of detection bias* *18 Serious heterogeneity. I-squared = 73%* *19 Louvet et al. 2005* *20 Poplin et al. 2006 (2009)* *21 Oettle et al. 2005* *22 Gonçalves et al. 2012* *23 Eckhardt et al. 2009* *24 Van-Cutsem et al. 2004* *25 Sudo et al. 2014*						

Table 188: Summary clinical evidence profile for gemcitabine versus other chemotherapy (Adverse events - fatigue)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Exp. Chemotherapy	GEM alone				
Grade 3/4 toxicities: Fatigue - S-1 single-agent	37 per 1000	66 per 1000 (31 to 141)	RR 1.81 (0.85 to 3.84)	545 (1 study[1])	⊕⊕⊕⊖ moderate[2]	
Grade 3/4 toxicities: Fatigue - GEM + Axitinib	68 per 1000	89 per 1000 (51 to 153)	RR 1.3 (0.75 to 2.25)	613 (1 study[3])	⊕⊕⊖⊖ low[4]	
Grade 3/4 toxicities: Fatigue - GEM + Cetuximab	180 per 1000	200 per 1000 (148 to 270)	RR 1.11 (0.82 to 1.5)	716 (1 study[5])	⊕⊕⊖⊖ low[2,6]	
Grade 3/4 toxicities: Fatigue - GEM + Erlotinib	54 per 1000	53 per 1000 (26 to 107)	RR 0.99 (0.49 to 1.99)	562 (1 study[7])	⊕⊕⊖⊖ low[4]	
Grade 3/4 toxicities: Fatigue -	32 per 1000	83 per 1000 (31 to 226)	RR 2.62 (0.96 to 7.1)	325 (1 study[8])	⊕⊖⊖⊖ very low[2,9]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
GEM + Exatecan						
Grade 3/4 toxicities: Fatigue - GEM + Irinotecan	154 per 1000	168 per 1000 (103 to 272)	RR 1.09 (0.67 to 1.77)	342 (1 study[10])	⊕⊖⊖⊖ very low[10,11]	
Grade 3/4 toxicities: Fatigue - GEM + Marimastat	59 per 1000	116 per 1000 (49 to 279)	RR 1.98 (0.83 to 4.74)	239 (1 study[12])	⊕⊕⊖⊖ low[4]	
Grade 3/4 toxicities: Fatigue - GEM + Oxaliplatin	189 per 1000	170 per 1000 (119 to 246)	RR 0.9 (0.63 to 1.3)	527 (1 study[13])	⊕⊕⊖⊖ low[2,9]	
Grade 3/4 toxicities: Fatigue - GEM + Pemetrexed	66 per 1000	150 per 1000 (88 to 255)	RR 2.28 (1.34 to 3.86)	546 (1 study[14])	⊕⊕⊕⊖ moderate[15]	
Grade 3/4 toxicities: Fatigue - GEM + Tipifarnib	133 per 1000	121 per 1000 (86 to 168)	RR 0.91 (0.65 to 1.27)	915 (2 studies[16,17])	⊕⊕⊖⊖ low[2]	
Grade 3/4 toxicities: Fatigue - GEM + S-1	34 per 1000	41 per 1000 (19 to 89)	RR 1.19 (0.55 to 2.57)	636 (2 studies[1,18])	⊕⊕⊖⊖ low[4]	

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio;

1 Ueno et al. 2013
2 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID
3 Kindler et al. 2011
4 Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs
5 Philip et al. 2010
6 The quality of the evidence was downgraded because of the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions) and detection bias (not masking of outcome assessors)
7 Moore et al. 2007
8 Abou-Alfa et al. 2006
9 The quality of the evidence was downgraded because of the unclear risk of selection bias (no details provided in the text), the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions), besides the unclear risk of detection bias
10 Rocha Lima et al. 2004
11 The quality of the evidence was downgraded because of the unclear risk of performance bias (no information on blinding of patients/ care providers delivering the interventions) and unclear risk of detection bias
12 Bramhall et al. 2002
13 Poplin et al. 2006 (2009)
14 Oettle et al. 2005
15 No explanation was provided
16 Eckhardt et al. 2009

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
17 Van-Cutsem et al. 2004 *18 Sudo et al. 2014*						

Table 189: Summary clinical evidence profile for gemcitabine versus other chemotherapy (Adverse events - neutropenia)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Exp. Chemotherapy	GEM alone				
Grade 3/4 toxicities: Neutropenia - 5-FU single-agent	254 per 1000	48 per 1000 (15 to 155)	RR 0.19 (0.06 to 0.61)	126 (1 study[1])	⊕⊕⊕⊕ high	
Grade 3/4 toxicities: Neutropenia - S-1 single-agent	410 per 1000	90 per 1000 (57 to 131)	RR 0.22 (0.14 to 0.32)	545 (1 study[2])	⊕⊕⊕⊕ high	
Grade 3/4 toxicities: Neutropenia - GEM + Axitinib	3 per 1000	1 per 1000 (0 to 27)	RR 0.34 (0.01 to 8.23)	613 (1 study[3])	⊕⊕⊖⊖ low[4]	
Grade 3/4 toxicities: Neutropenia - GEM + Bevacizumab	110 per 1000	119 per 1000 (75 to 191)	RR 1.08 (0.68 to 1.73)	540 (1 study[3])	⊕⊕⊖⊖ low[4]	
Grade 3/4 toxicities: Neutropenia - GEM + Capecitabine	190 per 1000	274 per 1000 (219 to 345)	RR 1.44 (1.15 to 1.81)	1017 (3 studies[5,6,25])	⊕⊕⊖⊖ low[7,8]	
Grade 3/4 toxicities: Neutropenia - GEM + Cetuximab	239 per 1000	232 per 1000 (180 to 302)	RR 0.97 (0.75 to 1.26)	716 (1 study[9])	⊕⊖⊖⊖ very low[4,10]	
Grade 3/4 toxicities: Neutropenia - GEM + Elpamotide	566 per 1000	481 per 1000 (351 to 657)	RR 0.85 (0.62 to 1.16)	153 (1 study[11])	⊕⊕⊕⊖ moderate 8	
Grade 3/4 toxicities: Neutropenia - GEM + Exatecan	146 per 1000	303 per 1000 (195 to 472)	RR 2.07 (1.33 to 3.22)	325 (1 study[12])	⊕⊕⊖⊖ low[13]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Grade 3/4 toxicities: Neutropenia - GEM + Irinotecan	157 per 1000	267 per 1000 (134 to 530)	RR 1.7 (0.85 to 3.37)	130 (1 study[14])	⊕⊕⊖⊖ low[8,15]	
Grade 3/4 toxicities: Neutropenia - GEM + Oxaliplatin	281 per 1000	242 per 1000 (194 to 306)	RR 0.86 (0.69 to 1.09)	840 (2 studies[16,17])	⊕⊖⊖⊖ very low[8,18,19]	
Grade 3/4 toxicities: Neutropenia - GEM + Pemetrexed	128 per 1000	450 per 1000 (322 to 631)	RR 3.51 (2.51 to 4.92)	546 (1 study[20])	⊕⊕⊕⊕ high	
Grade 3/4 toxicities: Neutropenia - GEM + Sorafenib	288 per 1000	260 per 1000 (138 to 490)	RR 0.9 (0.48 to 1.7)	102 (1 study[21])	⊕⊕⊖⊖ low[4]	
Grade 3/4 toxicities: Neutropenia - GEM + Tipifarnib	324 per 1000	408 per 1000 (347 to 486)	RR 1.26 (1.07 to 1.5)	915 (2 studies[22,23])	⊕⊕⊕⊖ moderate[8]	
Grade 3/4 toxicities: Neutropenia - GEM + S-1	379 per 1000	596 per 1000 (504 to 706)	RR 1.57 (1.33 to 1.86)	636 (2 studies[2,24])	⊕⊕⊕⊕ high	

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio;

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

1 Burris et al. 1997
2 Ueno et al. 2013
3 Kindler et al. 2010
4 Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs
5 Cunningham et al. 2009
6 Herrmann et al. 2007
7 The quality of the evidence was downgraded because of the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions) and detection bias (not masking of outcome assessors) in Cunningham et al. 2009, and the unclear risk of selection bias in Herrmann et al. 2007.
8 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID
9 Philip et al. 2010
10 The quality of the evidence was downgraded because of the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions) and detection bias (not masking of outcome assessors)
11 Yamaue et al. 2015
12 Abou-Alfa et al. 2006
13 The quality of the evidence was downgraded because of the unclear risk of selection bias (no details provided in the text), the potential risk of performance bias (no blinding of patients/ care providers delivering

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
the interventions), besides the unclear risk of detection bias *14 Stathopoulos et al. 2006#* *15 The quality of the evidence was downgraded because of the unclear risk of performance bias (no information on blinding of patients/ care providers delivering the interventions) and unclear risk of detection bias and the potential risk of attrition bias* *16 Louvet et al. 2005* *17 Poplin et al. 2006 (2009)* *18 The quality of the evidence was downgraded because of the unclear risk of performance bias (no information on blinding of patients/ care providers delivering the interventions) and unclear risk of detection bias* *19 Serious heterogeneity. I-squared = 89%* *20 Oettle et al. 2005* *21 Gonçalves et al. 2012* *22 Eckhardt et al. 2009* *23 Van-Cutsem et al. 2004* *24 Sudo et al. 2014* *25 Lee et al. 2017*						

Table 190: Summary clinical evidence profile for gemcitabine versus other chemotherapy (Adverse events - thrombocytopenia)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Exp. Chemotherapy	GEM alone				
Grade 3/4 toxicities: Thrombocytopenia - GEM + 5-FU	105 per 1000	190 per 1000 (109 to 331)	RR 1.81 (1.04 to 3.15)	320 (1 study[1])	⊕⊕⊖⊖ low[2,3]	
Grade 3/4 toxicities: Thrombocytopenia - GEM + Axitinib	3 per 1000	1 per 1000 (0 to 27)	RR 0.34 (0.01 to 8.23)	613 (1 study[4])	⊕⊕⊖⊖ low[5]	
Grade 3/4 toxicities: Thrombocytopenia - GEM + Bevacizumab	46 per 1000	43 per 1000 (20 to 95)	RR 0.95 (0.43 to 2.08)	540 (1 study[6])	⊕⊕⊖⊖ low[5]	
Grade 3/4 toxicities: Thrombocytopenia - GEM + Capecitabine	62 per 1000	70 per 1000 (44 to 112)	RR 1.14 (0.72 to 1.82)	1017 (3 studies[7,8,24])	⊕⊖⊖⊖ very low[3,9,10]	
Grade 3/4 toxicities: Thrombocytopenia - GEM + Cisplatin	103 per 1000	41 per 1000 (13 to 126)	RR 0.4 (0.13 to 1.22)	195 (1 study[11])	⊕⊕⊖⊖ low[3]	
Grade 3/4 toxicities:	151 per 1000	149 per 1000 (68 to 331)	RR 0.99	153 (1 study[12])	⊕⊕⊖⊖ low[5]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Thrombocytopenia - GEM + Elpamotide			(0.45 to 2.19)			
Grade 3/4 toxicities: Thrombocytopenia - GEM + Exatecan	45 per 1000	155 per 1000 (69 to 346)	RR 3.47 (1.55 to 7.77)	325 (1 study[13])	⊕⊕⊖⊖ low[14]	
Grade 3/4 toxicities: Thrombocytopenia - GEM + Irinotecan	0 per 1000	0 per 1000 (0 to 0)	RR 8.15 (0.43 to 154.64)	130 (1 study[15])	⊕⊖⊖⊖ very low[5]	
Grade 3/4 toxicities: Thrombocytopenia - GEM + Oxaliplatin	32 per 1000	140 per 1000 (54 to 361)	RR 4.37 (1.7 to 11.25)	313 (1 study[16])	⊕⊕⊕⊖ moderate[17]	
Grade 3/4 toxicities: Thrombocytopenia - GEM + Pemetrexed	62 per 1000	179 per 1000 (106 to 304)	RR 2.88 (1.7 to 4.88)	546 (1 study[18])	⊕⊕⊕⊕ high	
Grade 3/4 toxicities: Thrombocytopenia - GEM + Sorafenib	115 per 1000	60 per 1000 (16 to 227)	RR 0.52 (0.14 to 1.97)	102 (1 study[19])	⊕⊕⊖⊖ low[5]	
Grade 3/4 toxicities: Thrombocytopenia - GEM + Tipifarnib	135 per 1000	164 per 1000 (120 to 224)	RR 1.22 (0.89 to 1.66)	915 (2 studies[20,21])	⊕⊕⊕⊖ moderate[10]	
Grade 3/4 toxicities: Thrombocytopenia - GEM + S-1	16 per 1000	53 per 1000 (21 to 136)	RR 3.4 (1.33 to 8.7)	636 (2 studies[22,23])	⊕⊕⊕⊕ high	

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

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

1 Berlin et al. 2002
2 The quality of the evidence was downgraded because of the unclear risk of selection bias (no details given about the allocation method), besides the unclear risk of performance bias (no details given in the text)
3 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID
4 Kindler et al. 2011
5 Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
6 Kindler et al. 2010 *7 Cunningham et al. 2009* *8 Herrmann et al. 2007* *9 The quality of the evidence was downgraded because of the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions) and detection bias (not masking of outcome assessors) in Cunningham et al. 2009, and the unclear risk of selection bias in Herrmann et al. 2007.* *10 Serious heterogeneity. I-squared = 80%* *11 Heinemann et al. 2006* *12 Yamaue et al. 2015* *13 Abou-Alfa et al. 2006* *14 The quality of the evidence was downgraded because of the unclear risk of selection bias (no details provided in the text), the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions), besides the unclear risk of detection bias* *15 Stathopoulos et al. 2006* *16 Louvet et al. 2005* *17 The quality of the evidence was downgraded because of the unclear risk of performance bias (no information on blinding of patients/ care providers delivering the interventions) and unclear risk of detection bias* *18 Oettle et al. 2005* *19 Gonçalves et al. 2012* *20 Eckhardt et al. 2009* *21 Van-Cutsem et al. 2004* *22 Sudo et al. 2014* *23 Ueno et al. 2013* *24 Lee et al. 2017*						

Table 191: Summary clinical evidence profile for gemcitabine versus other chemotherapy (Adverse events - leucopenia)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Exp. Chemotherapy	GEM alone				
Grade 3/4 toxicities: Leucopoenia - S-1 single-agent	187 per 1000	37 per 1000 (19 to 71)	RR 0.2 (0.1 to 0.38)	545 (1 study[1])	⊕⊕⊕⊕ high	
Grade 3/4 toxicities: Leucopoenia - GEM + 5-FU	101 per 1000	183 per 1000 (104 to 324)	RR 1.81 (1.03 to 3.2)	316 (1 study[2])	⊕⊕⊖⊖ low[3,4]	
Grade 3/4 toxicities: Leucopoenia - GEM + Axitinib	See comments	See comments	Not estimable	613 (1 study[5])	⊕⊕⊕⊕ high	None event was registered
Grade 3/4 toxicities: Leucopoenia - GEM + Cetuximab	146 per 1000	111 per 1000 (75 to 163)	RR 0.76 (0.51 to 1.11)	716 (1 study[6])	⊕⊕⊖⊖ low[4,7]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Grade 3/4 toxicities: Leucopoenia - GEM + Cisplatin	82 per 1000	102 per 1000 (42 to 247)	RR 1.24 (0.51 to 3)	195 (1 study[8])	⊕⊖⊖⊖ very low[7,9]	
Grade 3/4 toxicities: Leucopoenia - GEM + Elpamotide	434 per 1000	308 per 1000 (204 to 473)	RR 0.71 (0.47 to 1.09)	153 (1 study[10])	⊕⊕⊕⊖ moderate[4]	
Grade 3/4 toxicities: Leucopoenia - GEM + Oxaliplatin	159 per 1000	121 per 1000 (80 to 186)	RR 0.76 (0.5 to 1.17)	527 (1 study[11])	⊕⊕⊕⊖ moderate[4]	
Grade 3/4 toxicities: Leucopoenia - GEM + S-1	185 per 1000	326 per 1000 (202 to 525)	RR 1.76 (1.09 to 2.84)	636 (2 studies[1,12])	⊕⊕⊕⊖ moderate[13]	
The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). *CI: Confidence interval; RR: Risk ratio;*						
1 Ueno et al. 2013 *2 Berlin et al. 2002* *3 The quality of the evidence was downgraded because of the unclear risk of selection bias (no details given about the allocation method), besides the unclear risk of performance bias (no details given in the text)* *4 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID* *5 Kindler et al. 2011* *6 Philip et al. 2010* *7 The quality of the evidence was downgraded because of the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions) and detection bias (not masking of outcome assessors)* *8 Heinemann et al. 2006* *9 Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs* *10 Yamaue et al. 2015* *11 Poplin et al. 2006 (2009)* *12 Sudo et al. 2014* *13 Serious heterogeneity. I-squared = 36%*						

Table 192: Summary clinical evidence profile for gemcitabine versus other chemotherapy (Health-related quality of life)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Exp. Chemotherapy	GEM alone				
HRQL: GEM + Capecitabine versus GEM - mean score difference at 6 months (linear-analogue self-assessment		The mean HRQL: GEM + Capecitabine versus GEM - mean score difference at 6 months (linear-analogue self-		319 (1 study[1])	⊕⊕⊖⊖ low[2,3]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
[LASA] indicators - Physical well-being		assessment [LASA] indicators - physical well-being in the intervention groups was 5 higher (4.8 lower to 14.8 higher)				
HRQL: GEM + Capecitabine versus GEM - mean score difference at 6 months (linear-analogue self-assessment [LASA] indicators - Mood		The mean HRQL: GEM + Capecitabine versus GEM - mean score difference at 6 months (linear-analogue self-assessment [LASA] indicators - mood in the intervention groups was 6 higher (3.8 lower to 15.8 higher)		319 (1 study[1])	⨁⨁⊖⊖ low[2,3]	
HRQL: GEM + Capecitabine versus GEM - mean score difference at 6 months (linear-analogue self-assessment [LASA] indicators - Pain		The mean HRQL: GEM + Capecitabine versus GEM - mean score difference at 6 months (linear-analogue self-assessment [LASA] indicators - pain in the intervention groups was 8 higher (1.8 lower to 17.8 higher)		319 (1 study[1])	⨁⨁⊖⊖ low[2,3]	
HRQL: GEM + Capecitabine versus GEM - mean score difference at 6 months (linear-analogue self-assessment [LASA] indicators - Tiredness		The mean HRQL: GEM + Capecitabine versus GEM - mean score difference at 6 months (linear-analogue self-assessment [LASA] indicators -		319 (1 study[1])	⨁⨁⊖⊖ low[2,3]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
		tiredness in the intervention groups was 2 higher (7.8 lower to 11.8 higher)				
HRQL: GEM + Capecitabine versus GEM - mean score difference at 6 months (linear-analogue self-assessment [LASA] indicators - Functional performance		The mean HRQL: GEM + Capecitabine versus GEM - mean score difference at 6 months (linear-analogue self-assessment [LASA] indicators - functional performance in the intervention groups was 8 higher (1.8 lower to 17.8 higher)		319 (1 study[1])	⊕⊕⊖⊖ low[2,3]	
HRQL: GEM + Capecitabine versus GEM - mean score difference at 6 months (linear-analogue self-assessment [LASA] indicators - Coping effort		The mean HRQL: GEM + Capecitabine versus GEM - mean score difference at 6 months (linear-analogue self-assessment [LASA] indicators - coping effort in the intervention groups was 4 higher (5.8 lower to 13.8 higher)		319 (1 study[1])	⊕⊕⊖⊖ low[2,3]	
HRQL: GEM + Capecitabine versus GEM - mean score difference at 6 months (linear-analogue self-assessment [LASA] indicators - Treatment burden		The mean HRQL: GEM + Capecitabine versus GEM - mean score difference at 6 months (linear-analogue self-assessment [LASA] indicators - treatment burden in the intervention		319 (1 study[1])	⊕⊕⊖⊖ low[2,4]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
		groups was 4 higher (5.8 lower to 13.8 higher)				
HRQL: GEM + Cetuximab versus alone - Emotional Well-Being Score at 5, 13, and 17 weeks follow-up - 5 weeks follow-up		The mean HRQL: GEM + cetuximab versus alone - emotional well-being score at 5, 13, and 17 weeks follow-up - 5 weeks follow-up in the intervention groups was 0.3 lower (0.69 lower to 0.09 higher)		540 (1 study[5])	⊕⊕⊖⊖ low[3,6]	
HRQL: GEM + Cetuximab versus alone - Emotional Well-Being Score at 5, 13, and 17 weeks follow-up - 13 weeks follow-up		The mean HRQL: GEM + cetuximab versus alone - emotional well-being score at 5, 13, and 17 weeks follow-up - 13 weeks follow-up in the intervention groups was 0.2 higher (0.34 lower to 0.74 higher)		340 (1 study[5])	⊕⊕⊖⊖ low[3,6]	
HRQL: GEM + Cetuximab versus alone - Emotional Well-Being Score at 5, 13, and 17 weeks follow-up - 17 weeks follow-up		The mean HRQL: GEM + cetuximab versus alone - emotional well-being score at 5, 13, and 17 weeks follow-up - 17 weeks follow-up in the intervention groups was 0.5 higher (0.01 lower to 1.01 higher)		288 (1 study[5])	⊕⊕⊖⊖ low[3,6]	
HRQL: GEM + cisplatin versus GEM alone at 6 treatment cycles (Spitzer 5-Item Index)		The mean HRQL: GEM + cisplatin versus GEM alone at 6 treatment cycles (spitzer		195 (1 study[7])	⊕⊕⊕⊖ moderate[6]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
		5-item index) in the intervention groups was 0.4 lower (0.66 to 0.14 lower)				
HRQL: PEFG versus GEM - Number of patients with a clinically significant improvement QLQ-C30 - Global health status	286 per 1000	551 per 1000 (251 to 1000)	RR 1.93 (0.88 to 4.22)	41 (1 study[8])	⊕⊕⊖⊖ low[3,4]	
HRQL: PEFG versus GEM - Number of patients with a clinically significant improvement QLQ-C30 - Physical functioning	87 per 1000	261 per 1000 (58 to 1000)	RR 3 (0.67 to 13.34)	46 (1 study[8])	⊕⊖⊖⊖ very low[3,9]	
HRQL: PEFG versus GEM - Number of patients with a clinically significant improvement QLQ-C30 - Role functioning	318 per 1000	216 per 1000 (80 to 582)	RR 0.68 (0.25 to 1.83)	45 (1 study[8])	⊕⊖⊖⊖ very low[3,9]	
HRQL: PEFG versus GEM - Number of patients with a clinically significant improvement QLQ-C30 - Emotional functioning	182 per 1000	429 per 1000 (155 to 1000)	RR 2.36 (0.85 to 6.5)	43 (1 study[8])	⊕⊕⊖⊖ low[3,4]	
HRQL: PEFG versus GEM - Number of patients with a clinically significant improvement QLQ-C30 -	208 per 1000	217 per 1000 (73 to 652)	RR 1.04 (0.35 to 3.13)	47 (1 study[8])	⊕⊖⊖⊖ very low[3,9]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Cognitive functioning						
HRQL: PEFG versus GEM - Number of patients with a clinically significant improvement QLQ-C30 - Social functioning	294 per 1000	332 per 1000 (129 to 865)	RR 1.13 (0.44 to 2.94)	38 (1 study[8])	⊕⊖⊖⊖ very low[3,9]	
HRQL: PEFG versus GEM - Number of patients with a clinically significant improvement QLQ-C30 - Fatigue	250 per 1000	410 per 1000 (175 to 962)	RR 1.64 (0.7 to 3.85)	46 (1 study[8])	⊕⊖⊖⊖ very low[3,9]	
HRQL: PEFG versus GEM - Number of patients with a clinically significant improvement QLQ-C30 - Nausea/vomiting	53 per 1000	95 per 1000 (9 to 968)	RR 1.81 (0.18 to 18.39)	40 (1 study[8])	⊕⊖⊖⊖ very low[3,9]	
HRQL: PEFG versus GEM - Number of patients with a clinically significant improvement QLQ-C30 - Pain	409 per 1000	638 per 1000 (352 to 1000)	RR 1.56 (0.86 to 2.82)	44 (1 study[8])	⊕⊕⊖⊖ low[3,4]	
HRQL: PEFG versus GEM - Number of patients with a clinically significant improvement QLQ-C30 - Dyspnea	130 per 1000	173 per 1000 (44 to 691)	RR 1.33 (0.34 to 5.3)	46 (1 study)	⊕⊖⊖⊖ very low[3,9]	
HRQL: PEFG versus GEM - Number of patients with a clinically significant improvement	333 per 1000	347 per 1000 (157 to 770)	RR 1.04 (0.47 to 2.31)	47 (1 study8)	⊕⊖⊖⊖ very low[3,9]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
QLQ-C30 - Insomnia						
HRQL: PEFG versus GEM - Number of patients with a clinically significant improvement QLQ-C30 - Loss of appetite	292 per 1000	260 per 1000 (102 to 659)	RR 0.89 (0.35 to 2.26)	47 (1 study[8])	⊕⊖⊖⊖ very low[3,9]	
HRQL: PEFG versus GEM - Number of patients with a clinically significant improvement QLQ-C30 - Constipation	304 per 1000	304 per 1000 (128 to 730)	RR 1 (0.42 to 2.4)	46 (1 study[8])	⊕⊖⊖⊖ very low[3,9]	
HRQL: PEFG versus GEM - Number of patients with a clinically significant improvement QLQ-C30 - Diarrhoea	87 per 1000	190 per 1000 (39 to 935)	RR 2.19 (0.45 to 10.75)	44 (1 study[8])	⊕⊖⊖⊖ very low[3,9]	
HRQL: PEFG versus GEM - Number of patients with a clinically significant improvement QLQ-C30 - Financial difficulties	95 per 1000	90 per 1000 (14 to 588)	RR 0.95 (0.15 to 6.17)	43 (1 study[8])	⊕⊖⊖⊖ very low[3,9]	

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio;

1 Bernhard et al. 2008
2 The quality of the evidence was downgraded because of the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions) and unclear risk of detection bias (no details on allocation concealment and randomization)
3 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID
4 The quality of the evidence was downgraded because of the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions) and unclear risk of detection bias (not information given on masking of outcome assessors)
5 Moinpour et al. 2010
6 The quality of the evidence was downgraded because of the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions) and detection bias (not masking of outcome assessors)
7 Heinemann et al. 2006
8 Reni et al. 2005
9 Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs

Table 193: Summary clinical evidence profile for gemcitabine and erlotinib versus gemcitabine, erlotinib and bevacizumab

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Exp. Chemotherapy (GEM + erlotinib + bevacizumab) (pure metastatic)	GEM + erlotinib				
Overall response rate (CR + PR) - GEM + erlotinib + bevacizumab	83 per 1000	130 per 1000 (81 to 210)	RR 1.57 (0.98 to 2.53)	607 (1 study[1])	⊕⊕⊕⊖ moderate [2]	
Progression Free Survival - GEM + erlotinib + bevacizumab	Median time: 4.6 (n.r.) months	Median time: 3.6 (n.r.) months	HR 0.73 (0.61 to 0.87)	607 (1 study[1])	⊕⊕⊕⊖ moderate [3]	
Grade 3/4 toxicities - Thrombocytopenia	59 per 1000	78 per 1000 (43 to 142)	RR 1.31 (0.72 to 2.4)	583 (1 study[1])	⊕⊕⊖⊖ low[4]	
Grade 3/4 toxicities - Neutropenia	171 per 1000	166 per 1000 (116 to 237)	RR 0.97 (0.68 to 1.39)	583 (1 study[1])	⊕⊕⊖⊖ low[4]	
Grade 3/4 toxicities - Diarrhoea	59 per 1000	40 per 1000 (20 to 84)	RR 0.68 (0.33 to 1.41)	583 (1 study[1])	⊕⊕⊖⊖ low[4]	
Grade 3/4 toxicities - Nausea/Vomiting	59 per 1000	91 per 1000 (51 to 163)	RR 1.54 (0.86 to 2.76)	583 (1 study[1])	⊕⊕⊖⊖ low[4]	

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;

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

1 Van-Cutsem et al. 2009
2 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID
3 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant
4 Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs

Table 194: Summary clinical evidence profile for gemcitabine and erlotinib versus capecitabine and erlotinib

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Exp. Chemotherapy (capecitabine + erlotinib)	GEM + erlotinib				
Overall response rate (CR + PR) - Capecitabine + erlotinib	53 per 1000	154 per 1000 (68 to 348)	RR 2.88 (1.27 to 6.52)	274 (1 study[1])	⊕⊕⊕⊖ moderate [2]	
Grade 3/4 toxicities - Leukocytopenia	0 per 1000	0 per 1000 (0 to 0)	RR 15.98 (0.93 to 273.93)	256 (1 study[1])	⊕⊕⊖⊖ low[2,3]	
Grade 3/4 toxicities - Thrombocytopenia	16 per 1000	83 per 1000 (19 to 369)	RR 5.17 (1.17 to 22.85)	256 (1 study[1])	⊕⊕⊖⊖ low[2,3]	
Grade 3/4 toxicities - Diarrhoea	97 per 1000	53 per 1000 (21 to 131)	RR 0.55 (0.22 to 1.35)	256 (1 study)	⊕⊖⊖⊖ very low[2,4]	
Grade 3/4 toxicities - Nausea/Vomiting	73 per 1000	99 per 1000 (44 to 222)	RR 1.36 (0.6 to 3.06)	256 (1 study)	⊕⊖⊖⊖ very low[2,4]	

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

1 Heinemann et al. 2012
2 The quality of the evidence was downgraded because of the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions) and detection bias (not masking of outcome assessors)
3 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID
4 Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs

11.2.4.3 Gemcitabine versus novel agents

Table 195: Summary clinical evidence profile for gemcitabine versus BAY 12-9566/ ZD9331 in adults with locally advanced or metastatic pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Novel agent	GEM alone				

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Overall response rate (CR + PR) at 8 weeks of therapy - BAY 12-9566	52 per 1000	9 per 1000 (1 to 76)	RR 0.18 (0.02 to 1.45)	223 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Overall response rate (CR + PR) at 8 weeks of therapy - ZD9331	80 per 1000	34 per 1000 (3 to 346)	RR 0.42 (0.04 to 4.33)	55 (1 study[5])	⊕⊖⊖⊖ very low[3,6]	
Progression Free Survival - BAY 12-9566	Median time: 1.7 (n.r.) months	Median time: 3.5 (n.r.) months	HR 0.53 (0.41 to 0.68)	277 (1 study[1])	⊕⊕⊕⊖ moderate[2]	
Overall Survival - BAY 12-9566	Median time: 3.74 (n.r.) months	Median time: 6.59 (n.r.) months	HR 0.57 (0.44 to 0.74)	277 (1 study[1])	⊕⊕⊕⊖ moderate[2]	
Grade 3/4 toxicities: Nausea - BAY 12-9566	36 per 1000	80 per 1000 (28 to 223)	RR 2.22 (0.79 to 6.21)	277 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Grade 3/4 toxicities: Nausea - ZD9331	40 per 1000	67 per 1000 (6 to 693)	RR 1.67 (0.16 to 17.32)	55 (1 study[4])	⊕⊖⊖⊖ very low[3,6]	
Grade 3/4 toxicities: Vomiting - BAY 12-9566	50 per 1000	29 per 1000 (9 to 97)	RR 0.58 (0.17 to 1.92)	277 (1 study[1])	⊕⊖⊖⊖⊖ very low[2,3]	
Grade 3/4 toxicities: Vomiting - ZD9331	0 per 1000	0 per 1000 (0 to 0)	RR 4.19 (0.21 to 83.5)	55 (1 study[4])	⊕⊖⊖⊖ very low[3,6]	
Grade 3/4 toxicities: Diarrhoea - BAY 12-9566	22 per 1000	14 per 1000 (2 to 85)	RR 0.67 (0.11 to 3.96)	277 (1 study[1])	⊕⊖⊖⊖⊖ very low[2,3]	
Grade 3/4 toxicities: Diarrhoea - ZD9331	40 per 1000	67 per 1000 (6 to 693)	RR 1.67 (0.16 to 17.32)	55 (1 study[5])	⊕⊖⊖⊖ very low[3,6]	
Grade 3/4 toxicities: Fatigue - ZD9331	0 per 1000	0 per 1000 (0 to 0)	RR 5.87 (0.32	55 (1 study[5])	⊕⊖⊖⊖ very low[3,6]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
			to 108.53)			
Grade 3/4 toxicities: Neutropenia - ZD9331	40 per 1000	167 per 1000 (21 to 1000)	RR 4.17 (0.52 to 33.37)	55 (1 study[5])	⊕⊖⊖⊖ very low[3,6]	
Health Related Quality of Life (EORTC C30,Domains) - Mean change From Baseline at 8 weeks follow-up - Physical		The mean health related quality of life (EORTC C30,domains) - mean change from baseline at 8 weeks follow-up - physical in the intervention groups was 13.2 lower (24.46 to 1.94 lower)		111 (1 study[1])	⊕⊕⊕⊖ moderate[2]	
Health Related Quality of Life (EORTC C30,Domains) - Mean change From Baseline at 8 weeks follow-up - Role		The mean health related quality of life (EORTC C30,domains) - mean change from baseline at 8 weeks follow-up - role in the intervention groups was 20.6 lower (34.97 to 6.23 lower)		111 (1 study[1])	⊕⊕⊕⊖ moderate[2]	
Health Related Quality of Life (EORTC C30,Domains) - Mean change From Baseline at 8 weeks follow-up - Emotional		The mean health related quality of life (EORTC C30,domains) - mean change from baseline at 8 weeks follow-up - emotional in the intervention groups was 7 lower (14.96 lower to 0.96 higher)		111 (1 study[1])	⊕⊕⊖⊖ low[2,4]	
Health Related Quality of Life (EORTC C30,Domains) - Mean change From Baseline at		The mean health related quality of life (EORTC C30,domains) - mean change from baseline at 8 weeks follow-up - cognitive in the		111 (1 study[1])	⊕⊕⊕⊖ moderate[2]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
8 weeks follow-up - Cognitive		intervention groups was 11.8 lower (20.18 to 3.42 lower)				
Health Related Quality of Life (EORTC C30,Domains) - Mean change From Baseline at 8 weeks follow-up - Social		The mean health related quality of life (EORTC C30,domains) - mean change from baseline at 8 weeks follow-up - social in the intervention groups was 11.5 lower (24.19 lower to 1.19 higher)		111 (1 study[1])	⊕⊕⊖⊖ low[4,7]	
Health Related Quality of Life (EORTC C30,Domains) - Mean change From Baseline at 8 weeks follow-up - Global		The mean health related quality of life (EORTC C30,domains) - mean change from baseline at 8 weeks follow-up - global in the intervention groups was 12.6 lower (20.87 to 4.33 lower)		111 (1 study[1])	⊕⊕⊕⊖ moderate [2]	
Health Related Quality of Life (EORTC C30,Symptoms) - Mean change From Baseline at 8 weeks follow-up - Fatigue		The mean health related quality of life (EORTC C30,symptoms) - mean change from baseline at 8 weeks follow-up - fatigue in the intervention groups was 13.1 higher (2.32 to 23.88 higher)		111 (1 study[1])	⊕⊕⊕⊖ moderate [2]	
Health Related Quality of Life (EORTC C30,Symptoms) - Mean change From Baseline at 8 weeks follow-up - Nausea		The mean health related quality of life (EORTC C30,symptoms) - mean change from baseline at 8 weeks follow-up - nausea in the intervention groups was 6.7 higher		111 (1 study[1])	⊕⊕⊖⊖ low[2,4]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
		(2.39 lower to 15.79 higher)				
Health Related Quality of Life (EORTC C30,Symptoms) - Mean change From Baseline at 8 weeks follow-up - Pain		The mean health related quality of life (EORTC C30,symptoms) - mean change from baseline at 8 weeks follow-up - pain in the intervention groups was 14.1 higher (3.17 to 25.03 higher)		111 (1 study[1])	⊕⊕⊕⊖ moderate [2]	
Health Related Quality of Life (EORTC C30,Symptoms) - Mean change From Baseline at 8 weeks follow-up - Dyspnea		The mean health related quality of life (EORTC C30,symptoms) - mean change from baseline at 8 weeks follow-up - dyspnea in the intervention groups was 7.3 higher (3.47 lower to 18.07 higher)		111 (1 study[1])	⊕⊕⊖⊖ low[2,4]	
Health Related Quality of Life (EORTC C30,Symptoms) - Mean change From Baseline at 8 weeks follow-up - Insomnia		The mean health related quality of life (EORTC C30,symptoms) - mean change from baseline at 8 weeks follow-up - insomnia in the intervention groups was 9.8 higher (3.51 lower to 23.11 higher)		111 (1 study[1])	⊕⊕⊖⊖ low[2,4]	
Health Related Quality of Life (EORTC C30,Symptoms) - Mean change From Baseline at 8 weeks follow-up - Constipation		The mean health related quality of life (EORTC C30,symptoms) - mean change from baseline at 8 weeks follow-up - constipation in the intervention groups was 19.3 higher (5.55 to 33.05 higher)		111 (1 study[1])	⊕⊕⊕⊖ moderate [7]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Health Related Quality of Life (EORTC C30,Symptoms) - Mean change From Baseline at 8 weeks follow-up - Diarrhoea		The mean health related quality of life (EORTC C30,symptoms) - mean change from baseline at 8 weeks follow-up - diarrhoea in the intervention groups was 1.4 lower (11.13 lower to 8.33 higher)		111 (1 study[1])	⊕⊕⊖⊖ low[2,4]	
Health Related Quality of Life (EORTC C30,Symptoms) - Mean change From Baseline at 8 weeks follow-up - Financial		The mean health related quality of life (EORTC C30,symptoms) - mean change from baseline at 8 weeks follow-up - financial in the intervention groups was 0.7 lower (9.62 lower to 8.22 higher)		111 (1 study[1])	⊕⊕⊖⊖ low[2,4]	

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;

1 Moore et al. 2003
2 The quality of the evidence was downgraded because of the unclear risk of selection bias (no details given about randomization and allocation methods)
3 Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs
4 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID
5 Smith et al. 2003
6 The quality of the evidence was downgraded because of the unclear risk of selection bias and the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions). Furthermore due to unclear risk of selective outcome reporting and potential risk of detection bias, the quality of the evidence was further downgraded to low

Table 196: Summary clinical evidence profile for gemcitabine and placebo versus gemcitabine and vandetanib in adults with locally advanced or metastatic pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	GEM + vandetanib	GEM + placebo				
Overall response rate (CR + PR)	129 per 1000	139 per 1000 (60 to 321)	RR 1.08 (0.47 to 2.5)	142 (1 study[1])	⊕⊕⊖⊖ low[2]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Progression Free Survival	Median time: 8.0 (4.5 to 10.1) months	Median time: 6.09 (5.0 to 9.9) months	HR 1.11 (0.87 to 1.41)	142 (1 study[1])	⊕⊕⊕⊖ moderate[3]	
Overall survival	Median time: 8.8 (7.1 to 11.6) months	Median time: 8.95 (6.6 to 11.7) months	HR 1.21 (0.96 to 1.53)	142 (1 study[1])	⊕⊕⊕⊖ moderate[3]	
Grade 3/4 toxicities - Thrombocytopenia	229 per 1000	279 per 1000 (158 to 491)	RR 1.22 (0.69 to 2.15)	142 (1 study[1])	⊕⊕⊖⊖ low[2]	
Grade 3/4 toxicities - Neutropenia	314 per 1000	487 per 1000 (321 to 739)	RR 1.55 (1.02 to 2.35)	142 (1 study[1])	⊕⊕⊕⊖ moderate[4]	
Grade 3/4 toxicities - Fatigue	214 per 1000	236 per 1000 (129 to 435)	RR 1.1 (0.6 to 2.03)	142 (1 study[1])	⊕⊕⊖⊖ low[2]	
Grade 3/4 toxicities - Leucopenia	186 per 1000	167 per 1000 (82 to 340)	RR 0.9 (0.44 to 1.83)	142 (1 study[1])	⊕⊕⊖⊖ low[2]	
Grade 3/4 toxicities - Hypertension	157 per 1000	126 per 1000 (55 to 283)	RR 0.8 (0.35 to 1.8)	142 (1 study[1])	⊕⊕⊖⊖ low[2]	
Grade 3/4 toxicities - ALT increased	157 per 1000	112 per 1000 (47 to 259)	RR 0.71 (0.3 to 1.65)	142 (1 study[1])	⊕⊕⊖⊖ low[2]	
Grade 3/4 toxicities - Hyponatraemia	114 per 1000	125 per 1000 (51 to 305)	RR 1.09 (0.45 to 2.67)	142 (1 study[1])	⊕⊕⊖⊖ low[2]	
Grade 3/4 toxicities - ALP increased	143 per 1000	111 per 1000 (47 to 266)	RR 0.78 (0.33 to 1.86)	142 (1 study[1])	⊕⊕⊖⊖ low[2]	
Grade 3/4 toxicities - Lethargy	100 per 1000	125 per 1000 (49 to 317)	RR 1.25 (0.49 to 3.17)	142 (1 study[1])	⊕⊕⊖⊖ low[2]	
Grade 3/4 toxicities - Lymphocyte count decreased	86 per 1000	125 per 1000 (47 to 333)	RR 1.46 (0.55	142 (1 study[1])	⊕⊕⊖⊖ low[2]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
			to 3.88)			
Grade 3/4 toxicities - Diarrhoea	57 per 1000	97 per 1000 (30 to 318)	RR 1.7 (0.52 to 5.56)	142 (1 study[1])	⊕⊕⊖⊖ low[2]	
Grade 3/4 toxicities - Blood bilirubin increased	29 per 1000	55 per 1000 (11 to 294)	RR 1.94 (0.37 to 10.28)	142 (1 study[1])	⊕⊕⊖⊖ low[2]	
Grade 3/4 toxicities - Abdominal pain	71 per 1000	28 per 1000 (6 to 139)	RR 0.39 (0.08 to 1.94)	142 (1 study[1])	⊕⊕⊖⊖ low[2]	
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;						
GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.						
1 Middleton et al. 2017 2 Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs 3 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. The quality of the evidence for this outcome was therefore downgraded for imprecision by one level as it was not statistically significant. 4 Evidence was downgraded by 1 due to very serious imprecision as 95%CI crossed one default MID						

11.2.4.4 Standard-dose versus low-dose gemcitabine

Table 197: Summary clinical evidence profile for standard-dose versus low-dose gemcitabine in adults with locally advanced or metastatic pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Low-dose GEM	Standard-dose GEM				
Overall response rate (CR + PR)	200 per 1000	182 per 1000 (32 to 1000)	RR 0.91 (0.16 to 5.3)	21 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Overall Survival	Median time: 7.2 (2.9 to	Median time: 5.2 (2 to 24.6) months	Not estimable [4]	21 (1 study[1])	⊕⊕⊖⊖ low[2,5]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	21.5) months					
Grade 3/4 toxicities. - Neutropenia	300 per 1000	90 per 1000 (12 to 738)	RR 0.3 (0.04 to 2.46)	21 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Grade 3/4 toxicities. - Anaemia	300 per 1000	39 per 1000 (3 to 678)	RR 0.13 (0.01 to 2.26)	21 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Grade 3/4 toxicities. - Thrombocytopenia	300 per 1000	39 per 1000 (3 to 678)	RR 0.13 (0.01 to 2.26)	21 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Grade 3/4 toxicities. - General fatigue	500 per 1000	275 per 1000 (85 to 860)	RR 0.55 (0.17 to 1.72)	21 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Grade 3/4 toxicities. - Nausea/vomiting	200 per 1000	90 per 1000 (10 to 856)	RR 0.45 (0.05 to 4.28)	21 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Grade 3/4 toxicities. - Diarrhoea	400 per 1000	92 per 1000 (12 to 684)	RR 0.23 (0.03 to 1.71)	21 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). *CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;*						
1 Sakamoto et al. 2006 *2 The quality of the evidence was downgraded because of the unclear risk of performance bias (no information on blinding of patients/ care providers delivering the interventions) and detection bias.* *3 The quality of the evidence was further downgraded from moderate to very low due to very serious imprecision as 95%CI crossed two default MIDs* *4 Survival did not differ significantly between the two groups (P = 0.47).* *5 From data provided by the authors about this outcome., is not possible estimate the precision in the effect size estimates.*						

11.2.4.5 5-FU versus combination 5-FU

Table 198: Summary clinical evidence profile for 5-FU versus combination 5-FU in adults with metastatic pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	5-FU combination chemotherapy	**5-FU alone**				
Overall response rate (CR + PR)	6 per 1000	53 per 1000 (10 to 291)	RR 8.62 (1.57 to 47.22)	319 (2 studies[1,2])	⊕⊕⊖⊖ low[3,4]	
Overall response rate	16 per 1000	34 per 1000 (3 to 364)	RR 2.17	123 (1 study[1])	⊕⊖⊖⊖ very low[5,6]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
(CR + PR) - 5-FU + doxorubicin + cisplatin			(0.2 to 23.31)			
Overall response rate (CR + PR) - 5-FU + cisplatin	0 per 1000	0 per 1000 (0 to 0)	RR 21 (1.25 to 353.49)	196 (1 study)	⊕⊖⊖⊖ very low[5,6]	
Progression Free Survival - 5-FU + cisplatin	Median time: 73 (n.r.) days	Median time: 7.2 (n.r.) days	HR 0.55 (0.41 to 0.74)	207 (1 study[2])	⊕⊕⊕⊖ moderate[7]	
Overall Survival	-	-	HR 0.97 (0.79 to 1.2)	319 (2 studies[1,2])	⊕⊕⊖⊖ low[3,6]	
Grade 3/4 toxicities: Nausea - 5-FU + doxorubicin + cisplatin	47 per 1000	220 per 1000 (71 to 511)	RR 4.7 (1.51 to 10.91)	123 (1 study[1])	⊕⊕⊖⊖ low[5]	
Grade 3/4 toxicities: Vomiting	43 per 1000	160 per 1000 (74 to 312)	RR 3.75 (1.73 to 7.32)	320 (2 studies[1,2])	⊕⊕⊕⊖ moderate[3]	
Grade 3/4 toxicities: Vomiting - 5-FU + doxorubicin + cisplatin	47 per 1000	152 per 1000 (44 to 412)	RR 3.25 (0.94 to 8.78)	123 (1 study[1])	⊕⊖⊖⊖ very low[5,13]	
Grade 3/4 toxicities: Vomiting - 5-FU + cisplatin	40 per 1000	165 per 1000 (60 to 381)	RR 4.12 (1.49 to 9.52)	197 (1 study[2])	⊕⊕⊕⊖ moderate[7]	
Grade 3/4 toxicities: Diarrhoea - 5-FU + cisplatin	20 per 1000	51 per 1000 (10 to 223)	RR 2.57 (0.51 to 11.15)	197 (1 study[2])	⊕⊕⊖⊖ low[6,7]	
Grade 3/4 toxicities: Leucopoenia - 5-FU + doxorubicin + cisplatin	312 per 1000	525 per 1000 (347 to 697)	RR 1.68 (1.11 to 2.23)	123 (1 study[1])	⊕⊕⊖⊖ low[5]	
Grade 3/4 toxicities: Stomatitis	85 per 1000	102 per 1000 (51 to 194)	RR 1.2 (0.6 to 2.27)	320 (2 studies[1,2])	⊕⊖⊖⊖ very low[3,6,9]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Grade 3/4 toxicities: Stomatitis - 5-FU + doxorubicin + cisplatin	141 per 1000	51 per 1000 (13 to 172)	RR 0.36 (0.09 to 1.22)	123 (1 study[1])	⊕⊖⊖⊖ very low[5,6]	
Grade 3/4 toxicities: Stomatitis - 5-FU + cisplatin	50 per 1000	134 per 1000 (50 to 312)	RR 2.68 (1.01 to 6.23)	197 (1 study)	⊕⊕⊖⊖ low[6,13]	
The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). *CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;*						
1 Cullinan et al. 1990 *2 Ducreux et al. 2002* *3 The quality of the evidence was downgraded because of the unclear risk of selection bias and performance bias in pooled studies* *4 Serious heterogeneity. I-squared = 40%* *5 The quality of the evidence was downgraded because of the unclear risk of selection bias and the high risk of performance bias (no blinding of patients/ care providers delivering the interventions).* *6 The quality of the evidence was downgraded due to very serious imprecision as 95%CI crossed two default MIDs* *7 The quality of the evidence was downgraded because of the unclear risk of selection bias and performance bias (no details given in the text to ascertain these criteria)* *8 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant* *9 Very serious heterogeneity. I-squared = 84%* *10 Spitzer's index values assessing quality of life were initially available at 1 and 2 months for 114 patients. Values was missing initially in 16% of patients. Mean index values in the FU group were 7.1 (initially), and 6.6 and 5.9 at 1 and 2 months, respectively (n = 54). For the FUP group values were 7.6, 7.4 and 7.0, respectively (n = 56).* *11 The quality of the evidence for this outcome. was downgraded because of the high risk of selective reporting of study findings.* *12 From data provided by the authors about this outcome., is not possible estimate the precision in the effect size estimates.* *13 Evidence was downgraded by 1 due to very serious imprecision as 95%CI crossed one default MID*						

Table 199: Summary clinical evidence profile for 5-FU versus combination 5-FU in adults with locally advanced or metastatic pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	5-FU combination chemotherapy	**5-FU alone**				
Overall response rate (CR + PR)	104 per 1000	177 per 1000 (92 to 344)	RR 1.7 (0.88 to 3.3)	220 (2 studies[1,2])	⊕⊖⊖⊖ very low[3,4,5]	
Overall response rate (CR + PR) - 5-	300 per 1000	78 per 1000 (9 to 633)	RR 0.26 (0.03	23 (1 study[1])	⊕⊖⊖⊖ very low[3,7]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
FU + doxorubicin + mitomycin			to 2.11)			
Overall response rate (CR + PR) - 5-FU + mitomycin	86 per 1000	195 per 1000 (93 to 414)	RR 2.28 (1.08 to 4.83)	144 (1 study[1])	⊕⊕⊕⊖ moderate[5]	
Progression Free Survival - 5-FU + mitomycin	-	-	HR 0.81 (0.62 to 1.06)	144 (1 study[1])	⊕⊕⊕⊖ moderate[6]	
Overall Survival	-	-	HR 0.97 (0.79 to 1.20)	353 (2 studies[1,2])	⊕⊕⊖⊖ low[4,6]	
Grade 3/4 toxicities: Diarrhoea - 5-FU + mitomycin	47 per 1000	49 per 1000 (14 to 155)	RR 1.05 (0.31 to 3.32)	209 (1 study[2])	⊕⊕⊖⊖ low[7]	
Grade 3/4 toxicities: Neutropenia - 5-FU + mitomycin	0 per 1000	0 per 1000 (0 to 0)	RR 7.34 (0.38 to 140.36)	209 (1 study)	⊕⊕⊖⊖ low[7]	
Grade 3/4 toxicities: Stomatitis - 5-FU + mitomycin	75 per 1000	108 per 1000 (45 to 257)	RR 1.44 (0.6 to 3.44)	209 (1 study[2])	⊕⊕⊖⊖ low[7]	

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio; OR: Odds ratio; HR: Hazard ratio;

1 Cullinan et al. 1985
2 Maisey et al. 2002
3 The quality of the evidence was downgraded because of the potential risk of selection bias and performance bias in one pooled study (Cullinan et al. 1985)
4 Very serious heterogeneity. I-squared = 73%
5 The quality of the evidence was downgraded due to serious imprecision as 95%CI crossed one default MID
6 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. The quality of the evidence for this outcome was therefore downgraded for imprecision by one level as it was not statistically significant.
7 Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs

11.2.4.6 Combination 5-FU (FSM) versus other chemotherapy

Table 200: Summary clinical evidence profile for combination 5-FU (FSM) versus other chemotherapy regimens in adults with locally advanced or metastatic pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	5-FU combination chemotherapy (FSM)				
Overall response rate (CR + PR) - FAM: 5-FU, Adriamycin, mitomycin	100 per 1000	32 per 1000 (9 to 114)	RR 0.32 (0.09 to 1.14)	184 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Overall response rate (CR + PR) - Mitomycin + 5-FU	71 per 1000	271 per 1000 (107 to 686)	RR 3.8 (1.5 to 9.61)	140 (1 study[4])	⊕⊕⊖⊖ low[2]	
Overall Survival - FAM: 5-FU, Adriamycin, mitomycin5	-	-	Not estimable 5	196 (1 study[1])	⊕⊕⊖⊖ low[2,6]	
Overall Survival - Mitomycin + 5-FU7	-	-	Not estimable 7	106 (1 study[4])	⊕⊕⊖⊖ low[2,6]	
Grade 3/4 toxicities: Diarrhoea - Mitomycin + 5-FU	29 per 1000	14 per 1000 (1 to 141)	RR 0.50 (0.05-5.39)	140 (1 study[4])	⊕⊖⊖⊖ very low[2,3]	
Grade 3/4 toxicities: Nausea/vomiting - FAM: 5-FU, Adriamycin, mitomycin	133 per 1000	160 per 1000 (79 to 321)	RR 1.2 (0.59 to 2.41)	184 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Grade 3/4 toxicities: Nausea/vomiting - Mitomycin + 5-FU	257 per 1000	414 per 1000 (255 to 674)	RR 1.61 (0.99 to 2.62)	140 (1 study[4])	⊕⊖⊖⊖ very low[2,8]	
Grade 3/4 toxicities: Leukopenia - FAM: 5-FU, Adriamycin, mitomycin	267 per 1000	128 per 1000 (69 to 240)	RR 0.48 (0.26 to 0.9)	184 (1 study[1])	⊕⊖⊖⊖ very low[2,8]	
Grade 3/4 toxicities: Leukopenia - Mitomycin + 5-FU	157 per 1000	129 per 1000 (57 to 291)	RR 0.82 (0.36 to 1.85)	140 (1 study[4])	⊕⊖⊖⊖ very low[2,3]	
Grade 3/4 toxicities: Thrombocytopenia - FAM: 5-FU, Adriamycin, mitomycin	367 per 1000	213 per 1000 (132 to 341)	RR 0.58 (0.36 to 0.93)	184 (1 study[1])	⊕⊖⊖⊖ very low[2,8]	
Grade 3/4 toxicities: Thrombocytopenia - Mitomycin + 5-FU	229 per 1000	142 per 1000 (71 to 293)	RR 0.62 (0.31 to 1.28)	140 (1 study[4])	⊕⊖⊖⊖ very low[2,3]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Drug-related deaths - Mitomycin + 5-FU	57 per 1000	14 per 1000 (2 to 125)	RR 0.25 (0.03 to 2.18)	140 (1 study[4])	⊕⊖⊖⊖ very low[2,3]	
The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). *CI: Confidence interval; RR: Risk ratio; OR: Odds ratio;*						
1 Oster et al. 1986 *2 The quality of the evidence was downgraded because of the unclear risk of selection bias and performance bias (no details given in the text to ascertain these criteria), and likely selective reporting of study findings/outcomes* *3 The quality of the evidence was downgraded due to very serious imprecision as 95%CI crossed two default MIDs* *4 Bukowski et al. 1983* *5 Overall survival did not differ significantly between the treatments (median, 18.3 weeks on FSM; 26.4 weeks on FAM; P = 0.21).* *6 From data provided by the authors about this outcome is not possible estimate the precision in the effect size estimates.* *7 no differences between groups (Median survival (wks, measurable and non-measurable disease): SFM= 18-21, MF=17-18)* *8 The quality of the evidence was downgraded due to serious imprecision as 95%CI crossed one default MID*						

11.2.4.7 Intra-arterial chemotherapy versus systemic chemotherapy

Table 201: Summary clinical evidence profile for intra-arterial chemotherapy versus systemic chemotherapy in adults with locally advanced or metastatic pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Systemic chemotherapy	Intra-arterial chemotherapy				
Overall response rate (CR + PR)	72 per 1000	252 per 1000 (113 to 560)	RR 2.76 (1.23-6.18)	181 (3 studies[1,2,3])	⊕⊕⊖⊖ low[4]	
Overall Survival	-	-	HR 1.02 (0.63 to 1.66)	138 (1 study[2])	⊕⊕⊖⊖ low[5,6]	
Grade 3/4 toxicities - Thrombocytopenia	15 per 1000	239 per 1000 (33 to 1000)	RR 16.04 (2.2 to 117.24)	138 (1 study[2])	⊕⊕⊕⊖ moderate[5]	
Grade 3/4 toxicities - Nausea/vomiting	45 per 1000	6 per 1000 (0 to 115)	RR 0.13 (0.01 to 2.56)	138 (1 study[2])	⊕⊖⊖⊖ very low[5,7]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Grade 3/4 toxicities - Diarrhoea	30 per 1000	6 per 1000 (0 to 115)	RR 0.19 (0.01 to 3.86)	138 (1 study[2])	⊕⊖⊖⊖ very low[5,7]	
Grade 3/4 toxicities - Leukopenia	75 per 1000	197 per 1000 (75 to 518)	RR 2.64 (1.01 to 6.94)	138 (1 study[2])	⊕⊕⊖⊖ low[5,8]	

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;

1 Aigner et al. 1998
2 Cantore et al. 2004
3 Ji et al. 2003
4 The quality of the evidence was downgraded because of the unclear risk of selection bias in two studies (Aigner et., 1998 and Ji 2003), the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions) and detection bias in all studies included in the meta-analysis.
5 The quality of the evidence was downgraded because of the unclear risk of performance bias (no blinding of patients/ care providers delivering the interventions) and detection bias (no blinding of investigators/outcome assessors).
6 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant
7 The quality of the evidence was downgraded due to very serious imprecision as 95%CI crossed two default MIDs
8 The quality of the evidence was downgraded due to serious imprecision as 95%CI crossed one default MID

11.2.4.8 Chemotherapy versus chemotherapy and prophylactic anticoagulant

Table 202: Summary clinical evidence profile for gemcitabine versus gemcitabine and weight-adjusted dalteparin in adults with locally advanced or metastatic pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Weight-adjusted dalteparin + gemcitabine	GEM alone				
Overall Survival	-	-	Not estimable1	121 (1 study[2])	⊕⊕⊕⊖ moderate[2,3,4]	
Adverse effects: Grade 3/4 toxicities - Haematological	424 per 1000	369 per 1000 (233 to 581)	RR 0.87 (0.55 to 1.37)	116 (1 study[2])	⊕⊖⊖⊖ very low[3,5]	
Adverse effects: Grade 3/4 toxicities -	305 per 1000	333 per 1000 (195 to 567)	RR 1.09 (0.64 to 1.86)	116 (1 study)	⊕⊖⊖⊖ very low[3,5]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Hepatic function impairment						
Adverse effects: vascular thromboembolism (VTE) - Total patients with VTEs	306 per 1000	120 per 1000 (55 to 260)	RR 0.39 (0.18 to 0.85)	121 (1 study)	⊕⊕⊕⊖ moderate[3]	
The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). *CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;*						
1 Median OS was 9.7 months for GEM and 8.7 months for GEMWAD (p = 0.682) *2 Maraveyas et al. 2012* *3 The quality of the evidence was downgraded because of the unclear risk of performance bias (no blinding of patients/ care providers delivering the interventions). Furthermore due to unclear risk of selective outcome reporting and potential risk of detection bias, the quality of the evidence was further downgraded to moderate.* *4 From data provided by the authors about this outcome is not possible estimate the precision in the effect size estimates.* *5 The quality of the evidence was further downgraded from moderate to low due to very serious imprecision as 95%CI crossed two default MIDs*						

Table 203: Summary clinical evidence profile for gemcitabine and enoxaparin versus gemcitabine in adults with locally advanced or metastatic pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	GEM	Enoxaparin + GEM				
Progression Free Survival	Median time: 5.4 (4.2 to 5.8) months	Median time: 5.0 (3.7 to 5.5) months	HR 1.06 (0.84 to 1.34)	312 (1 study[1])	⊕⊕⊖⊖ low[2,3]	
Overall Survival	Median time: 8.0 (6.8 to 9.7) months	Median time: 8.5 (7.0 to 9.8) months	HR 1.1 (0.87 to 1.39)	312 (1 study[1])	⊕⊕⊖⊖ low[2,3]	
Adverse effects: vascular thromboembolism (VTE) - Symptomatic VTE	145 per 1000	62 per 1000 (30 to 127)	RR 0.43 (0.21 to 0.88)	312 (1 study[1])	⊕⊕⊖⊖ low[2,5]	
Adverse effects: vascular thromboembolism (VTE) - Major haemorrhages	66 per 1000	82 per 1000 (37 to 180)	RR 1.24 (0.56 to 2.73)	312 (1 study[1])	⊕⊖⊖⊖ very low[2,4]	
The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). *CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;*						
1 Pelzer et al. 2015						

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
2 The quality of the evidence was downgraded because of the high risk of performance bias (no blinding of patients/ care providers delivering the interventions) and the unclear risk of detection bias (no details about the blinding of outcome assessors) *3 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. The quality of the evidence for this outcome was therefore downgraded for imprecision by one level as it was not statistically significant.* *4 The quality of the evidence was downgraded from moderate to very low due to very serious imprecision as 95%CI crossed two default MIDs* *5 The quality of the evidence was downgraded from moderate to low due to serious imprecision as 95%CI crossed one default MID*						

11.2.4.9 Second-line chemotherapy versus best supportive care

Table 204: Summary clinical evidence profile for second-line chemotherapy versus best supportive care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Chemotherapy (second-line)	BSC				
Progression Free Survival	Median time: 46 (1-351) days	Median time: 43 (1-372) days	HR 0.76 (0.57 to 1.01)	286 (1 study[1])	⊕⊕⊖⊖ low[2,3]	
Overall Survival	Median time: 105 (5–875) days	Median time: 84 (2-271) days	HR 0.85 (0.66 to 1.09)	286 (1 study[1])	⊕⊕⊖⊖ low[2,3]	
Grade 3/4/5 adverse effects - Asthenia/fatigue	76 per 1000	85 per 1000 (39 to 187)	RR 1.12 (0.51 to 2.46)	286 (1 study[1])	⊕⊖⊖⊖ very low[2,4]	
Grade 3/4/5 adverse effects - Abdominal pain	90 per 1000	78 per 1000 (36 to 169)	RR 0.87 (0.4 to 1.88)	286 (1 study[1])	⊕⊖⊖⊖ very low[2,4]	
Grade 3/4/5 adverse effects - Anaemia	21 per 1000	50 per 1000 (13 to 188)	RR 2.4 (0.63 to 9.1)	286 (1 study[1])	⊕⊖⊖⊖ very low[2,4]	
Grade 3/4/5 adverse effects - Vomiting	14 per 1000	50 per 1000 (10 to 235)	RR 3.6 (0.76 to 17.03	286 (1 study[1])	⊕⊖⊖⊖ very low[2,4]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Grade 3/4/5 adverse effects - Nausea	14 per 1000	43 per 1000 (9 to 207)	RR 3.09 (0.63 to 15.03)	286 (1 study[1])	⊕⊖⊖⊖ very low[2,4]	
Grade 3/4/5 adverse effects - Deep vein thrombosis	7 per 1000	35 per 1000 (4 to 300)	RR 5.14 (0.61 to 43.46)	286 (1 study[1])	⊕⊖⊖⊖ very low[2,4]	
Grade 3/4/5 adverse effects - Renal failure	0 per 1000	0 per 1000 (0 to 0)	RR 11.31 (0.63 to 202.65)	286 (1 study[1])	⊕⊖⊖⊖ very low[2,4]	
Grade 3/4/5 adverse effects - Hyperbilirubinemia	14 per 1000	28 per 1000 (5 to 152)	RR 2.06 (0.38 to 11.05)	286 (1 study[1])	⊕⊖⊖⊖ very low[2,4]	
Grade 3/4/5 adverse effects - Leucopoenia	0 per 1000	0 per 1000 (0 to 0)	RR 9.25 (0.5 to 170.31)	286 (1 study[1])	⊕⊖⊖⊖ very low[2,4]	

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;

1 Ciuleanu et al. 2009
2 The quality of the evidence was downgraded because of the unclear risk of selection bias and the potential risk of performance bias (no blinding of patients/ care providers)
3 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. The quality of the evidence for this outcome was therefore downgraded for imprecision by one level as it was not statistically significant.
4 The quality of the evidence was further downgraded from moderate to low due to very serious imprecision as 95%CI crossed two default MIDs

11.2.4.10 Second-line chemotherapy versus other chemotherapy regimens

Table 205: Summary clinical evidence profile for LV5FU2-CDDP then gemcitabine versus gemcitabine then LV5FU2-CDDP in adults with metastatic pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	GEM followed by LV5FU2-CDDP	**LV5FU2-CDDP followed by gemcitabine**				

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Overall response rate (CR + PR)	220 per 1000	187 per 1000 (108 to 323)	RR 0.85 (0.49 to 1.47)	202 (1 study[1])	⊕⊕⊖⊖ low[2]	
Progression free-survival	Median time: 3.4 (2.4 to 4.4) months	Median time: 3.5 (2.4 to 4.1) months	HR 1.06 (0.80 to 1.40)	202 (1 study[1])	⊕⊕⊕⊖ moderate [3]	
Overall survival	Median time: 6.7 (5.4 to 8.6) months	Median time: 8.03 (5.9 to 9.8) months	HR 0.97 (0.73 to 1.79)	202 (1 study[1])	⊕⊕⊕⊖ moderate [3]	
Grade 3/4 toxicities: Nausea/vomiting	150 per 1000	138 per 1000 (70 to 270)	RR 0.92 (0.47 to 1.8)	202 (1 study[1])	⊕⊕⊖⊖ low[2]	

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;

1 Dahan et al. 2010
2 Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs
3 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. The quality of the evidence for this outcome was therefore downgraded for imprecision by one level as it was not statistically significant.

Table 206: Summary clinical evidence profile for irinotecan and raltitrexed versus raltitrexed in adults with metastatic pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Raltitrexed alone	Irinotecan + raltitrexed				
Objective response	158 per 1000	22 per 1000 (2 to 409)	RR 0.14 (0.01 to 2.59)	38 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Grade 3/4 toxicities - Leukocytopenia	211 per 1000	263 per 1000 (84 to 832)	RR 1.25 (0.4 to 3.95)	38 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Grade 3/4 toxicities - Neutropenia	158 per 1000	210 per 1000 (54 to 816)	RR 1.33 (0.34 to 5.17)	38 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Grade 3/4 toxicities - Thrombocytopenia	-	-	Not estimable	38 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	There were no cases of thrombocytopenia in either group

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Grade 3/4 toxicities - Nausea/vomiting	53 per 1000	53 per 1000 (4 to 782)	RR 1 (0.07 to 14.85)	38 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Grade 3/4 toxicities - Stomatitis	-	-	Not estimable	38 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	There were no cases of stomatitis in either group
Grade 3/4 toxicities - Fatigue	-	-	Not estimable	38 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	There were no cases of fatigue in either group
Grade 3/4 toxicities - Diarrhoea	105 per 1000	105 per 1000 (17 to 672)	RR 1 (0.16 to 6.38)	38 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). *CI: Confidence interval; RR: Risk ratio;*						
1 Ulrich-Pur et al. 2003 *2 The quality of the evidence was downgraded because of the unclear risk of performance bias (no details given about the blinding of patients/ care providers delivering the interventions), besides the unclear risk of detection bias (no details given in the text)* *3 Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs* *5 The quality of the evidence was downgraded because of the unclear risk of performance bias and the unclear risk of detection bias (no details given in the text), besides the potential risk of selective findings reporting for this outcome..* *6 From data provided by the authors about this outcome it was not possible estimate the precision in the effect size estimates.*						

Table 207: Summary clinical evidence profile for Oxaliplatin and 5-FU versus bolus 5-FU and bolus folinic acid in adults with locally advanced or metastatic pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Bolus leucovorin + bolus 5-FU	Oxaliplatin + 5-FU				
Overall response rate (CR + PR)	83 per 1000	125 per 1000 (23 to 682)	RR 1.5 (0.27 to 8.19)[4]	48 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Progression Free Survival5	-	-	Not estimable [5]	48 (1 study[1])	⊕⊕⊖⊖ low[2,6]	
Overall Survival5	-	-	Not estimable 5	48 (1 study[1])	⊕⊕⊖⊖ low[2,6]	
Grade 3/4 toxicities - Diarrhoea	208 per 1000	208 per 1000 (69 to 627)	RR 1 (0.33 to 3.01)	48 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Grade 3/4 toxicities - Nausea/vomiting	125 per 1000	166 per 1000 (41 to 666)	RR 1.33 (0.33 to 5.33)	48 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Grade 3/4 toxicities - Stomatitis	42 per 1000	42 per 1000 (3 to 628)	RR 1 (0.07 to 15.08)	48 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Grade 3/4 toxicities - Haematological	83 per 1000	125 per 1000 (23 to 682)	RR 1.5 (0.27 to 8.19)	48 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio

1 Azmy et al. 2013
2 The quality of the evidence was downgraded because of the unclear risk of detection bias (no details given in the text to ascertain these criteria) and the high risk of performance bias (no blinding of patients/ care providers delivering the interventions).
3 Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs
4 No complete response in both groups
5 There was no statistical significance in progression-free survival between the 2 regimens (p value by log rank test = .4619), and so was the situation in overall survival (p-value by log rank test = .5248).
6 From data provided by the authors about this outcome., is not possible estimate the precision in the effect size estimates
7 The quality of the evidence was downgraded because of the unclear risk of detection bias (no details given in the text to ascertain these criteria), the high risk of performance bias (no blinding of patients/ care providers delivering the interventions), and the potential risk of selective reporting of findings for this outcome.

Table 208: Summary clinical evidence profile for mFOLFOX6 versus 5-FU and folinic acid in adults with locally advanced or metastatic pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Leucovorin /5-FU	mFOLFOX6 (5-FU + leucovorin + oxaliplatin)				
Overall response rate (CR + PR)	93 per 1000	130 per 1000 (44 to 383)	RR 1.4 (0.47 to 4.14)	108 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Progression Free Survival	Median time: 2.9 (n.r.) months	Median time: 3.1 (n.r.) months	HR 1 (0.66 to 1.52)	108 (1 study[1])	⊕⊕⊖⊖ low[2,4]	
Overall Survival	Median time: 9.9 (n.r.) months	Median time: 3.1 (n.r.) months	HR 1.78 (1.08 to 2.93)	108 (1 study[1])	⊕⊕⊕⊖ moderate[5]	
Grade 3/4 toxicities - Neutropenia	38 per 1000	326 per 1000 (79 to 1000)	RR 8.65 (2.1 to 35.72)	102 (1 study[1])	⊕⊕⊕⊖ moderate[2]	

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Grade 3/4 toxicities - Febrile neutropenia	0 per 1000	0 per 1000 (0 to 0)	RR 5.4 (0.27 to 109.76)	102 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Grade 3/4 toxicities - Fatigue	19 per 1000	143 per 1000 (18 to 1000)	RR 7.57 (0.97 to 59.34)	102 (1 study[1])	⊕⊕⊖⊖ low[2,5]	
Grade 3/4 toxicities - Thrombocytopenia	19 per 1000	82 per 1000 (9 to 705)	RR 4.33 (0.5 to 37.39)	102 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Grade 3/4 toxicities - Dehydration	0 per 1000	0 per 1000 (0 to 0)	RR 9.72 (0.54 to 176)	102 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Grade 3/4 toxicities - Pulmonary embolism	0 per 1000	0 per 1000 (0 to 0)	RR 5.4 (0.27 to 109.76)	102 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Grade 3/4 toxicities - Vomiting	0 per 1000	0 per 1000 (0 to 0)	RR 5.4 (0.27 to 109.76)	102 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Grade 3/4 toxicities - Hypokalaemia	0 per 1000	0 per 1000 (0 to 0)	RR 5.4 (0.27 to 109.76)	102 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Grade 3/4 toxicities - Peripheral neuropathy	0 per 1000	0 per 1000 (0 to 0)	RR 5.4 (0.27 to 109.76)	102 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Health Related Quality of Life	See comment	See comment	Not estimable	0 (1 study[1])	⊕⊕⊖⊖ low[4,6]	No significant differences were observed in time to deterioration on the EORTC QLQ-C30 global health scale.

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;

1 Gill et al. 2016
2 The quality of the evidence was downgraded because of the unclear risk of selection bias (no details given in the text about methods of allocation) and potential risk of performance bias (open-label trial)
3 Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs
4 The quality of the evidence was downgraded because of the unclear risk of selection bias (no details given in the text about methods of allocation), potential risk of performance bias (open-label trial) and the high risk of selective reporting of study findings for this outcome.
5 The committee decided to consider all survival outcomes that were statistically significant, regardless of

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant *6 From data provided by the authors about this outcome is not possible estimate the precision in the effect size estimates.*						

Table 209: Summary clinical evidence profile for capecitabine and erlotinib then gemcitabine versus gemcitabine and erlotinib then capecitabine in adults with locally advanced or metastatic pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	GEM + erlotinib followed by capecitabine	Capecitabine + erlotinib followed by GEM				
Overall response rate (CR + PR)	65 per 1000	32 per 1000 (6 to 149)	RR 0.49 (0.1 to 2.29)	140 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Overall survival	Median time: 6.2 (n.r.) months	Median time: 6.9 (n.r.) months	HR 1.02 (0.79 to 1.31)	274 (1 study[1])	⊕⊕⊖⊖ low[2,4]	
Grade 3/4 toxicities - Nausea/vomiting	130 per 1000	113 per 1000 (45 to 279)	RR 0.87 (0.35 to 2.15)	139 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Grade 3/4 toxicities - Diarrhoea	39 per 1000	7 per 1000 (0 to 131)	RR 0.18 (0.01 to 3.36)	139 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Grade 3/4 toxicities - Leukocytopenia	52 per 1000	32 per 1000 (6 to 170)	RR 0.62 (0.12 to 3.28)	139 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Grade 3/4 toxicities - Thrombocytopenia	65 per 1000	32 per 1000 (6 to 160)	RR 0.5 (0.1 to 2.47)	139 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). *CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;*						
1 Heinemann et al. 2012 *2 The quality of the evidence was downgraded because of the high risk of detection bias (no masking of investigators/outcome assessors) and the high risk of performance bias (no blinding of patients/ care providers*						

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
delivering the interventions). *3 The quality of the evidence was downgraded due to very serious imprecision as 95%CI crossed two default MIDs* *4 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. The quality of the evidence for this outcome was therefore downgraded for imprecision by one level as it was not statistically significant*						

Table 210: Summary clinical evidence profile for 5-FU and folinic acid versus oxaliplatin and 5-FU in adults with locally advanced or metastatic pancreatic cancer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Oxaliplatin + 5-FU	FA + 5-FU				
Progression Free Survival	Median time: 2.9 (2.4 to 3.2) months	Median time: 2.0 (0.5 to 0.9) months	HR 0.68 (0.49 to 0.94)	160 (1 study[1])	⊕⊕⊕⊖ moderate [2]	
Overall Survival	Median time: 5.9 (4.1 to 7.4) months	Median time: 3.3 (2.7 to 4.0) months	HR 0.66 (0.48 to 0.91)	160 (1 study[1])	⊕⊕⊕⊖ moderate 2	
Grade 3/4 toxicities - Anaemia	24 per 1000	40 per 1000 (7 to 230)	RR 1.66 (0.28 to 9.66)	160 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Grade 3/4 toxicities - Nausea/emesis	36 per 1000	13 per 1000 (1 to 124)	RR 0.37 (0.04 to 3.47)	160 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Grade 3/4 toxicities - Paresthesia	0 per 1000	0 per 1000 (0 to 0)	RR 7.73 (0.41 to 147.21)	160 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Grade 3/4 toxicities - Pain	405 per 1000	316 per 1000 (206 to 482)	RR 0.78 (0.51 to 1.19)	160 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Grade 3/4 toxicities - Leucopoenia	-	-	Not estimable	160 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	No cases of leucopenia occurred in either group
Grade 3/4 toxicities - Thrombocytopenia	0 per 1000	0 per 1000 (0 to 0)	RR 3.31 (0.14 to 80.09)	160 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
Grade 3/4 toxicities - Diarrhoea	0 per 1000	0 per 1000 (0 to 0)	RR 3.31 (0.14 to 80.09)	160 (1 study[1])	⊕⊖⊖⊖ very low[2,3]	
The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison						

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
group and the relative effect of the intervention (and its 95% CI). *CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;*						
1 Oettle et al. 2014 *2 The quality of the evidence was downgraded because of the unclear risk of detection bias (no details given in the text to ascertain these criteria) and the high risk of performance bias (no blinding of patients/ care providers delivering the interventions).* *3 The quality of the evidence was downgraded due to very serious imprecision as 95%CI crossed two default MIDs*						

11.2.5 Economic evidence

11.2.5.1 Systematic literature review

Two studies (Tam et al. 2013, Attard et al. 2014) were included in the review of published economic evidence for this topic. Both papers reported cost-utility studies of chemotherapy interventions in people with metastatic pancreatic cancer from a Canadian health payer perspective and reported outcomes in terms of cost (Canadian dollars) per QALY. Both studies used gemcitabine chemotherapy as the base case compared to FOLFIRINOX. Tam 2013 also included gemcitabine with the addition of capecitabine and gemcitabine with the addition of erlotinib in their analysis. Effectiveness data to inform both economic models were based on phase III randomised trials and the same trial was used to inform the effectiveness of FOLFIRINOX and gemcitabine in both studies. Tam 2013 used a cost year of 2010 compared to Attard 2014 which used a cost year of 2013. Both studies were deemed partially applicable to the decision problem that we are evaluating. This is because they did not take a NHS+PSS perspective.

Potentially serious limitations were identified with both studies. There were potential conflicts of interest with the studies either being funded by, or the authors having received funding from a manufacturer of one of the interventions considered. Both studies performed probabilistic sensitivity analyses although these were inadequately reported with descriptions of the distributions missing.

The base cases in Tam 2013 and Attard 2014 suggested an ICER of CA$133,184 and CA$57,858 for FOLFIRINOX compared to gemcitabine. This discrepancy can largely be explained by Tam 2013 having an upper limit for the number of cycles of FOLFIRINOX, a more detailed costing and used a different method for estimating quality of life weightings.

Deterministic sensitivity analysis suggested these results were robust to alternative clinical assumptions. Probabilistic sensitivity analyses suggested that in Tam 2013, FOLFIRNOX had a less than 5% chance of being cost effective compared to gemcitabine under the conventionally held Canadian willingness to pay threshold of CA$100,000. Alternatively, Attard 2014 reported an 85% chance of being cost effective at the same WTP threshold. This again can be accounted for by the more favourable assumptions towards FOLFIRINOX in Attard 2014.

References to all included studies and evidence tables for all economic evaluations included in the systematic literature review of the economic evidence are presented in Appendix L. Economic evidence profiles of these studies are presented in Appendix K.

11.2.6 Evidence statements

11.2.6.1 Chemotherapy versus chemoimmunotherapy

11.2.6.1.1 First-line chemotherapy and sequential/concurrent immunotherapy versus chemotherapy

Response rate

Very low quality evidence from 1 Multicentre Phase III RCT (n=1062) showed no clinically important difference between 1st-line chemotherapy with sequential GV1001, first-line chemotherapy with concurrent GV1001 and first-line chemotherapy alone about the relative probability of objective response rate (CR + PR) in adults with locally advanced or metastatic pancreatic cancer: RR 0.98 (95% CI 0.58-1.67- sequential group) and RR 1.13 (95% CI 0.68-1.88 - concurrent group), where RR less than 1 favours the chemotherapy alone arm.

Progression-free survival

Low quality evidence from 1 Multicentre Phase III RCT (n=712) showed no clinically important difference between first-line chemotherapy with concurrent GV1001 and first-line chemotherapy alone in time to progression rates in adults with locally advanced or metastatic pancreatic cancer: HR 1.00 (95% CI 0.84-1.19), where HR higher than 1 favours the chemotherapy alone arm.

Moderate quality evidence from 1 Multicentre Phase III RCT (n=708) showed that there is a clinically important difference favouring first-line chemotherapy alone on PFS rates when compared with first-line chemotherapy plus sequential GV1001 in adults with locally advanced or metastatic pancreatic cancer: HR 1.5 (95% CI 1.26-1.79)

Overall Survival

Low quality evidence from 1 Multicentre Phase III RCT (n=712) showed no clinically important difference between first-line chemotherapy with concurrent GV1001 and first-line chemotherapy alone in overall survival rates in adults with locally advanced or metastatic pancreatic cancer: HR 1.05 (95% CI 0.85-1.29), where HR higher than 1 favours the chemotherapy alone arm.

Low quality evidence from 1 Multicentre Phase III RCT (n=708) showed no clinically important difference between first-line chemotherapy with sequential GV1001 and first-line chemotherapy alone in overall survival rates in adults with locally advanced or metastatic pancreatic cancer: HR 1.19 (95% CI 0.97-1.48), where HR higher than 1 favours the chemotherapy alone arm.

Adverse Events

Very low and low quality evidence from 1 Multicentre Phase III RCT (n=1062) showed no clinically important difference between first-line chemotherapy with sequential GV1001, first-line chemotherapy with concurrent GV1001 and first-line chemotherapy alone about the relative risk of grade 3/4/5 toxicities (including nausea, vomiting, diarrhoea, fatigue, neutropenia, and pain) in adults with locally advanced or metastatic pancreatic cancer.

Health-related quality of life

Low quality evidence from 1 Multicentre Phase III RCT (n=1062) showed no clinically important difference between first-line chemotherapy with sequential GV1001, first-line chemotherapy with concurrent GV1001 and first-line chemotherapy alone on the improvement of quality of life (measured as mean of the EORTC QLQ-C30) in adults with locally advanced or metastatic pancreatic cancer.

11.2.6.1.2 Second-line chemoimmunotherapy versus chemotherapy

Response rate

Very low quality evidence from 1 Phase III RCT (n=58) showed no clinically important difference between chemotherapy + concurrent ICT [CIK - Cytokine-induced killer cells] and chemotherapy as second-line treatments on the relative probability of objective response rate (CR + PR) in adults with locally advanced/metastatic pancreatic cancer: RR 1.07 (95% CI 0.16-7.1), where RR less than 1 favours the chemotherapy alone arm.

Progression-free survival

Very low quality evidence from 1 Phase III RCT (n=58) showed no clinically important difference between chemotherapy + concurrent ICT [CIK - Cytokine-induced killer cells] and chemotherapy alone as second-line treatments on progression-free survival in adults with locally advanced/metastatic pancreatic cancer (relative effect not estimable).

Overall Survival

Very low quality evidence from 1 Phase III RCT (n=58) showed no clinically important difference between chemotherapy + concurrent ICT [CIK - Cytokine-induced killer cells] and chemotherapy alone as second-line treatments on survival rates in adults with locally advanced/metastatic pancreatic cancer (relative effect not estimable).

Adverse Events

Very low quality evidence from 1 Phase III RCT (n=58) showed no clinically important difference between chemotherapy + concurrent ICT [CIK - Cytokine-induced killer cells] and chemotherapy alone as second-line treatments on the relative risk of grade 3/4 toxicities (including neutropenia, nausea/vomiting, diarrhoea, and fatigue) in adults with locally advanced/metastatic pancreatic cancer: RR 1.07 (95% CI 0.07-16.32), RR 0.36 (95% CI 0.02-8.4), RR 1.07 (95% CI 0.16-7.1), and RR 0.36 (95% CI 0.02-8.4) where RR less than 1 favours the chemotherapy + concurrent ICT arm.

Health-related quality of life

No evidence was identified to inform this outcome.

11.2.6.2 Gemcitabine versus other chemotherapy

11.2.6.2.1 In adults with metastatic disease

Response rate

High quality evidence from 1 Multicentre Phase III RCT (n=342) showed that there is a clinically important difference favouring gemcitabine single-agent on objective response rate (CR + PR) compared to FOLFIRINOX in adult with metastatic pancreatic cancer: RR 3.38 (95% CI 2.01-5.65).

Very low quality evidence from a meta-analysis of 2 Phase III RCTs (n=425) showed no clinically important difference between gemcitabine + Cisplatin and gemcitabine single-agent about the relative probability of objective response rate (CR + PR) in adult with metastatic pancreatic cancer: RR 1.25 (95% CI 0.73-2.12), where RR higher less 1 favours the gemcitabine arm.

Moderate quality evidence from 1 Phase III RCT (n=619) showed no clinically important difference between gemcitabine + Ganitumab [12 mg/kg] and in the gemcitabine single-agent about the relative probability of objective response rate (CR + PR) in adult with metastatic pancreatic cancer: RR 1.58 (95% CI 1.04-2.39), where RR less than 1 favours the gemcitabine arm.

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Moderate quality evidence from 1 Phase III RCT (n=464) showed no clinically important difference between gemcitabine + Ganitumab [20 mg/kg] and gemcitabine single-agent about the relative probability of objective response rate (CR + PR) in adult with metastatic pancreatic cancer: RR 1.44 (95% CI 0.87-2.39), where RR less than 1 favours the gemcitabine arm.

Moderate quality evidence from 1 Phase III RCT (n=607) showed no clinically important difference between gemcitabine + erlotinib + bevacizumab group and gemcitabine + erlotinib about the relative probability of objective response rate (CR + PR) in adult with metastatic pancreatic cancer: RR 1.57 (95% CI 0.98-2.53), where RR less than 1 favours the gemcitabine + erlotinib arm.

Low quality evidence from 1 Phase IIb RCT (n=120) showed no clinically important difference between gemcitabine + capecitabine + erlotinib group and gemcitabine + erlotinib about the relative probability of objective response rate (CR + PR) in adult with metastatic pancreatic cancer: RR 1.18 (95% CI 0.58-2.43), where RR higher than 1 favours the gemcitabine + erlotinib + capecitabine arm.

Progression-free survival

High quality evidence from 1 Multicentre Phase III RCT (n=342) showed that there is a clinically important difference favouring FOLFIRINOX in PFS compared to gemcitabine single-agent in adult with metastatic pancreatic cancer: HR 0.47 (95% CI 0.32-0.69)

Moderate quality evidence from 1 Phase III RCT (n=411) showed no clinically important difference between gemcitabine + Aflibercept and gemcitabine single-agent in PFS rates in adult with metastatic pancreatic cancer: HR 1.02 (95% CI 0.83-1.25), where HR less than 1 favours the gemcitabine + Aflibercept arm.

Low quality evidence from 1 Phase III RCT (n=375) showed no clinically important difference between gemcitabine + Cisplatin and gemcitabine single-agent in PFS rates in adult with metastatic pancreatic cancer: HR 0.97 (95% CI 0.8-1.18), where HR less than 1 favours the gemcitabine + Cisplatin arm.

Moderate quality evidence from 1 Phase III RCT (n=619) showed no clinically important difference between gemcitabine + Ganitumab [12 mg/kg] and gemcitabine single-agent in PFS rates in adult with metastatic pancreatic cancer: HR 1 (95% CI 0.84-1.19), where HR less than 1 favours the gemcitabine + Ganitumab arm.

Moderate quality evidence from 1 Phase III RCT (n=464) showed no clinically important difference between gemcitabine + Ganitumab [20 mg/kg] and gemcitabine single-agent in PFS rates in adult with metastatic pancreatic cancer: HR 0.97 (95% CI 0.77-1.22), where HR less than 1 favours the gemcitabine + Ganitumab arm.

Moderate1.35) quality evidence from 1 Phase III RCT (n=707) showed that there is a clinically important difference favouring gemcitabine + erlotinib + bevacizumab in PFS compared to gemcitabine + erlotinib in adult with metastatic pancreatic cancer: HR 0.73 (95% CI 0.61-0.87).

Low quality evidence from 1 Phase IIb RCT (n=120) showed no clinically important difference between gemcitabine + capecitabine + erlotinib and gemcitabine + erlotinib in PFS rates in adult with metastatic pancreatic cancer: HR 0.88 (95% CI 0.58-1.34), where HR less than 1 favours the gemcitabine + erlotinib + capecitabine arm.

Overall Survival

Moderate quality evidence from 1 Phase III RCT (n=411) showed no clinically important difference between gemcitabine + Aflibercept and gemcitabine single-agent in overall

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survival in adult with metastatic pancreatic cancer: HR 1.17 (95% CI 0.92-1.49), where HR less than 1 favours the gemcitabine + Aflibercept arm.

Low quality evidence from a meta-analysis of 2 Phase III RCTs (n=425) showed no clinically important difference between gemcitabine + Cisplatin and gemcitabine single-agent in overall survival in adult with metastatic pancreatic cancer: HR 0.92 (95% CI 0.76-1.11), where HR less than 1 favours the gemcitabine + Cisplatin arm.

Moderate quality evidence from 1 Phase III RCT (n=619) showed no clinically important difference between gemcitabine + Ganitumab [12 mg/kg] and gemcitabine single-agent in overall survival in adult with metastatic pancreatic cancer: HR 1 (95% CI 0.82-1.22), where HR less than 1 favours the gemcitabine + Ganitumab arm.

Moderate quality evidence from 1 Phase III RCT (n=464) showed no clinically important difference between gemcitabine + Ganitumab [20 mg/kg] and gemcitabine single-agent in overall survival in adult with metastatic pancreatic cancer: HR 0.97 (95% CI 0.76-1.24), where HR less than 1 favours the gemcitabine + Ganitumab arm.

Low quality evidence from 1 Phase IIb RCT (n=120) showed no clinically important difference between gemcitabine + capecitabine + erlotinib and gemcitabine + erlotinib in overall survival in adult with metastatic pancreatic cancer: HR 1.09 (95% CI 0.72-1.65), where HR less than 1 favours the gemcitabine + erlotinib + capecitabine arm.

Adverse Events

a) Grade 3/4 toxicities: diarrhoea

High quality evidence from 1 Multicentre Phase III RCT (n=342) showed that there is a clinically important difference favouring gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (diarrhoea) compared to FOLFIRINOX in adult with metastatic pancreatic cancer: RR 7.17 (95% CI 2.18-23.58)

Low quality evidence from 1 Phase III RCT (n=541 patients: 270) showed no clinically important difference between gemcitabine + Aflibercept and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (diarrhoea) in adult with metastatic pancreatic cancer: RR 1 (95% CI 0.2-4.93), where RR less than 1 favours the gemcitabine + Aflibercept arm.

Very low quality evidence from a meta-analysis of 2 Phase III RCTs (n=421) showed no clinically important difference between gemcitabine + Cisplatin and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (diarrhoea) in adult with metastatic pancreatic cancer: RR 0.34 (95% CI 0.04-3.23), where RR less than 1 favours the gemcitabine + Cisplatin arm.

Low quality evidence from 1 Phase III RCT (n=632) showed no clinically important difference between gemcitabine + Ganitumab [12 mg/kg] and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (diarrhoea) in adult with metastatic pancreatic cancer: RR 3.02 (95% CI 0.32-28.87), where RR less than 1 favours the gemcitabine + Ganitumab arm.

Low quality evidence from 1 Phase III RCT (n=477) showed no clinically important difference between gemcitabine + Ganitumab [20 mg/kg] and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (diarrhoea) in adult with metastatic pancreatic cancer: RR 3.96 (95% CI 0.36-43.37), where RR less than 1 favours the gemcitabine + Ganitumab arm.

b) Grade 3/4 toxicities: fatigue

Moderate quality evidence from 1 Multicentre Phase III RCT (n=334) showed no clinically important difference between FOLFIRINOX and gemcitabine single-agent on the relative risk

of drug-related grade 3/4 toxicities (fatigue) in adult with metastatic pancreatic cancer: RR 1.33 (95% CI 0.87-2.04), where RR less than 1 favours the FOLFIRINOX arm.

Very low quality evidence from 1 Phase III RCT (n=375) showed no clinically important difference between gemcitabine + Cisplatin and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (fatigue) in adult with metastatic pancreatic cancer: RR 1.69 (95% CI 0.63-4.57), where RR less than 1 favours the gemcitabine + Cisplatin arm.

Low quality evidence from 1 Phase III RCT (n=632) showed no clinically important difference between gemcitabine + Ganitumab [12 mg/kg] and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (fatigue) in adult with metastatic pancreatic cancer: RR 1.59 (95% CI 0.79-3.23), where RR less than 1 favours the gemcitabine + Ganitumab arm.

Low quality evidence from 1 Phase III RCT (n=477) showed no clinically important difference between gemcitabine + Ganitumab [20 mg/kg] and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (fatigue) in adult with metastatic pancreatic cancer: RR 1.32 (95% CI 0.55-1.17), where RR less than 1 favours the gemcitabine + Ganitumab arm.

c) Grade 3/4 toxicities: Neutropenia

High quality evidence from 1 Multicentre Phase III RCT (n=331) showed that there is a clinically important difference favouring gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (Neutropenia) compared to FOLFIRINOX in adult with metastatic pancreatic cancer: RR 2.18 (95% CI 1.56-3.06)

Moderate quality evidence from 1 Phase III RCT (n=541) showed no clinically important difference between gemcitabine + Aflibercept and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (neutropenia) in adult with metastatic pancreatic cancer: RR 1.27 (95% CI 0.96-1.67), where RR less than 1 favours the gemcitabine + Aflibercept arm.

Low quality evidence from a meta-analysis of 2 Phase III RCTs (n=421) showed no clinically important difference between gemcitabine + Cisplatin and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (neutropenia) in adult with metastatic pancreatic cancer: RR 1.84 (95% CI 1.21-2.8), where RR less than 1 favours the gemcitabine + Cisplatin arm.

High quality evidence from 1 Phase III RCT (n=632) showed that there is a clinically important difference favouring gemcitabine + Ganitumab [12 mg/kg] on the relative risk of drug-related grade 3/4 toxicities (neutropenia) compared to gemcitabine single-agent in adult with metastatic pancreatic cancer: RR 0.48 (95% CI 0.32-0.71)

High quality evidence from 1 Phase III RCT (n=477) showed that there is a clinically important difference favouring gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (neutropenia) compared to those treated with gemcitabine + Ganitumab [20 mg/kg] in adult with metastatic pancreatic cancer: RR 2.26 (95% CI 1.72-2.97)

Low quality evidence from 1 Phase III RCT (n=583) showed no clinically important difference between gemcitabine + erlotinib + bevacizumab and gemcitabine + erlotinib on the relative risk of drug-related grade 3/4 toxicities (neutropenia) in adult with metastatic pancreatic cancer: RR 0.97 (95% CI 0.68-1.39), where RR less than 1 favours the gemcitabine + erlotinib arm.

d) Grade 3/4 toxicities: Nausea/vomiting

Moderate quality evidence from 1 Multicentre Phase III RCT (n=335) showed no clinically important difference between FOLFIRINOX and gemcitabine single-agent on the relative risk

of drug-related grade 3/4 toxicities (nausea/vomiting) in adult with metastatic pancreatic cancer: RR 1.75 (95% CI 0.94-3.26), where RR less than 1 favours the FOLFIRINOX arm.

Moderate quality evidence from 1 Phase III RCT (n=541) showed no clinically important difference between gemcitabine + Aflibercept and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (nausea/vomiting) in adult with metastatic pancreatic cancer: RR 2.11 (95% CI 1.01-4.39), where RR less than 1 favours the gemcitabine + Aflibercept arm.

Very low quality evidence from a meta-analysis of 2 Phase III RCTs (n=421) showed no clinically important difference between gemcitabine + Cisplatin and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (nausea/vomiting) in adult with metastatic pancreatic cancer: RR 1.83 (95% CI 0.54-6.2), where RR less than 1 favours the gemcitabine + Cisplatin arm.

Low quality evidence from 1 Phase III RCT (n=632) showed no clinically important between gemcitabine + Ganitumab [12 mg/kg] and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (nausea/vomiting) in adult with metastatic pancreatic cancer: RR 0.96 (95% CI 0.52-1.76), where RR less than 1 favours the gemcitabine + Ganitumab arm.

Low quality evidence from 1 Phase III RCT (n=477) showed no clinically important difference between Ganitumab [20 mg/kg] and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (nausea/vomiting) in adult with metastatic pancreatic cancer: RR 0.5 (95% CI 0.19-1.3), where RR less than 1 favours the gemcitabine + Ganitumab arm.

Low quality evidence from 1 Phase III RCT (n=583) showed no clinically important difference between gemcitabine + erlotinib + bevacizumab and gemcitabine + erlotinib on the relative risk of drug-related grade 3/4 toxicities (nausea/vomiting) in adult with metastatic pancreatic cancer: RR 1.54 (95% CI 0.86-2.79), where RR less than 1 favours the gemcitabine + erlotinib arm.

e) Grade 3/4 toxicities: Thrombocytopenia

Moderate quality evidence from 1 Multicentre Phase III RCT (n=333) showed no clinically important difference between FOLFIRINOX and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (thrombocytopenia) in adult with metastatic pancreatic cancer: RR 2.55 (95% CI 1.01-6.4), where RR less than 1 favours the FOLFIRINOX arm.

Moderate quality evidence from 1 Phase III RCT (n=541) showed no clinically important difference between gemcitabine + Aflibercept and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (thrombocytopenia) in adult with metastatic pancreatic cancer: RR 1.77 (95% CI 1-3.13), where RR less than 1 favours the gemcitabine + Aflibercept arm.

Moderate quality evidence from a meta-analysis of 2 Phase III RCTs (n=421) showed that there is a clinically important difference favouring gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (Thrombocytopenia) compared to gemcitabine + Cisplatin: RR 3.2 (95% CI 1.67-6.14), where RR less than 1 favours the gemcitabine + Cisplatin arm.

Low quality evidence from 1 Phase III RCT (n=632) showed no clinically important difference between gemcitabine + Ganitumab [12 mg/kg] and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (thrombocytopenia) in adult with metastatic pancreatic cancer: RR 1.29 (95% CI 0.75-2.24), where RR less than 1 favours the gemcitabine + Ganitumab arm.

Low quality evidence from 1 Phase III RCT (n=477) showed no clinically important difference between gemcitabine + Ganitumab [20 mg/kg] and gemcitabine single-agent on the relative

risk of drug-related grade 3/4 toxicities (thrombocytopenia) in adult with metastatic pancreatic cancer: RR 1.13 (95% CI 0.57-2.24), where RR less than 1 favours the gemcitabine + Ganitumab arm.

Low quality evidence from 1 Phase III RCT (n=583) showed no clinically important difference between gemcitabine + erlotinib + bevacizumab and gemcitabine + erlotinib on the relative risk of drug-related grade 3/4 toxicities (thrombocytopenia) in adult with metastatic pancreatic cancer: RR 1.31 (95% CI 0.72-2.40), where RR less than 1 favours the gemcitabine + erlotinib arm.

f) Grade 3/4 toxicities: Leucopoenia

Low quality evidence from a meta-analysis of 2 Phase III RCTs (n=421) suggests not significant differences between gemcitabine + Cisplatin and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (leucopoenia) in adult with metastatic pancreatic cancer: RR 1.89 (95% CI 0.9-3.98)

Low quality evidence from 1 Phase III RCT (n=632) showed no clinically important difference between gemcitabine + Ganitumab [12 mg/kg] and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (leucopoenia) in adult with metastatic pancreatic cancer: RR 1.68 (95% CI 0.74-3.78), where RR less than 1 favours the gemcitabine + Ganitumab arm.

Low quality evidence from 1 Phase III RCT (n=477) showed no clinically important difference between gemcitabine + Ganitumab [20 mg/kg] and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (leucopoenia) in adult with metastatic pancreatic cancer: RR 0.88 (95% CI 0.28-2.82), where RR less than 1 favours the gemcitabine + Ganitumab arm.

g) Grade 3/4 toxicities: Any

Low quality evidence from 1 Phase IIb RCT (n=118) showed no clinically important difference between gemcitabine + capecitabine + erlotinib and gemcitabine + erlotinib on the relative risk of drug-related grade 3/4 toxicities (including asthenia, diarrhoea, neutropenia, reduced appetite, thrombocytopenia, nausea, anaemia, rash, constipation, mucositis, vomiting, pyrexia, elevated GGT, hand - foot syndrome, and peripheral oedema): RR 1.28 (95% CI 0.97-1.68), where RR less than 1 favours the gemcitabine + erlotinib + capecitabine arm.

Health-related quality of life

High quality evidence from 1 Multicentre Phase III RCT (n=320) showed that there is a clinically important difference favouring gemcitabine single-agent on quality of life scores (global health status, measured as mean of the QLQ-C30 questionnaire) compared to FOLFINOROX at the end of the treatment (6 months) in adult with metastatic pancreatic cancer: RR 0.39 (95% CI 0.21-0.72)

High to low quality evidence from 1 Multicentre Phase III RCT (n=320) showed that there is a clinically important difference favouring gemcitabine single-agent on quality of life scores (including social functioning, role functioning, and financial difficulties - measured as mean of the QLQ-C30) compared to FOLFINOROX at the end of the treatment (6 months) in adult with metastatic pancreatic cancer.

Moderate and low quality evidence from 1 Multicentre Phase III RCT (n=333) showed no clinically important difference between FOLFIRINOX and gemcitabine single-agent at the end of the treatment (6 months) on the improvement of quality of life in physical functioning, emotional functioning, cognitive functioning, fatigue, nausea/vomiting, pain, dyspnoea, insomnia, loss of appetite, constipation and diarrhoea (measured as mean of the QLQ-C30) in adult with metastatic pancreatic cancer.

11.2.6.2.2 In adults with locally advanced and metastatic pancreatic cancer

Response rate

Low quality evidence from 1 Multicentre Phase III RCT (n=126) showed no clinically important difference between 5-FU single agent and gemcitabine single-agent about the relative probability of objective response rate (CR + PR) in adults with locally advanced/metastatic pancreatic cancer: RR 0.14 (95% CI 0.01-2.71), where RR less than 1 favours the gemcitabine arm.

Moderate quality evidence from 1 Multicentre Phase III RCT (n=489) showed that there is a clinically important difference favouring S-1 chemotherapy about the relative probability of objective response rate compared to gemcitabine alone in adults with locally advanced/metastatic pancreatic cancer: RR 1.58 (95% CI 1.06-2.36)

Very low quality evidence from 1 Multicentre Phase III RCT (n=322) showed no clinically important difference between gemcitabine + 5-FU and gemcitabine single-agent about the relative probability of objective response rate (CR + PR) in adults with locally advanced/metastatic pancreatic cancer: RR 1.24 (95% CI 0.53-2.91), where RR less than 1 favours the gemcitabine arm.

Moderate quality evidence from 1 Multicentre Phase III RCT (n=613) showed no clinically important difference between gemcitabine + Axitanib group and gemcitabine single-agent about the relative probability of objective response rate (CR + PR) in adults with locally advanced/metastatic pancreatic cancer: RR 3.03 (95% CI 0.99-9.29), where RR less than 1 favours the gemcitabine arm.

Low quality evidence from 1 Multicentre Phase III RCT (n=602) showed no clinically important difference between gemcitabine + Bevacizumab and gemcitabine single-agent about the relative probability of objective response rate (CR + PR) in adults with locally advanced/metastatic pancreatic cancer: RR 1.29 (95% CI 0.82-2.02), where RR less than 1 1 favours the gemcitabine arm.

Low quality evidence from a meta-analysis of 3 Multicentre Phase III RCTs (n=1050) showed that there is a clinically important difference favouring gemcitabine + Capecitabine about the relative probability of objective response rate (CR + PR) compared to gemcitabine alone in adults with locally advanced/metastatic pancreatic cancer: RR 1.70 (95% CI 1.27-2.27)

Very low quality evidence from 1 Multicentre Phase III RCT (n=660) showed no clinically important difference between gemcitabine + Cetuximab and gemcitabine single-agent about the relative probability of objective response rate (CR + PR) in adults with locally advanced/metastatic pancreatic cancer: RR 1.22 (95% CI 0.72-2.08), where RR less than 1 1 favours the gemcitabine arm.

Very low quality evidence from 1 Multicentre Phase III RCT (n=195) showed no clinically important difference between gemcitabine + Cisplatin and gemcitabine single-agent about the relative probability of objective response rate (CR + PR) in adults with locally advanced/metastatic pancreatic cancer: RR 1.24 (95% CI 0.51-3.00), where RR less than 1 1 favours the gemcitabine arm.

Moderate quality evidence from 1 Phase III RCT (n=99) showed that there is a clinically important difference favouring PEFG about the relative probability of objective response rate (CR + PR) compared to gemcitabine alone in adults with locally advanced/metastatic pancreatic cancer: RR 4.52 (95% CI 1.67-12.27)

Very low quality evidence from 1 Multicentre Phase III RCT (n=349) showed no clinically important difference between gemcitabine + Exatecan and gemcitabine single-agent about the relative probability of objective response rate (CR + PR) in adults with locally

advanced/metastatic pancreatic cancer: RR 1.33 (95% CI 0.57-3.07), where RR less than 1 favours the gemcitabine arm.

Low quality evidence from a meta-analysis of 2 Multicentre Phase III RCTs (n=490) showed that there is a clinically important difference favouring gemcitabine + Irinotecan chemotherapy about the relative probability of objective response rate (CR + PR) compared to gemcitabine alone in adults with locally advanced/metastatic pancreatic cancer: RR 2.50 (95% CI 1.43-4.39).

Low quality evidence from 1 Phase III RCT (n=319) showed no clinically important difference between gemcitabine + Marimastat and gemcitabine single-agent about the relative probability of objective response rate (CR + PR) in adults with locally advanced/metastatic pancreatic cancer: RR 0.78 (95% CI 0.37-1.65), where RR less than 1 favours the gemcitabine arm.

Low quality evidence from a meta-analysis of 2 Multicentre Phase III RCTs (n=313) showed that there is a clinically important difference favouring gemcitabine + Oxaliplatin chemotherapy about the relative probability of objective response rate (CR + PR) compared to gemcitabine alone in adults with locally advanced/metastatic pancreatic cancer: RR 1.55 (95% CI 1.01-2.38).

Moderate quality evidence from 1 Multicentre Phase III RCT (n=565) showed that there is a clinically important difference favouring gemcitabine + Pemetrexed chemotherapy about the relative probability of objective response rate (CR + PR) compared to gemcitabine alone in adults with locally advanced/metastatic pancreatic cancer: RR 2.09 (95% CI 1.26-3.47).

Low quality evidence from 1 Phase III RCT (n=104) showed no clinically important difference between gemcitabine + Sorafenib and gemcitabine single-agent about the relative probability of objective response rate (CR + PR) in adults with locally advanced/metastatic pancreatic cancer: RR 0.54 (95% CI 0.22-1.33), where RR less than 1 favours the gemcitabine arm.

Low quality evidence from 1 Phase III RCT (n=688) showed no clinically important difference between gemcitabine + Tipifarnib and gemcitabine single-agent about the relative probability of objective response rate (CR + PR) in adults with locally advanced/metastatic pancreatic cancer: RR 0.73 (95% CI 0.42-1.26), where RR less than 1 favours the gemcitabine arm.

High quality evidence from a meta-analysis of 2 Multicentre Phase III RCTs (n=584) showed that there is a clinically important difference favouring gemcitabine + S-1 chemotherapy about the relative probability of objective response rate (CR + PR) compared to gemcitabine alone in adults with locally advanced/metastatic pancreatic cancer: RR 2.33 (95% CI 1.62-3.34).

Moderate quality evidence from 1 Phase III RCT (n=274) showed that there is a clinically important difference favouring gemcitabine + erlotinib chemotherapy about the relative probability of objective response rate (CR + PR) compared to Capecitabine + erlotinib in adults with locally advanced/metastatic pancreatic cancer: RR 2.88 (95% CI 1.27-6.52).

Progression free survival

Moderate quality evidence from 1 Multicentre Phase III RCT (n=489) showed no clinically important difference between S-1 single agent and gemcitabine single-agent in PFS rates in adults with locally advanced/metastatic pancreatic cancer: HR 1.09 (95% CI 0.9-1.32), where HR less than 1 favours the S-1 arm.

Moderate quality evidence from 1 Multicentre Phase III RCT (n=322) showed that there is a clinically important difference favouring gemcitabine + 5-FU in PFS rates compared to gemcitabine single-agent in adults with locally advanced/metastatic pancreatic cancer: HR 0.77 (95% CI 0.62-0.96)

Moderate quality evidence from 1 Multicentre Phase III RCT (n=613) showed no clinically important difference between gemcitabine + Axitanib and gemcitabine single-agent in PFS rates in adults with locally advanced/metastatic pancreatic cancer: HR 1.01 (95% CI 0.78-1.30), where HR less than 1 favours the gemcitabine + Axitanib arm.

Moderate quality evidence from a meta-analysis of 3 Multicentre Phase III RCTs (n=1050) showed that there is a clinically important difference favouring gemcitabine + Capecitabine in PFS rates compared to gemcitabine single-agent in adults with locally advanced/metastatic pancreatic cancer: HR 0.80 (95% CI 0.72-0.90)

Moderate quality evidence from 1 Multicentre Phase III RCT (n=602) showed no clinically important difference between gemcitabine + Bevacizumab and gemcitabine single-agent in PFS rates in adults with locally advanced/metastatic pancreatic cancer: HR 0.96 (95% CI 0.81-1.15), where HR less than 1 favours the gemcitabine + Bevacizumab arm.

Low quality evidence from 1 Multicentre Phase III RCT (n=660) showed no clinically important difference between gemcitabine + Cetuximab and gemcitabine single-agent in PFS rates in adults with locally advanced/metastatic pancreatic cancer: HR 1.07 (95% CI 0.93-1.23), where HR less than 1 favours the gemcitabine + Cetuximab arm.

Moderate quality evidence from 1 Multicentre Phase III RCT (n=195) showed that there is a clinically important difference favouring gemcitabine + Cisplatin in PFS rates compared to gemcitabine single-agent in adults with locally advanced/metastatic pancreatic cancer: HR 0.69 (95% CI 0.50-0.95)

Moderate quality evidence from 1 Phase III RCT (n=99) showed that there is a clinically important difference favouring PEFG in PFS rates compared to gemcitabine single-agent in adults with locally advanced/metastatic pancreatic cancer: HR 0.51 (95% CI 0.33-0.78)

High quality evidence from 1 Multicentre Phase III RCT (n=569) showed that there is a clinically important difference favouring gemcitabine + Erlotinib in PFS rates compared to gemcitabine single-agent in adults with locally advanced/metastatic pancreatic cancer: HR 0.77 (95% CI 0.65-0.92)

Moderate quality evidence from 1 Multicentre Phase III RCT (n=360) showed no clinically important difference between gemcitabine + Irinotecan and gemcitabine single-agent in PFS rates in adults with locally advanced/metastatic pancreatic cancer: HR 0.98 (95% CI 0.77-1.25), where HR less than 1 favours the gemcitabine + Irinotecan arm.

Moderate quality evidence from 1 Phase III RCT (n=319) showed no clinically important difference between gemcitabine + Marimastat and gemcitabine single-agent in PFS rates in adults with locally advanced/metastatic pancreatic cancer: HR 0.95 (95% CI 0.73-1.23), where HR less than 1 favours the gemcitabine + Marimastat arm.

Moderate quality evidence from a meta-analysis of 2 Multicentre Phase III RCTs (n=313) showed that there is a clinically important difference favouring gemcitabine + Oxaliplatin in PFS rates when compared to gemcitabine single-agent in adults with locally advanced/metastatic pancreatic cancer: HR 0.83 (95% CI 0.72-0.97)

Moderate quality evidence from 1 Phase III RCT (n=104) showed no clinically important difference between gemcitabine + Sorafenib and gemcitabine single-agent in PFS rates in adults with locally advanced/metastatic pancreatic cancer: HR 1.04 (95% CI 0.70-1.55), where HR less than 1 favours the gemcitabine + Sorafenib arm.

Moderate quality evidence from 1 Phase III RCT (n=688) showed no clinically important difference between gemcitabine + Tipifarnib and gemcitabine single-agent in PFS rates in adults with locally advanced/metastatic pancreatic cancer: HR 1.03 (95% CI 0.87-1.22), where HR less than 1 favours the gemcitabine + Tipifarnib arm.

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High quality evidence from a meta-analysis of 2 Multicentre Phase III RCTs (n=584) showed that there is a clinically important difference favouring gemcitabine + S-1 group in PFS rates when compared to gemcitabine single-agent in adults with locally advanced/metastatic pancreatic cancer: HR 0.65 (95% CI 0.57-0.75)

Overall survival

High quality evidence from a network meta-analysis of 23 Phase III RCTs involving 9.989 patients with locally advanced/metastatic pancreatic cancer showed that there is a clinically important difference favouring FOLFIRINOX, PEFG, gemcitabine + erlotinib+/-bevacizumab, gemcitabine+capecitabine, and gemcitabine+oxaliplatin in OS when compared to gemcitabine single-agent and several other gemcitabine-based chemotherapy treatments in adults with locally advanced/metastatic PC.

High quality evidence from 1 Multicentre Phase III RCT (n=126) showed that there is a clinically important difference favouring gemcitabine single-agent chemotherapy in long-term survival compared with the 5-FU single-agent in adults with locally advanced/metastatic pancreatic cancer: HR 1.75 (95% CI 1.21-0.2.54)

Moderate quality evidence from 1 Multicentre Phase III RCT (n=489) showed no clinically important difference between S-1 single agent and gemcitabine single-agent in long-term survival rates in adults with locally advanced/metastatic pancreatic cancer: HR 0.96 (95% CI 0.71-1.30), where HR less than 1 favours the S-1 arm.

Moderate quality evidence from 1 Multicentre Phase III RCT (n=602) showed no clinically important difference between gemcitabine + Bevacizumab and gemcitabine single-agent in long-term survival rates in adults with locally advanced/metastatic pancreatic cancer: HR 0.96 (95% CI 0.81-1.15), where HR less than 1 favours the gemcitabine + Bevacizumab arm.

Moderate quality evidence from 1 Multicentre Phase III RCT (n=159) showed no clinically important difference between gemcitabine + elpamotide and gemcitabine single-agent in long-term survival rates in adults with locally advanced/metastatic pancreatic cancer: HR 0.87 (95% CI 0.49-1.56), where HR less than 1 favours the gemcitabine + elpamotide arm.

Moderate quality evidence from 1 Multicentre Phase III RCT (n=602) showed no clinically important difference between gemcitabine + masitinib and gemcitabine single-agent in long-term survival rates in adults with locally advanced/metastatic pancreatic cancer: HR 0.89 (95% CI 0.70-1.13), where HR less than 1 favours the gemcitabine + masitinib arm.

Moderate quality evidence from a meta-analysis of 2 Multicentre Phase III RCTs (n=584) showed no clinically important difference between gemcitabine + S-1 and gemcitabine single-agent in long-term survival rates in adults with locally advanced/metastatic pancreatic cancer: HR 0.89 (95% CI 0.74-1.08), where HR less than 1 favours the gemcitabine + S-1 arm.

Adverse Events

a) Grade 3/4 toxicities: Nausea/Vomiting

Low quality evidence from 1 Multicentre Phase III RCT (n=126) showed no clinically important difference between 5-FU single agent and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (nausea/vomiting) in adults with locally advanced/metastatic pancreatic cancer: RR 0.38 (95% CI 0.1-1.35), where RR less than 1 favours the 5-FU arm.

Very low quality evidence from 1 Multicentre Phase III RCT (n=545) showed no clinically important difference between S-1 single agent and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (nausea/vomiting) in adults with locally

advanced/metastatic pancreatic cancer: RR 1.29 (95% CI 0.49-3.42), where RR less than 1 favours the S-1 arm.

Very low quality evidence from 1 Multicentre Phase III RCT (n=316) showed no clinically important difference between gemcitabine + 5-FU and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (nausea/vomiting) in adults with locally advanced/metastatic pancreatic cancer: RR 0.79 (95% CI 0.42-1.50), where RR less than 1 favours the gemcitabine + 5-FU arm.

Low quality evidence from 1 Multicentre Phase III RCT (n=613) showed no clinically important difference between gemcitabine+ Axitanib and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (nausea/vomiting) in adults with locally advanced/metastatic pancreatic cancer: RR 1.40 (95% CI 0.78-2.52), where RR less than 1 favours the gemcitabine + Axitanib arm.

Low quality evidence from a meta-analysis of 2 Multicentre Phase III RCTs (n=1017) showed no clinically important difference between gemcitabine + Capecitabine and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (nausea/vomiting) in adults with locally advanced/metastatic pancreatic cancer: RR 1.20 (95% CI 0.83-1.74), where RR less than 1 favours the gemcitabine + Capecitabine arm.

Low quality evidence from 1 Multicentre Phase III RCT (n=726) showed no clinically important difference between gemcitabine + Cetuximab and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (nausea/vomiting) in adults with locally advanced/metastatic pancreatic cancer: RR 1.71 (95% CI 0.99-2.95), where RR less than 1 favours the gemcitabine + Cetuximab arm.

Moderate quality evidence from 1 Multicentre Phase III RCT (n=195) showed that there is a clinically important difference favouring gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (Nausea/vomiting) compared to gemcitabine + Cisplatin in adults with locally advanced/metastatic pancreatic cancer: RR 3.63 (95% CI 1.54-8.56)

Low quality evidence from 1 Multicentre Phase III RCT (n=153) showed no clinically important difference between gemcitabine + elpamotide and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (nausea/vomiting) in adults with locally advanced/metastatic pancreatic cancer: RR 0.53 (95% CI 0.08-3.66), where RR less than 1 favours the gemcitabine + elpamotide arm.

Very low quality evidence from 1 Multicentre Phase III RCT (n=325) showed no clinically important difference between gemcitabine + Exatecan and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (nausea/vomiting) in adults with locally advanced/metastatic pancreatic cancer: RR 1.56 (95% CI 0.70-3.46), where RR less than 1 favours the gemcitabine + Exatecan arm.

Low quality evidence from a meta-analysis of 2 Multicentre Phase III RCTs (n=472) showed no clinically important difference between gemcitabine + Irinotecan and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (nausea/vomiting) in adults with locally advanced/metastatic pancreatic cancer: RR 1.60 (95% CI 1.09-2.33), where RR less than 1 favours the gemcitabine + Irinotecan arm.

Moderate quality evidence from 1 Phase III RCT (n=319) showed no clinically important difference between gemcitabine + Marimastat and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (nausea/vomiting) in adults with locally advanced/metastatic pancreatic cancer: RR 0.50 (95% CI 0.27-0.92), where RR less than 1 favours the gemcitabine + Marimastat arm.

Moderate evidence [GRADE] from a meta-analysis of 2 Multicentre Phase III RCTs (n=840) showed that there is a clinically important difference favouring gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (Nausea/vomiting) compared to

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gemcitabine + Oxaliplatin in adults with locally advanced/metastatic pancreatic cancer: RR 2.77 (95% CI 1.81-4.25)

Very low quality evidence from 1 Multicentre Phase III RCT (n=546) showed no clinically important difference between gemcitabine + Pemetrexed and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (nausea/vomiting) in adults with locally advanced/metastatic pancreatic cancer: RR 1 (95% CI 0.53-1.88), where RR less than 1 favours the gemcitabine + Pemetrexed arm.

Moderate quality evidence from a meta-analysis of 2 Phase III RCTs (n=915) showed no clinically important difference between gemcitabine + Tipifarnib and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (nausea/vomiting) in adults with locally advanced/metastatic pancreatic cancer: RR 0.75 (95% CI 0.55-1.01), where RR less than 1 favours the gemcitabine + Tipifarnib arm.

High quality evidence from a meta-analysis of 2 Multicentre Phase III RCTs (n=636) showed that there is a clinically important difference favouring gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (Nausea/vomiting) compared to gemcitabine + S-1 in adults with locally advanced/metastatic pancreatic cancer: RR 2.99 (95% CI 1.49-5.99)

Moderate quality evidence from 1 Phase III RCT (n=256) showed no clinically important difference between Capecitabine + erlotinib and gemcitabine + erlotinib on the relative risk of drug-related grade 3/4 toxicities (nausea/vomiting) in adults with locally advanced/metastatic pancreatic cancer: RR 15.98 (95% CI 0.93-273.93), where RR less than 1 favours the gemcitabine + erlotinib

b) Grade 3/4 toxicities: diarrhoea

Low quality evidence from 1 Multicentre Phase III RCT (n=126) showed no clinically important difference between5-FU single-agent and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (diarrhoea) in adults with locally advanced/metastatic pancreatic cancer: RR 3 (95% CI 0.32-28.07), where RR less than 1 favours the 5-FU arm.

High quality evidence from 1 Multicentre Phase III RCT (n=545) showed that there is a clinically important difference favouring gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (diarrhoea) compared to S-1 single-agent in adults with locally advanced/metastatic pancreatic cancer: RR 5.02 (95% CI 1.47-17.14)

Very low quality evidence from 1 Multicentre Phase III RCT (n=316) showed no clinically important difference between gemcitabine + 5-FU and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (diarrhoea) in adults with locally advanced/metastatic pancreatic cancer: RR 2.5 (95% CI 0.8-7.8), where RR less than 1 favours the gemcitabine + 5-FU arm.

Low quality evidence from 1 Multicentre Phase III RCT (n=613) showed no clinically important difference between gemcitabine + Axitanib and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (diarrhoea) in adults with locally advanced/metastatic pancreatic cancer: RR 0.81 (95% CI 0. 22-2.98), where RR less than 1 favours the gemcitabine + Axitanib arm.

Low quality evidence from 1 Multicentre Phase III RCT (n=602) showed no clinically important difference between gemcitabine + Bevacizumab and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (diarrhoea) in adults with locally advanced/metastatic pancreatic cancer: RR 1 (95% CI 0.22-2.98), where RR less than 1 favours the gemcitabine + Bevacizumab arm.

Very low quality evidence from a meta-analysis of 3 Multicentre Phase III RCTs (n=1017) showed no clinically important difference between gemcitabine + Capecitabine and

gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (diarrhoea) in adults with locally advanced/metastatic pancreatic cancer: RR 1.53 (95% CI 0.80-2.91), where RR less than 1 favours the gemcitabine + Capecitabine arm.

Very low quality evidence from 1 Multicentre Phase III RCT (n=716) showed no clinically important difference between gemcitabine + Cetuximab and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (diarrhoea) in adults with locally advanced/metastatic pancreatic cancer: RR 1.09 (95% CI 0.45-2.66), where RR less than 1 favours the gemcitabine + Cetuximab arm.

Very low quality evidence from 1 Multicentre Phase III RCT (n=195) showed no clinically important difference between gemcitabine + Cisplatin and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (diarrhoea) in adults with locally advanced/metastatic pancreatic cancer: RR 0.59 (95% CI 0.15-2.42), where RR less than 1 favours the gemcitabine + Cisplatin arm.

Low quality evidence from 1 Multicentre Phase III RCT (n=562) showed no clinically important difference between gemcitabine + Erlotinib and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (diarrhoea) in adults with locally advanced/metastatic pancreatic cancer: RR 2.98 (95% CI 0.61-14.63), where RR less than 1 favours the gemcitabine + Erlotinib arm.

Very low quality evidence from 1 Multicentre Phase III RCT (n=325) showed no clinically important difference between gemcitabine + Exatecan and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (diarrhoea) in adults with locally advanced/metastatic pancreatic cancer: RR 1.87 (95% CI 0.17-20.41), where RR less than 1 favours the gemcitabine + Exatecan arm.

Low quality evidence from a meta-analysis of 2 Multicentre Phase III RCTs (n=472) showed that there is a clinically important difference favouring gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (diarrhoea) compared to gemcitabine + Irinotecan in adults with locally advanced/metastatic pancreatic cancer: RR 6.92 (95% CI 2.71-17.67)

Low quality evidence from a meta-analysis of 2 Multicentre Phase III RCTs (n=840) showed no clinically important difference between gemcitabine + Oxaliplatin and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (diarrhoea) in adults with locally advanced/metastatic pancreatic cancer: RR 2.50 (95% CI 1.22-5.11), where RR less than 1 favours the gemcitabine + Oxaliplatin arm.

Low quality evidence from 1 Multicentre Phase III RCT (n=546) showed no clinically important difference between gemcitabine + Pemetrexed and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (diarrhoea) in adults with locally advanced/metastatic pancreatic cancer: RR 4 (95% CI 0.86-18.67), where RR less than 1 favours the gemcitabine + Pemetrexed arm.

Low quality evidence from 1 Phase III RCT (n=102) showed no clinically important difference between gemcitabine + Sorafenib and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (diarrhoea) in adults with locally advanced/metastatic pancreatic cancer: RR 0.69 (95% CI 0.12-3.98), where RR less than 1 favours the gemcitabine + Sorafenib arm.

Low quality evidence from a meta-analysis of 2 Phase III RCTs (n=915) showed no clinically important difference between gemcitabine + Tipifarnib and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (diarrhoea) in adults with locally advanced/metastatic pancreatic cancer: RR 1.34 (95% CI 0.60-3.02), where RR less than 1 favours the gemcitabine + Tipifarnib arm.

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Moderate quality evidence from a meta-analysis of 2 Multicentre Phase III RCTs (n=636) showed no clinically important difference between gemcitabine + S-1 and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (diarrhoea) in adults with locally advanced/metastatic pancreatic cancer: RR 2.59 (95% CI 0.94-7.14), where RR less than 1 favours the gemcitabine + S-1 arm.

Moderate quality evidence from 1 Phase III RCT (n=256) showed no clinically important difference between Capecitabine + erlotinib and gemcitabine + erlotinib on the relative risk of drug-related grade 3/4 toxicities (diarrhoea) in adults with locally advanced/metastatic pancreatic cancer: RR 0.55 (95% CI 0.22-1.35), where RR less than 1 favours the gemcitabine + erlotinib arm.

c) Grade 3/4 toxicities in adults with locally advanced/metastatic pancreatic cancer: Fatigue

Moderate quality evidence from 1 Multicentre Phase III RCT (n=545) showed no clinically important difference between S-1 single agent and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (fatigue) in adults with locally advanced/metastatic pancreatic cancer: RR 1.81 (95% CI 0.85-3.84), where RR less than 1 favours the S-1 arm.

Low quality evidence from 1 Multicentre Phase III RCT (n=613) showed no clinically important difference between gemcitabine + Axitanib and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (fatigue) in adults with locally advanced/metastatic pancreatic cancer: RR 1.3 (95% CI 0.75-2.25), where RR less than 1 favours the gemcitabine + Axitanib arm.

Low quality evidence from 1 Multicentre Phase III RCT (n=716) showed no clinically important difference between gemcitabine + Cetuximab and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (fatigue) in adults with locally advanced/metastatic pancreatic cancer: RR 1.11 (95% CI 0.82-1.5), where RR less than 1 favours the gemcitabine + Cetuximab arm.

Low quality evidence from 1 Multicentre Phase III RCT (n=362) showed no clinically important difference between gemcitabine + Erlotinib and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (fatigue) in adults with locally advanced/metastatic pancreatic cancer: RR 0.99 (95% CI 0.49-1.99), where RR less than 1 favours the gemcitabine + Erlotinib arm.

Very low quality evidence from 1 Multicentre Phase III RCT (n=325) showed no clinically important difference between gemcitabine + Exatecan and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (fatigue) in adults with locally advanced/metastatic pancreatic cancer: RR 2.62 (95% CI 0.96-7.10), where RR less than 1 favours the gemcitabine + Exatecan arm.

Very low quality evidence from 1 Multicentre Phase III RCT (n=342) showed no clinically important difference between gemcitabine + Irinotecan and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (fatigue) in adults with locally advanced/metastatic pancreatic cancer: RR 1.09 (95% CI 0.67-1.77), where RR less than 1 favours the gemcitabine + Irinotecan arm.

Low quality evidence from 1 Phase III RCT (n=319) showed no clinically important difference between gemcitabine + Marimastat and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (fatigue) in adults with locally advanced/metastatic pancreatic cancer: RR 1.98 (95% CI 0.83-4.74), where RR less than 1 favours the gemcitabine + Marimastat arm.

Low quality evidence from 1 Multicentre Phase III RCT (n=527) showed no clinically important difference between gemcitabine + Oxaliplatin and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (fatigue) in adults with locally

advanced/metastatic pancreatic cancer: RR 0.90 (95% CI 0.63-1.30), where RR less than 1 favours the gemcitabine + Oxaliplatin arm.

Moderate quality evidence from 1 Multicentre Phase III RCT (n=546) showed that there is a clinically important difference favouring gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (fatigue) compared to gemcitabine + Pemetrexed in adults with locally advanced/metastatic pancreatic cancer: RR 2.28 (95% CI 1.34-3.86)

Low quality evidence from a meta-analysis of 2 Phase III RCTs (n=915) showed no clinically important difference between gemcitabine + Tipifarnib and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (fatigue) in adults with locally advanced/metastatic pancreatic cancer: RR 0.91 (95% CI 0.65-1.27), where RR less than 1 favours the gemcitabine + Tipifarnib arm.

Low quality evidence from a meta-analysis of 2 Multicentre Phase III RCTs (n=636) showed no clinically important difference between gemcitabine + S-1 and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (fatigue) in adults with locally advanced/metastatic pancreatic cancer: RR 1.19 (95% CI 0.55-2.57), where RR less than 1 favours the gemcitabine + S-1 arm.

d) Grade 3/4 toxicities: Neutropenia

High quality evidence from 1 Multicentre Phase III RCT (n=126) showed that there is a clinically important difference favouring 5-FU single-agent on the relative risk of drug-related grade 3/4 toxicities (Neutropenia) compared to gemcitabine single-agent in adults with locally advanced/metastatic pancreatic cancer: RR 0.19 (95% CI 0.06-0.61)

High quality evidence from 1 Multicentre Phase III RCT (n=545) showed that there is a clinically important difference favouring S-1 single-agent on the relative risk of drug-related grade 3/4 toxicities (Neutropenia) compared to gemcitabine single-agent in adults with locally advanced/metastatic pancreatic cancer: RR 0.22 (95% CI 0.14-0.32)

Low quality evidence from 1 Multicentre Phase III RCT (n=613) showed no clinically important difference between gemcitabine + Axitanib and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (neutropenia) in adults with locally advanced/metastatic pancreatic cancer: RR 0.34 (95% CI 0.01-8.23), where RR less than 1 favours the gemcitabine + Axitanib arm.

Low quality evidence from 1 Multicentre Phase III RCT (n=530) showed no clinically important difference between gemcitabine + Bevacizumab and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (neutropenia) in adults with locally advanced/metastatic pancreatic cancer: RR 1.08 (95% CI 0.68-1.73), where RR less than 1 favours the gemcitabine + Bevacizumab arm.

Low quality evidence from a meta-analysis of 3 Multicentre Phase III RCTs (n=1017) showed no clinically important difference between gemcitabine + Capecitabine and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (Neutropenia) in patients treated with gemcitabine compared to those treated with gemcitabine + Capecitabine in adults with locally advanced/metastatic pancreatic cancer: RR 1.44 (95% CI 1.15-1.81)

Very low quality evidence from 1 Multicentre Phase III RCT (n=716) showed no clinically important difference between gemcitabine + Cetuximab and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (neutropenia) in adults with locally advanced/metastatic pancreatic cancer: RR 0.97 (95% CI 0.75-1.26), where RR less than 1 favours the gemcitabine + Cetuximab arm.

Moderate quality evidence from 1 Multicentre Phase III RCT (n=159) showed no clinically important difference between gemcitabine + elpamotide and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (neutropenia) in adults with locally

advanced/metastatic pancreatic cancer: RR 0.85 (95% CI 0.62-1.16), where RR less than 1 favours the gemcitabine + elpamotide arm.

Low quality evidence from 1 Multicentre Phase III RCT (n=325) showed that there is a clinically important difference favouring gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (Neutropenia) compared to in adults with locally advanced/metastatic pancreatic cancer: RR 2.07 (95% CI 1.33-3.22)

Low quality evidence from 1 Multicentre Phase III RCT (n=130) showed no clinically important difference between gemcitabine + Irinotecan and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (neutropenia) in adults with locally advanced/metastatic pancreatic cancer: RR 1.70 (95% CI 0.85-3.37), where RR less than 1 favours the gemcitabine + Irinotecan arm.

Very low quality evidence from a meta-analysis of 2 Multicentre Phase III RCTs (n=840) showed no clinically important difference between gemcitabine + Oxaliplatin and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (neutropenia) in adults with locally advanced/metastatic pancreatic cancer: RR 0.86 (95% CI 0.69-1.09), where RR less than 1 favours the gemcitabine + Oxaliplatin arm.

Moderate quality evidence from 1 Multicentre Phase III RCT (n=546) showed that there is a clinically important difference favouring gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (Neutropenia) compared to gemcitabine + Pemetrexed in adults with locally advanced/metastatic pancreatic cancer: RR 3.51 (95% CI 2.51-4.92)

Low quality evidence from 1 Phase III RCT (n=102) showed no clinically important difference between gemcitabine + Sorafenib and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (neutropenia) in adults with locally advanced/metastatic pancreatic cancer: RR 0.9 (95% CI 0.48-1.70), where RR less than 1 favours the gemcitabine + Sorafenib arm.

Moderate quality evidence from a meta-analysis of 2 Phase III RCTs (n=915) showed no clinically important difference between gemcitabine + Tipifarnib and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (neutropenia) in adults with locally advanced/metastatic pancreatic cancer: RR 1.26 (95% CI 1.07-1.5), where RR less than 1 favours the gemcitabine + Tipifarnib arm.

High quality evidence from a meta-analysis of 2 Multicentre Phase III RCTs (n=636) showed that there is a clinically important difference favouring gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (Neutropenia) compared to gemcitabine + S-1 in adults with locally advanced/metastatic pancreatic cancer: RR 1.57 (95% CI 1.33-1.86)

e) Grade 3/4 toxicities: Thrombocytopenia

Low quality evidence from 1 Multicentre Phase III RCT (n=320) showed no clinically important difference between gemcitabine+ 5-FU and gemcitabine single-agent gemcitabine compared to those treated with gemcitabine + 5-FU: RR 1.81 (95% CI 1.04-3.15), where RR less than 1 favours the gemcitabine + 5-FU arm.

Low quality evidence from 1 Multicentre Phase III RCT (n=613) showed no clinically important difference between gemcitabine + Axitanib and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (thrombocytopenia) in adults with locally advanced/metastatic pancreatic cancer: RR 0.34 (95% CI 0.01-8.23), where RR less than 1 favours the gemcitabine + Axitanib arm.

Low quality evidence from 1 Multicentre Phase III RCT (n=540) showed no clinically important difference between gemcitabine + Bevacizumab and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (thrombocytopenia) in adults with locally

advanced/metastatic pancreatic cancer: RR 0.95 (95% CI 0.43-2.08), where RR less than 1 favours the gemcitabine + Bevacizumab arm.

Very low quality evidence from a meta-analysis of 3 Multicentre Phase III RCTs (n=1017) showed no clinically important difference between gemcitabine + Capecitabine and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (thrombocytopenia) in adults with locally advanced/metastatic pancreatic cancer: RR 1.14 (95% CI 0.72-1.82), where RR less than 1 favours the gemcitabine + Capecitabine arm.

Low quality evidence from 1 Multicentre Phase III RCT (n=195) showed no clinically important difference between gemcitabine + Cisplatin and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (thrombocytopenia) in adults with locally advanced/metastatic pancreatic cancer: RR 0.4 (95% CI 0.13-1.22), where RR less than 1 favours the gemcitabine + Cisplatin arm.

Low quality evidence from 1 Multicentre Phase III RCT (n=153) showed no clinically important difference between gemcitabine + elpamotide and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (thrombocytopenia) in adults with locally advanced/metastatic pancreatic cancer: RR 0.99 (95% CI 0.45-2.19), where RR less than 1 favours the gemcitabine + elpamotide arm.

Low quality evidence from 1 Multicentre Phase III RCT (n=325) showed that there is a clinically important difference favouring gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (Thrombocytopenia) compared to gemcitabine + Exatecan in adults with locally advanced/metastatic pancreatic cancer: RR 3.47 (95% CI 1.55-7.77)

Very low quality evidence from 1 Multicentre Phase III RCT (n=130) showed no clinically important difference between gemcitabine + Irinotecan and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (thrombocytopenia) in adults with locally advanced/metastatic pancreatic cancer: RR 8.15 (95% CI 0.43-154.64), where RR less than 1 favours the gemcitabine + Irinotecan arm.

Moderate quality evidence from 1 Multicentre Phase III RCT (n=313) showed that there is a clinically important difference favouring gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (Thrombocytopenia) compared to gemcitabine + Oxaliplatin in adults with locally advanced/metastatic pancreatic cancer: RR 4.37 (95% CI 1.7-11.25), where RR less than 1 favours the gemcitabine + Oxaliplatin arm

High quality evidence from 1 Multicentre Phase III RCT (n=546) showed that there is a clinically important difference favouring gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (Thrombocytopenia) compared to gemcitabine + Pemetrexed in adults with locally advanced/metastatic pancreatic cancer: RR 2.88 (95% CI 1.70-4.88)

Low quality evidence from 1 Phase III RCT (n=102) showed no clinically important difference between gemcitabine + Sorafenib and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (thrombocytopenia) in adults with locally advanced/metastatic pancreatic cancer: RR 0.52 (95% CI 0.14-1.97), where RR less than 1 favours the gemcitabine + Sorafenib arm.

Moderate quality evidence from a meta-analysis of 2 Phase III RCTs (n=915) showed no clinically important difference between gemcitabine + Tipifarnib and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (thrombocytopenia) in adults with locally advanced/metastatic pancreatic cancer: RR 1.22 (95% CI 0.89-1.66), where RR less than 1 favours the gemcitabine + Tipifarnib arm.

High quality evidence from a meta-analysis of 2 Multicentre Phase III RCTs (n=636) showed that there is a clinically important difference favouring gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (Thrombocytopenia) compared to gemcitabine + S-1 in adults with locally advanced/metastatic pancreatic cancer: RR 3.4 (95% CI 1.33-8.7)

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Low quality evidence from 1 Phase III RCT (n=256) showed no clinically important difference between Capecitabine + erlotinib and gemcitabine + erlotinib on the relative risk of drug-related grade 3/4 toxicities (thrombocytopenia) in adults with locally advanced/metastatic pancreatic cancer: RR 5.17 (95% CI 1.17-22.85), where RR less than 1 favours the gemcitabine + erlotinib arm

f) Grade 3/4 toxicities: Leucopoenia

High quality evidence from 1 Multicentre Phase III RCT (n=545) showed that there is a clinically important difference favouring S-1 single-agent on the relative risk of drug-related grade 3/4 toxicities (Leucopoenia) compared to gemcitabine single-agent in adults with locally advanced/metastatic pancreatic cancer: RR 0.2 (95% CI 0.1-0.38)

Low quality evidence from 1 Multicentre Phase III RCT (n=316) showed no clinically important difference between gemcitabine + 5-FU and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (leucopoenia) in adults with locally advanced/metastatic pancreatic cancer: RR 1.81 (95% CI 1.03-3.2), where RR less than 1 favours the gemcitabine + 5-FU arm.

High quality evidence from 1 Multicentre Phase III RCT (n=613) showed no clinically important difference between gemcitabine + Axitanib and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (leucopoenia) in adults with locally advanced/metastatic pancreatic cancer: no drug-related grade 3/4 toxicities (Leucopoenia) were reported.

Low quality evidence from 1 Multicentre Phase III RCT (n=716) showed no clinically important difference between gemcitabine + Cetuximab and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (leucopoenia) in adults with locally advanced/metastatic pancreatic cancer: RR 0.76 (95% CI 0.51-1.11), where RR less than 1 favours the gemcitabine + Cetuximab arm.

Very low quality evidence from 1 Multicentre Phase III RCT (n=195) showed no clinically important difference between gemcitabine + Cisplatin and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (leucopoenia) in adults with locally advanced/metastatic pancreatic cancer: RR 1.24 (95% CI 0.51-3), where RR less than 1 favours the gemcitabine + Cisplatin arm.

Moderate quality evidence from 1 Multicentre Phase III RCT (n=153) showed no clinically important difference between gemcitabine + elpamotide and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (leucopoenia) in adults with locally advanced/metastatic pancreatic cancer: RR 0.71 (95% CI 0.47-1.09), where RR less than 1 favours the gemcitabine + elpamotide arm.

Moderate quality evidence from 1 Multicentre Phase III RCT (n=527) showed no clinically important difference between gemcitabine + Oxaliplatin and gemcitabine single-agent on the relative risk of drug-related grade 3/4 toxicities (leucopoenia) in adults with locally advanced/metastatic pancreatic cancer: RR 0.76 (95% CI 0.5-1.17), where RR less than 1 favours the gemcitabine + Oxaliplatin arm.

Moderate quality evidence from a meta-analysis of 2 Multicentre Phase III RCTs (n=636) showed no clinically important difference between gemcitabine + S-1 and gemcitabine single-agent between patients treated with gemcitabine compared to those treated with gemcitabine + S-1 on the relative risk of drug-related grade 3/4 toxicities (leucopoenia) in adults with locally advanced/metastatic pancreatic cancer: RR 1.76 (95% CI 1.09-2.84), where RR less than 1 favours the gemcitabine + S-1 arm.

Low quality evidence from 1 Phase III RCT (n=256) showed no clinically important difference between Capecitabine + erlotinib and gemcitabine + erlotinib on the relative risk of drug-related grade 3/4 toxicities (leucopoenia) in adults with locally advanced/metastatic

pancreatic cancer: RR 15.98 (95% CI 0.93-273.93), where RR less than 1 favours the gemcitabine + erlotinib arm

Health-related quality of life

Low quality evidence from a meta-analysis of 2 Multicentre Phase III RCTs (n=319) showed no clinically important difference between gemcitabine + Capecitabine and gemcitabine single-agent on the improvement of quality of life in physical well-being, mood, pain, tiredness, functional performance, coping effort, and treatment burden (measured as mean of the linear-analogue self-assessment [LASA] indicators) in adults with locally advanced/metastatic pancreatic cancer at 6 months follow-up.

Low quality evidence from 1 Multicentre Phase III RCT (n=540) showed no clinically important difference between gemcitabine + Cetuximab and gemcitabine single-agent group at 5, 13, and 17 weeks follow-up on the improvement of quality of life in emotional well-being (measured as mean of the linear-analogue self-assessment [LASA] indicators) in adults with locally advanced/metastatic pancreatic cancer.

Moderate low quality evidence from 1 Multicentre Phase III RCT (n=195) showed that there is a clinically important difference favouring gemcitabine + Cisplatin on quality of life (measured as mean of the Spitzer 5-Item Index) compared to gemcitabine alone at the end of treatment in adults with locally advanced/metastatic pancreatic cancer: MD -0.40 (95% CI -0.66 to -0.14)

Very low and low quality evidence from 1 Phase III RCT (n=46) indicates showed no clinically important difference between PEFG and gemcitabine single-agent on the relative probability of improving quality of life in adults with locally advanced/metastatic pancreatic cancer at 6 months follow-up (measured as mean of the number of patients with a clinically significant improvement QLQ-C30).

11.2.6.3 Gemcitabine versus novel agents

Response rate

Low quality evidence from 1 Multicentre Phase II RCT (n=142) showed no clinically important difference between gemcitabine + novel agents [vandetanib] and gemcitabine + placebo about the relative probability of objective response rate (CR + PR) in adults with locally advanced/metastatic pancreatic cancer: RR 1.08 (95% CI 0.47-2.50), where RR less than 1 favours the gemcitabine + vandenitab arm.

Very low quality evidence from 1 Multicentre Phase III RCT (n=277) showed no clinically important difference between novel agents [BAY 12-9566] and gemcitabine single-agent chemotherapy for patients treated with the BAY 12-9566 when compared to those who received gemcitabine about the relative probability of objective response rate (CR + PR) in adults with locally advanced/metastatic pancreatic cancer: RR 0.18 (95% CI 0.02-1.45), where RR less than 1 favours the gemcitabine single-agent chemotherapy arm.

Very low quality evidence from 1 Multicentre Phase III RCT (n=55) showed no clinically important difference between novel agents [ZD9331] and gemcitabine single-agent chemotherapy for patients treated with the ZD9331 when compared to those who received gemcitabine about the relative probability of objective response rate (CR + PR) in adults with locally advanced/metastatic pancreatic cancer: RR 0.42 (95% CI 0.04-4.33), where RR less than 1 favours the gemcitabine single-agent chemotherapy arm.

Progression-free survival

Moderate quality evidence from 1 Multicentre Phase II RCT (n=142) showed no clinically important difference between gemcitabine + novel agents [vandetanib] and gemcitabine + placebo in progression-free survival rates in adults with locally advanced/metastatic

pancreatic cancer: HR 1.11 (95% CI 0.87-1.41), where HR less than 1 favours the gemcitabine + placebo arm.

Moderate quality evidence from 1 Multicentre Phase III RCT (n=277) showed that there is a clinically important difference favouring gemcitabine single-agent chemotherapy in progression-free survival rates when compared with the BAY 12-9566: HR 0.53 (95% CI 0.41-0.68)

Overall Survival

Moderate quality evidence from 1 Multicentre Phase II RCT (n=142) showed no clinically important difference between gemcitabine + novel agents [vandetanib] and gemcitabine + placebo in overall survival in adults with locally advanced/metastatic pancreatic cancer: HR 1.21 (95% CI 0.96-1.53), where HR less than 1 favours the gemcitabine + vandenitab arm.

Moderate quality evidence from 1 Multicentre Phase III RCT (n=277) showed that there is a clinically important difference favouring gemcitabine single-agent chemotherapy in overall survival rates compared to BAY 12-9566 in adults with locally advanced/metastatic pancreatic cancer: HR 0.57 (95% CI 0.44-0.74), where HR less than 1 favours the gemcitabine single-agent chemotherapy arm.

Adverse Events

Moderate quality evidence from 1 Multicentre Phase II RCT (n=142) showed no clinically important difference between gemcitabine + novel agents [vandetanib] and gemcitabine + placebo about the relative risk of grade 3/4 toxicities (neutropenia) in adults with locally advanced/metastatic pancreatic cancer: RR 1.55 (95% CI 1.02-2.35), where RR less than 1 favours the gemcitabine + vandenitab arm

Low quality evidence from 1 Multicentre Phase II RCT (n=142) showed no clinically important difference between gemcitabine + novel agents [vandetanib] and gemcitabine + placebo about the relative risk of grade 3/4 toxicities (including thrombocytopenia, fatigue, leucopenia, hypertension, ALT increased, hyponatraemia, ALP increased, lethargy, lymphocyte count decreased, diarrhoea, blood bilirubin increased, and abdominal pain) in adults with locally advanced/metastatic pancreatic cancer.

Very low quality evidence from 1 Multicentre Phase III RCT (n=277) showed no clinically important difference between novel agents [BAY 12-9566] and gemcitabine single-agent chemotherapy the relative risk of grade 3/4 toxicities (including nausea, vomiting, and diarrhoea) in adults with locally advanced/metastatic pancreatic cancer.

Very low quality evidence from 1 Multicentre Phase III RCT (n=55) showed no clinically important difference between novel agents [ZD9331] and gemcitabine single-agent chemotherapy about the relative risk of grade 3/4 toxicities (including nausea, vomiting, diarrhoea, fatigue, and neutropenia) in adults with locally advanced/metastatic pancreatic cancer.

Health-related quality of life

Moderate quality evidence from 1 Multicentre Phase III RCT (n=277) showed that there is a clinically important difference favouring novel agents [BAY 12-9566] on global quality of life and several functional domains: including physical, role and cognitive (measured as mean of the EORTC QLQ C-30) compared to gemcitabine single-agent chemotherapy in adults with locally advanced/metastatic pancreatic cancer at 8 weeks follow-up.

Moderate quality evidence from 1 Multicentre Phase III RCT (n=277) showed that there is a clinically important difference favouring novel agents [BAY 12-9566] on perceived symptom burden: including fatigue, pain and constipation (measured as mean of the EORTC QLQ C-

30) compared to gemcitabine single-agent chemotherapy in adults with locally advanced/metastatic pancreatic cancer at 8 weeks follow-up

Low quality evidence from 1 Multicentre Phase III RCT (n=277) showed no clinically important difference between novel agents [BAY 12-9566] and gemcitabine single-agent chemotherapy in quality of life: including emotional and social functional domains; and nausea, dyspnoea, insomnia, diarrhoea, and financial perceived symptom burden (measured as mean of the EORTC QLQ C-30) in adults with locally advanced/metastatic pancreatic cancer at 8 weeks follow-up.

11.2.6.4 Standard-dose gemcitabine versus low-dose

Response rate

Very low quality evidence from 1 Phase III RCT (n=21) showed no clinically important difference between gemcitabine infusion at a standard dose and gemcitabine infusion at a low dose chemotherapy about the relative probability of objective response rate (CR + PR) in adults with locally advanced/metastatic pancreatic cancer: RR 0.91 (95% CI 0.16-5.3) where RR higher than 1 favours the standard dose arm.

Progression-free survival

No evidence was identified to inform this outcome.

Overall Survival

Moderate quality evidence from 1 Phase III RCT (n=21) showed no clinically important difference in between survival rates gemcitabine infusion at a standard dose and gemcitabine infusion at a low dose chemotherapy in adults with locally advanced/metastatic pancreatic cancer.

Adverse Events

Very low quality evidence from 1 Phase III RCT (n=21) showed no clinically important difference between gemcitabine infusion at a standard dose and gemcitabine infusion at a low dose chemotherapy about the relative risk of grade 3/4 toxicities (including neutropenia, anaemia, thrombocytopenia, general fatigue, nausea/vomiting, and diarrhoea) in adults with locally advanced/metastatic pancreatic cancer.

Health-related quality of life

No evidence was identified to inform this outcome.

11.2.6.5 5-FU versus combination 5-FU

11.2.6.5.1 In adults with metastatic disease

Response rate

Low quality evidence from a meta-analysis of 2 Phase III RCTs (n=319) showed that there is a clinically important difference favouring 5-FU combination chemotherapy on objective response rate (CR + PR) compared to 5-FU single-agent chemotherapy in adults with metastatic pancreatic cancer: RR 8.62 (95% CI 1.57-47.22)

Very low quality evidence from 1 Phase III RCT (n=123) showed no clinically important difference between 5-FU single-agent chemotherapy and 5-FU combination chemotherapy [5-FU + doxorubicin + cisplatin] in objective response rate (CR + PR) in adults with metastatic pancreatic cancer: RR 2.17 (95% CI 0.2-23.31), where RR higher than 1 favours the 5-FU combination arm.

Very low quality evidence from 1 Phase III RCT (n=196) showed no clinically important difference between 5-FU single-agent chemotherapy and 5-FU combination chemotherapy [5-FU + cisplatin] in objective response rate (CR + PR) in adults with metastatic pancreatic cancer: RR 21 (95% CI 1.25-353.49), where RR higher than 1 favours the 5-FU combination arm.

Progression-free survival

Low quality evidence from 1 Phase III RCT (n=196) showed that there is a clinically important difference favouring 5-FU + cisplatin chemotherapy in progression-free survival rates compared to 5-FU single-agent chemotherapy in adults with metastatic pancreatic cancer: HR 0.55 (95% CI 0.41-0.74)

Overall Survival

Low quality evidence from a meta-analysis of 2 Phase III RCTs (n=319) showed no clinically important difference between 5-FU single-agent chemotherapy and 5-FU combination chemotherapy in overall survival rates in adults with metastatic pancreatic cancer: HR 0.97 (95% CI 0.79-1.2), where HR less than 1 favours the 5-FU combination arm.

Adverse Events

Very low quality evidence from 1 Phase III RCT (n=123) showed that there is a clinically important difference favouring 5-FU single-agent chemotherapy on the relative risk of grade 3/4 toxicities (nausea) compared to 5-FU + doxorubicin + cisplatin in adults with metastatic pancreatic cancer: RR 4.70 (95% CI 1.51-10.91)

Moderate quality evidence from a meta-analysis of III Phase III RCTs (n=319) showed that there is a clinically important difference favouring 5-FU combination chemotherapy on the relative risk of grade 3/4 toxicities (vomiting) compared to 5-FU single-agent chemotherapy in adults with metastatic pancreatic cancer: RR 3.75 (95% CI 1.73-7.32)

Very low quality evidence from 1 Phase III RCT (n=123) showed no clinically important difference between 5-FU single-agent chemotherapy and 5-FU combination chemotherapy [5-FU + doxorubicin + cisplatin] about the relative risk of grade 3/4 toxicities (vomiting) in adults with metastatic pancreatic cancer: RR 3.25 (95% CI 0.94-8.78), where RR higher than 1 favours the 5-FU single-agent arm.

Moderate quality evidence from 1 Phase III RCT (n=196) showed that there is a clinically important difference favouring 5-FU combination [5-FU + cisplatin] chemotherapy on the relative risk of grade 3/4 toxicities (vomiting) compared to 5-FU single-agent chemotherapy in adults with metastatic pancreatic cancer: RR 4.12 (95% CI 1.49-9.52)

Very low quality evidence from 1 Phase III RCT (n=196) showed no clinically important difference between 5-FU single-agent chemotherapy group & 98 in the 5-FU combination chemotherapy [5-FU + cisplatin] about the relative risk of grade 3/4 toxicities diarrhoea between intervention groups in adults with metastatic pancreatic cancer: RR 2.57 (95% CI 0.51-11.15), where RR higher than 1 favours the 5-FU single-agent arm.

Very low quality evidence from 1 Phase III RCT (n=123) showed no clinically important difference between 5-FU single-agent chemotherapy and 5-FU combination chemotherapy [5-FU + doxorubicin + cisplatin] about the relative risk of grade 3/4 toxicities (leucopoenia) in adults with metastatic pancreatic cancer: RR 1.68 (95% CI 1.11-2.23), where RR higher than 1 favours the 5-FU single-agent arm.

Very low quality evidence from a meta-analysis of 2 Phase III RCTs (n=320) showed no clinically important difference between 5-FU single-agent chemotherapy and 5-FU combination chemotherapy about the relative risk of grade 3/4 toxicities (stomatitis) in adults

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with metastatic pancreatic cancer: RR 1.2 (95% CI 0.6-2.27), where RR higher than 1 favours the 5-FU single-agent arm.

Very low quality evidence from 1 Phase III RCT (n=123) showed no clinically important difference between 5-FU single-agent chemotherapy and 5-FU combination chemotherapy [5-FU + doxorubicin + cisplatin] about the relative risk of grade 3/4 toxicities (stomatitis) in adults with metastatic pancreatic cancer: RR 0.36 (95% CI 0.09-1.22), where RR higher than 1 favours the 5-FU single-agent arm.

Low quality evidence from 1 Phase III RCT (n=197) showed no clinically important difference 5-FU single-agent chemotherapy and 5-FU combination chemotherapy [5-FU + cisplatin] about the relative risk of grade 3/4 toxicities (stomatitis) in adults with metastatic pancreatic cancer: RR 2.68 (95% CI 1.01-6.23), where RR higher than 1 favours the 5-FU single-agent arm.

Health-related quality of life

No evidence was identified to inform this outcome.

1.2.6.5.2 In adults with locally advanced and metastatic pancreatic cancer

Response rate

Low quality evidence from a meta-analysis of 2 Phase III RCTs (n=220) showed no clinically important difference between 5-FU single-agent and 5-FU combination chemotherapy in objective response rate (CR + PR) in adults with locally advanced/metastatic pancreatic cancer: RR 1.7 (95% CI 0.88-3.3), where RR higher than 1 favours the 5-FU combination arm.

Very low quality evidence from 1 Phase III RCT (n=23) showed no clinically important difference between 5-FU single-agent and 5-FU combination chemotherapy [5-FU + doxorubicin + mitomycin] on objective response rate (CR + PR) in adults with locally advanced/metastatic pancreatic cancer: RR 0.26 (95% CI 0.03-2.11), where RR higher than 1 favours the 5-FU combination arm.

Moderate quality evidence from 1 Phase III RCT (n=197) showed no clinically important difference between 5-FU single-agent and 5-FU combination chemotherapy [5-FU + mitomycin] the 5-FU combination chemotherapy when compared to those who received 5-FU chemotherapy alone objective response rate (CR + PR) in adults with locally advanced/metastatic pancreatic cancer: RR 2.28 (95% CI 1.08-4.83), where RR higher than 1 favours the 5-FU combination arm.

Progression-free survival

Moderate quality evidence from 1 Phase III RCT (n=197) showed no clinically important difference between 5-FU single-agent and 5-FU combination chemotherapy [5-FU + mitomycin] on progression-free survival rates in adults with locally advanced/metastatic pancreatic cancer: HR 0.81 (95% CI 0.62-1.06), where HR less than 1 favours the 5-FU combination arm.

Overall Survival

Low quality evidence from a meta-analysis of 2 Phase III RCTs (n=220) showed no clinically important difference between 5-FU single-agent and 5-FU combination chemotherapy on overall survival in adults with locally advanced/metastatic pancreatic cancer: HR 0.97 (95% CI 0.79-1.20), where HR less than 1 favours the 5-FU combination arm.

Adverse Events

Low quality evidence from 1 Phase III RCT (n=197) showed no clinically important difference between 5-FU single-agent and 5-FU combination chemotherapy [5-FU + mitomycin] about the relative risk of grade 3/4 toxicities (diarrhoea) in adults with locally advanced/metastatic pancreatic cancer: RR 1.05 (95% CI 0.31-3.52) where RR higher than 1 favours the 5-FU combination arm.

Low quality evidence from 1 Phase III RCT (n=197) showed no clinically important difference between 5-FU single-agent and 5-FU combination chemotherapy [5-FU + mitomycin] about the relative risk of grade 3/4 toxicities (neutropenia) in adults with locally advanced/metastatic pancreatic cancer: RR 7.34 (95% CI 0.38-140.36) where RR higher than 1 favours the 5-FU combination arm.

Low quality evidence from 1 Phase III RCT (n=209) showed no clinically important difference between about the relative risk of grade 3/4 toxicities (stomatitis) 5-FU single-agent and 5-FU combination chemotherapy [5-FU + mitomycin] in adults with locally advanced/metastatic pancreatic cancer: RR 1.44 (95% CI 0.60-3.44) where RR higher than 1 favours the 5-FU combination arm.

Health-related quality of life

No evidence was identified to inform this outcome.

11.2.6.6 Combination 5-FU (FSM) versus other chemotherapy

Response rate

Very low quality evidence from 1 phase 3 RCT (n=184) showed no clinically important difference between FSM [5-FU+ streptozotocin + mitomycin] and FAM chemotherapy [5-FU + Adriamycin + mitomycin] about the relative probability of objective response rate (CR + PR) in adults with locally advanced/metastatic pancreatic cancer: RR 0.32 (95% CI 0.09-1.14), where RR higher than 1 favours the FSM arm.

Low quality evidence from 1 phase 3 RCT (n=140) showed that there is a clinically important difference favouring FSM group [5-FU+ streptozotocin + mitomycin] in objective response rate (CR + PR) compared to FM chemotherapy [5-FU + mitomycin] in adults with locally advanced/metastatic pancreatic cancer: RR 3.8 (95% CI 1.5-9.61)

Progression-free survival

No evidence was identified to inform this outcome.

Overall Survival

Low quality evidence from 1 phase 3 RCT (n=184) showed no clinically important difference between FSM [5-FU+ streptozotocin + mitomycin] and FAM chemotherapy [5-FU + Adriamycin + mitomycin] in overall survival rates.

Low quality evidence from 1 phase 3 RCT (n=140) showed no clinically important difference between FSM [5-FU+ streptozotocin + mitomycin] and FM [5-FU + mitomycin] chemotherapy in overall survival rates.

Adverse Events

Very low quality evidence from 1 phase 3 RCT (n=140) showed no clinically important difference between FSM [5-FU+ streptozotocin + mitomycin] and FM [5-FU + mitomycin] chemotherapy about the relative risk of drug-related grade 3/4 toxicities (diarrhoea) in adults with locally advanced/metastatic pancreatic cancer: RR 0.50 (95% CI 0.05-5.39) where RR less than 1 favours the FSM arm.

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Very low quality evidence from 1 phase 3 RCT (n=184) showed no clinically important difference between FSM [5-FU+ streptozotocin + mitomycin] and FAM chemotherapy [5-FU + Adriamycin + mitomycin] about the relative risk of drug-related grade 3/4 toxicities (nausea/vomiting) in adults with locally advanced/metastatic pancreatic cancer: RR 1.20 (95% CI 0.59-2.41) where RR less than 1 favours the FSM arm.

Very low quality evidence from 1 phase 3 RCT (n=140) showed no clinically important difference between FSM [5-FU+ streptozotocin + mitomycin] and FM [5-FU + mitomycin] chemotherapy about drug-related grade 3/4 toxicities (nausea/vomiting) in adults with locally advanced/metastatic pancreatic cancer: RR 1.61 (95% CI 0.99-2.62), where RR less than 1 favours the FSM arm.

Very low quality evidence from 1 phase 3 RCT (n=184) showed no clinically important difference between FSM [5-FU+ streptozotocin + mitomycin] and FAM chemotherapy [5-FU + Adriamycin + mitomycin] on the relative risk of drug-related grade 3/4 toxicities (leukopenia) in adults with locally advanced/metastatic pancreatic cancer: RR 0.48 (95% CI 0.26-0.90), where RR less than 1 favours the FSM arm.

Very low quality evidence from 1 phase 3 RCT (n=140) showed no clinically important difference between FSM [5-FU+ streptozotocin + mitomycin] and FM [5-FU + mitomycin] chemotherapy in the relative risk of drug-related grade 3/4 toxicities (leukopenia) in adults with locally advanced/metastatic pancreatic cancer: RR 0.82 (95% CI 0.36-1.85) where RR less than 1 favours the FSM arm.

Very low quality evidence from 1 phase 3 RCT (n=184) showed no clinically important difference between FSM [5-FU+ streptozotocin + mitomycin] and FAM chemotherapy [5-FU + Adriamycin + mitomycin] on the relative risk of drug-related grade 3/4 toxicities (thrombocytopenia) in adults with locally advanced/metastatic pancreatic cancer: RR 0.58 (95% CI 0.36-0.93), where RR less than 1 favours the FSM arm

Very low quality evidence from 1 phase 3 RCT (n=140) showed no clinically important difference between FSM [5-FU+ streptozotocin + mitomycin] and FM [5-FU + mitomycin] chemotherapy in the relative risk of drug-related grade 3/4 toxicities (thrombocytopenia) in adults with locally advanced/metastatic pancreatic cancer: RR 0.62 (95% CI 0.31-1.28) where RR less than 1 favours the FSM arm.

Very low quality evidence from 1 phase 3 RCT (n=140) showed no clinically important difference between FSM [5-FU+ streptozotocin + mitomycin] and FM [5-FU + mitomycin] chemotherapy in the relative risk of drug-related deaths in adults with locally advanced/metastatic pancreatic cancer: RR 0.25 (95% CI 0.03-2.18) where RR less than 1 favours the FSM arm.

Health-related quality of life

No evidence was identified to inform this outcome.

11.2.6.7 Intra-arterial chemotherapy versus systemic chemotherapy

Response rate

Low quality evidence from a meta-analysis of 3 phase III RCTs (n=181) showed that there is a clinically important difference favouring intra-arterial chemotherapy on objective response rate (CR + PR) compared to systemic chemotherapy in adults with locally advanced/metastatic pancreatic cancer: RR 2.76 (95% CI 1.23-6.18)

Progression-free survival

No evidence was identified to inform this outcome.

Overall Survival

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Low quality evidence from 1 Phase III RCT (n=138) showed no clinically important difference between intra-arterial and systemic chemotherapy in overall survival rates in adults with locally advanced/metastatic pancreatic cancer: HR 1.02 (95% CI 0.63-1.66), where HR less than 1 intra-arterial chemotherapy arm.

Adverse Events

Moderate quality evidence from 1 Phase III RCT (n=138) showed that there is a clinically important difference favouring intra-arterial chemotherapy on the relative risk of drug-related grade 3/4 toxicities (thrombocytopenia) compared to systemic chemotherapy in adults with locally advanced/metastatic pancreatic cancer: RR 16.04 (95% CI 2.20-117.24)

Low and very low quality evidence from 1 Phase III RCT (n=138) showed no clinically important difference between the intra-arterial and systemic chemotherapy about the relative risk of drug-related grade 3/4 toxicities (including nausea/vomiting, diarrhoea, and leucopoenia) in adults with locally advanced/metastatic pancreatic cancer: RR 0.13 (95% CI 0.01-2.56), RR 0.19 (95% CI 0.01-3.86), and RR 2.64 (95% CI 1.01-6.94); where RR less than 1 favours the intra-arterial chemotherapy arm.

Health-related quality of life

No evidence was identified to inform this outcome.

11.2.6.8 Chemotherapy versus chemotherapy and prophylactic anticoagulant

Response rate

No evidence was identified to inform this outcome.

Progression-free survival

Low quality evidence from 1 multicentre Phase III RCT (n=312) showed no clinically important difference between gemcitabine combined with enoxaparin and gemcitabine only on progression-free survival in adults with locally advanced or metastatic pancreatic cancer: HR 1.06 (95% CI 0.84-1.34), where HR less than 1 favours the gemcitabine + enoxaparin arm.

Overall Survival

Moderate quality evidence from 1 Phase IIb RCT (n=121) showed no clinically important difference between gemcitabine with weight-adjusted dalteparin and gemcitabine only on overall survival in adults with locally advanced or metastatic pancreatic cancer.

Low quality evidence from 1 multicentre Phase III RCT (n=312) showed no clinically important difference between gemcitabine combined with enoxaparin and gemcitabine only on overall survival in adults with locally advanced or metastatic pancreatic cancer: HR 1.10 (95% CI 0.87-1.39), where HR less than 1 favours the gemcitabine + enoxaparin arm.

Adverse Events

Very low quality evidence from 1 Phase IIb RCT (n=116) showed no clinically important difference between gemcitabine with weight-adjusted dalteparin and gemcitabine only on drug-related Grade 3/4 haematological impairment (RR 0.87 [95% CI 0.55-1.37]) and hepatic functional impairment (RR 1.09 [95% CI 0.64-1.86]) in adults with locally advanced or metastatic pancreatic cancer, where RR less than 1 favours the gemcitabine and weight-adjusted dalteparin arm.

Moderate quality evidence from 1 Phase IIb RCT (n=123) showed no clinically important difference between gemcitabine combined with weight-adjusted dalteparin and gemcitabine only on vascular thromboembolism in adults with locally advanced or metastatic pancreatic

cancer: RR 0.39 (95% CI 0.18-0.85), where RR less than 1 favours the gemcitabine and weight-adjusted dalteparin arm.

Very low and low quality evidence from 1 multicentre Phase III RCT (n=312) showed no clinically important difference between gemcitabine combined with enoxaparin and gemcitabine only on symptomatic VTE (RR 0.43 [95% CI 0.21-0.88]) and major haemorrhages (RR 1.24 [95% CI 0.56-2.73]) in adults with locally advanced or metastatic pancreatic cancer, where RR less than 1 favours the gemcitabine and weight-adjusted dalteparin arm.

Health-related quality of life

No evidence was identified to inform this outcome.

11.2.6.8.1 Second-line chemotherapy versus best supportive care

Response rate

No evidence was identified to inform this outcome.

Progression-free survival

Low quality evidence from 1 multicentre Phase III RCT (n=303) showed no clinically important difference between second-line chemotherapy and best supportive care on progression-free survival in adults with metastatic pancreatic cancer: HR 0.76 (95% CI 0.57-1.01), where HR less than 1 favours the chemotherapy arm.

Overall Survival

Low quality evidence from 1 multicentre Phase III RCT (n=303) showed no clinically important difference between second-line chemotherapy and best supportive care on overall survival in adults with metastatic pancreatic cancer: HR 0.85 (95% CI 0.66-1.09), where HR less than 1 favours the chemotherapy arm.

Adverse Events

Very quality evidence from 1 multicentre Phase III RCT (n=286) showed no clinically important difference between second-line chemotherapy and best supportive care on Grade 3, 4 or 5 toxicities (including asthenia/fatigue, abdominal pain, anaemia, vomiting, nausea, deep vein thrombosis, renal failure, hyperbilirubinemia, and leukopenia) in adults with metastatic pancreatic cancer: RR 1.12 (95% CI 0.51-2.46), RR 0.87 (95% CI 0.4-1.88), RR 2.4 (95% CI 0.63-9.1), RR 3.6 (95% CI 0.76-17.03), RR 3.09 (95% CI 0.63-15.03), RR 5.14 (95% CI 0.61-43.46), RR 11.31 (95% CI 0.63-202.65), RR 2.06 (95% CI 0.38-11.05), and RR 9.25 (95% CI 0.5-170.31), where RR less than 1 favours the chemotherapy arm.

Health-related quality of life

No evidence was identified to inform this outcome.

11.2.6.8.2 Second-line chemotherapy versus other chemotherapy

In adults with metastatic disease

Response rate

Low quality evidence from 1 Multicentre Phase III RCT (n=202) showed no clinically important difference between LV5FU2-CDDP followed by gemcitabine single-agent [LV5FU2-CDDP/Gem] and gemcitabine single-agent followed by LV5FU2-CDDP [Gem/LV5FU2-CDDP] about the relative probability of objective response rate (CR + PR) in adults with metastatic pancreatic cancer: RR 0.85 (95% CI 0.49-1.47), where RR higher than 1 favours the LV5FU2-CDDP/Gem arm.

Very low quality evidence from 1 Multicentre Phase III RCT (n=38) showed no clinically important difference between irinotecan + raltitrexed and raltitrexed single-agent as second-line chemotherapy about the relative probability of objective response rate (CR + PR) in adults with metastatic pancreatic cancer: RR 0.14 (95% CI 0.01-2.59), where RR higher than 1 favours the irinotecan + raltitrexed arm.

Progression-free survival

Moderate quality evidence from 1 Multicentre Phase III RCT (n=202) showed no clinically important difference between LV5FU2-CDDP followed by gemcitabine single-agent [LV5FU2-CDDP/Gem] and gemcitabine single-agent followed by LV5FU2-CDDP [Gem/LV5FU2-CDDP] in PFS rates between intervention groups in adults with metastatic pancreatic cancer: HR 1.06 (95% CI 0.80-1.40), where HR less than 1 favours the LV5FU2-CDDP/Gem arm.

Overall Survival

Moderate quality evidence from 1 Multicentre Phase III RCT (n=202) showed no clinically important difference between LV5FU2-CDDP followed by gemcitabine single-agent [LV5FU2-CDDP/Gem] and gemcitabine single-agent followed by LV5FU2-CDDP [Gem/LV5FU2-CDDP] in long-term survival rates in adults with metastatic pancreatic cancer: HR 1.06 (95% CI 0.80-1.40), where HR less than 1 favours the LV5FU2-CDDP/Gem arm.

Adverse Events

Low quality evidence from 1 Multicentre Phase III RCT (n=202) showed no clinically important difference between LV5FU2-CDDP followed by gemcitabine single-agent [LV5FU2-CDDP/Gem] and gemcitabine single-agent followed by LV5FU2-CDDP [Gem/LV5FU2-CDDP] about the relative risk of drug-related grade 3/4 toxicities (including nausea/vomiting) in adults with metastatic pancreatic cancer: RR 0.92 (95% CI 0.47-1.80), where RR less than 1 favours the LV5FU2-CDDP/Gem arm.

Very low quality evidence from 1 Multicentre Phase III RCT (n=38) showed no clinically important difference between irinotecan + raltitrexed and raltitrexed single-agent as second-line chemotherapy about the relative risk of drug-related grade 3/4 toxicities in adults with metastatic pancreatic cancer, including leukocytopenia (RR 1.25 [95% CI 0.4-3.95]), neutropenia (RR 1.33 [95% CI 0.34-5.17]), nausea/vomiting (RR 1.0 [95% CI 0.07-14.85]), and diarrhoea (RR 1.0 [95% CI 0.16-6.38]), where RR less than 1 favours the raltitrexed alone arm. (There were no cases of thrombocytopenia, stomatitis, and fatigue).

Health-related quality of life

No evidence was identified to inform this outcome.

In adults with locally advanced and metastatic pancreatic cancer

Response rate

Very low quality evidence from 1 Phase III RCT (n=110) showed no clinically important difference between the oxaliplatin + 5-FU and folinic acid + 5-FU second-line chemotherapy in adults with locally advanced/metastatic pancreatic cancer: RR 1.5 (95% CI 0.27-8.19), where RR higher than 1 favours the oxaliplatin + 5-FU arm.

Very low quality evidence from 1 Multicentre Phase III RCT (n=274) showed no clinically important difference between gemcitabine + erlotinib followed by capecitabine [Gem+E/Cap] and capecitabine + erlotinib followed by gemcitabine [Cap+E/ Gem] second-line chemotherapy about the relative probability of objective response rate (CR + PR) in adults with locally advanced/metastatic pancreatic cancer: RR 0.49 (95% CI 0.1-2.29), where RR higher than 1 favours the Gem+E/Cap arm.

Very low quality evidence from 1 Phase III RCT (n=108) showed no clinically important difference between 5-FU + folinic acid + oxaliplatin [mFOLFOX6] and folinic acid/5-FU second-line chemotherapy about the relative probability of objective response rate (CR + PR) in adults with locally advanced/metastatic pancreatic cancer: RR 1.4 (95% CI 0.47-4.14), where RR higher than 1 favours the mFOLFOX6 arm.

Progression-free Survival

Low quality evidence from 1 Phase III RCT (n=110) showed no clinically important difference between oxaliplatin + 5-FU and folinic acid + 5-FU second-line chemotherapy in PFS rates in adults with locally advanced/metastatic pancreatic cancer.

Low quality evidence from 1 Multicentre Phase III RCT (n=168) showed that there is a clinically important difference favouring OFF is associated with a marked improvement in PFS when compared with FF in adults with locally advanced/metastatic pancreatic cancer: HR 0.68 (95% CI 0.49-0.94), where HR less than 1 favours the OFF group.

Moderate quality evidence from 1 Phase III RCT (n=108) showed no clinically important difference between 5-FU + folinic acid + oxaliplatin [mFOLFOX6] and folinic acid/5-FU second-line chemotherapy in PFS rates in adults with locally advanced/metastatic pancreatic cancer: HR 1.00 (95% CI 0.66-1.52), where HR less than 1 favours the mFOLFOX6 arm.

Overall Survival

Low quality evidence from 1 Phase III RCT (n=110) showed no clinically important difference between oxaliplatin + 5-FU and folinic acid + 5-FU second-line chemotherapy in survival rates in adults with locally advanced/metastatic pancreatic cancer.

Moderate quality evidence from 1 Multicentre Phase III RCT (n=168) showed that there is a clinically important difference favouring oxaliplatin + 5-FU group [OFF] second-line chemotherapy in overall survival compared to FA + 5-FU group [FF] second-line chemotherapy in adults with locally advanced/metastatic pancreatic cancer: HR 0.66 (95% CI 0.48-0.91), where HR less than 1 favours the OFF group.

Low quality evidence from 1 Multicentre Phase III RCT (n=274) showed no clinically important difference between gemcitabine + erlotinib followed by capecitabine [Gem+E/Cap] and capecitabine + erlotinib followed by gemcitabine [Cap+E/ Gem] second-line chemotherapy in survival rates.

Moderate quality evidence from 1 Phase III RCT (n=108) showed that there is a clinically important difference favouring folinic acid/5-FU second-line chemotherapy in overall survival compared to 5-FU + folinic acid + oxaliplatin [mFOLFOX6] second-line chemotherapy in adults with locally advanced/metastatic pancreatic cancer: HR 1.78 (95% CI 1.08-2.93), where HR less than 1 favours the mFOLFOX6 arm.

Adverse Events

Very low quality evidence from 1 Phase III RCT (n=110) showed no clinically important difference between oxaliplatin + 5-FU and folinic acid + 5-FU second-line chemotherapy about the relative risk of drug-related grade 3/4 toxicities (including nausea/vomiting, diarrhoea, stomatitis and haematological -neutropenia, anaemia, thrombocytopenia).

Low quality evidence from 1 Multicentre Phase III RCT (n=168) showed no clinically important difference between oxaliplatin + 5-FU [OFF] and FA + 5-FU group [FF] second-line chemotherapy about the relative risk of drug-related grade 3/4 toxicities (including anaemia, nausea/emesis, paresthesia, pain, leucopoenia, thrombocytopenia, and diarrhoea).

Very low quality evidence from 1 Multicentre Phase III RCT (n=274) showed no clinically important difference between gemcitabine + erlotinib followed by capecitabine [Gem+E/Cap] and capecitabine + erlotinib followed by gemcitabine [Cap+E/ Gem] second-line

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chemotherapy about the relative risk of drug-related grade 3/4 toxicities (including nausea/vomiting, leucopoenia, thrombocytopenia, and diarrhoea).

Low to very low quality evidence from 1 Phase III RCT (n=102) showed no clinically important difference between 5-FU + folinic acid + oxaliplatin [mFOLFOX6] and folinic acid/5-FU second-line chemotherapy about the relative risk of drug-related grade 3/4 toxicities (including febrile neutropenia, fatigue, thrombocytopenia, dehydration, pulmonary embolism, vomiting, hypokalaemia, and peripheral neuropathy).

Moderate quality evidence from 1 Phase III RCT (n=102) showed that there is a clinically important difference favouring 5-FU + folinic acid + oxaliplatin [mFOLFOX6] second-line chemotherapy on the relative risk of drug-related grade 3/4 toxicities (neutropenia) compared to folinic acid/5-FU in adults with locally advanced/metastatic pancreatic cancer: RR 8.65 (95% CI 2.10-35.72)

Health-related quality of life

Very low quality evidence from 1 Phase III RCT (n=108) showed no clinically important difference between 5-FU + folinic acid + oxaliplatin [mFOLFOX6] and folinic acid/5-FU second-line chemotherapy in health related quality of life in adults with locally advanced/metastatic pancreatic cancer.

11.2.7 Recommendations

First-line treatment

47. Offer FOLFIRINOX[4] to people with metastatic pancreatic cancer and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1.

48. Consider gemcitabine combination therapy[5] for people who are not well enough to tolerate FOLFIRINOX.

49. Offer gemcitabine to people who are not well enough to tolerate combination chemotherapy.

Second-line treatment

50. Consider oxaliplatin-based chemotherapy[6] as second-line treatment for people who have not had first-line oxaliplatin.

[4] Although this use is common in UK clinical practice, at the time of consultation (July 2017) FOLFIRINOX did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[5] Although this use is common in UK clinical practice, at the time of consultation (July 2017) gemcitabine combination therapy did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[6] Although this use is common in UK clinical practice, at the time of consultation (July 2017) oxaliplatin-based chemotherapy did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

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51. Consider gemcitabine-based chemotherapy[7] as second-line treatment for people whose cancer has progressed after first-line FOLFIRINOX.

Venous thromboembolism prophylaxis

52. For guidance on venous thromboembolism prophylaxis for people with pancreatic cancer, see patients with cancer in the NICE guideline on venous thromboembolism.

11.2.8 Evidence to recommendations

11.2.8.1 Relative value placed on the outcomes considered

Response rate, progression free survival, overall survival, adverse events, health related quality of life, patient experience, PROMS and symptom were considered the critical outcomes for this question.

Overall survival and adverse events were reported by all studies. Response rate was reported for all studies except one. Health related quality of life and progression free survival were reported only by some studies. The outcomes of patient experience/patient reported outcome measures and symptom control were not reported by any studies.

11.2.8.2 Quality of evidence

The quality of the evidence was assessed by GRADE and the Cochrane risk of bias checklist. AMSTAR was used for assessing the methodological quality of systematic reviews.

The quality of the outcomes for the comparisons identified by this review were as follows:

- Chemotherapy versus immunochemotherapy for second line treatment - very low.
- 5-FU combination chemotherapy versus other chemotherapy regimens – ranged from very low to low
- Second-line chemotherapy versus other chemotherapy regimens for metastatic disease – ranged from very low to low
- Gemcitabine versus novel agents – ranged from very low to moderate
- 5-FU alone versus 5-FU combination chemotherapy (both metastatic and locally advanced disease) – ranged from very low to moderate
- Second-line chemotherapy versus other chemotherapy regimens for mixed metastatic and locally advanced disease – ranged from low to moderate
- Chemotherapy versus immunochemotherapy for first line treatment - ranged from low to moderate quality.
- Chemotherapy (second-line) versus best supportive care – ranged from low to moderate
- Standard-dose versus low-dose gemcitabine – ranged from low to moderate
- Intra-arterial chemotherapy versus systemic chemotherapy – ranged from low to moderate
- Chemotherapy versus prophylactic anticoagulation + chemotherapy – ranged from low to moderate
- Gemcitabine versus other chemotherapy regimens for locally advanced disease - ranged from very low to high.

[7] Although this use is common in UK clinical practice, at the time of consultation (July 2017) gemcitabine-based chemotherapy did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

- Gemcitabine versus other chemotherapy regimens for metastatic disease - ranged from low to high

A substantial number of studies in the evidence base included mixed locally advanced and metastatic cancer populations, but did not report the subgroups separately. Given that there is a continuum between locally advanced and metastatic disease, the committee agreed it was appropriate to use evidence with mixed populations to base their recommendations on. However, during their discussions the committee applied more weight to those studies that had exclusively metastatic populations or had reported metastatic populations separately.

The committee noted that no RCT evidence was identified which evaluated surgical resection of metastases in people with pancreatic cancer. The committee therefore agreed to recommend further research in this area, as the role of surgery in managing metastatic pancreatic cancer is a common question asked by patients.

11.2.8.3 Consideration of clinical benefits and harms

First line treatment

The committee noted that high quality evidence from a network meta-analysis of 23 RCTs had shown improvements in overall survival with the use of FOLFIRINOX in people with metastatic disease and ECOG performance status 0-1. They also noted the potential for increased toxicity with FOLFIRINOX chemotherapy, and that its use was contraindicated for people with significantly impaired liver function. However, the committee agreed that the benefits in overall survival from this intervention outweighed the potential side effects experienced by those fitter people receiving it and made a strong recommendation for its use in the appropriate subgroup of people reported by the PRODIGE4/ACCORD11 trial.

Given the potential for toxicity with FOLFIRINOX, the committee agreed to make additional recommendations that covered first line treatment for those people who would be unlikely to tolerate FOLFIRINOX. They noted that the evidence for both gemcitabine combination therapy and gemcitabine monotherapy had shown improved overall survival and progression free survival in people with metastatic disease. Whilst the survival advantage for gemcitabine combination therapy was larger compared with monotherapy, this needed to be balanced against the potential for increased side effects and a recognition that some patients were not sufficiently fit to tolerate combination chemotherapy. Gemcitabine monotherapy is remarkably well tolerated, even in relatively unfit people. The committee therefore agreed to make a weaker recommendation on gemcitabine combination and monotherapy as the balance between the benefits and harms was less certain.

It was not possible, based on the evidence, to determine the optimal gemcitabine combination therapy as several were shown to have some benefits. Therefore the committee did not recommend a particular regimen.

The committee noted that the potential benefits of the recommendations made could be improvements in overall survival, progression free survival and quality of life. The potential harms were considered to be side effects from chemotherapy. The committee agreed that the potential benefits of offering chemotherapy outweighed the harms of not doing so.

Second line treatment

The committee noted, based on the evidence, that oxaliplatin-based chemotherapy had shown improved progression-free survival when given second line. However the results for overall survival were inconsistent, with one study showing a statistically significant benefit on overall survival whilst another showed no difference. The committee therefore agreed it was only possible to make a weak recommendation for this intervention.

Based on their clinical knowledge and experience the committee also agreed to recommend gemcitabine or gemcitabine-based chemotherapy as second line treatment for those people who progress on first line FOLFIRINOX. The committee noted that 80% of patients treated in the PRODIG4/ACCORD11 trial of first line FOLFIRINOX received gemcitabine or gemcitabine-based combination chemotherapy second line, and that they had based their first line treatment recommendations on results of this clinical trial. It is also the current standard of care.

Based on their knowledge and experience, the committee noted that treatment options for metastatic disease are currently very limited and second line treatment is often not considered as an option due to the poor prognosis of the disease. These factors generate an impression of futility which has a significant negative psychological impact on people with pancreatic cancer. The committee considered that making recommendations for second line treatment would help promote the active treatment of people with metastatic disease thereby helping to alleviate some of this psychological impact. They noted that other more tangible benefits could be improvements in overall survival, progression free survival and quality of life. The potential harms of the recommendations made were considered to be side effects from chemotherapy. The committee agreed that the potential benefits outweighed the harms of treatment.

11.2.8.4 Consideration of economic benefits and harms

The economic evidence review identified two previous economic evaluations for this topic both from a Canadian public healthcare payer perspective. Both studies compared FOLFIRINOX to gemcitabine in a metastatic population with one study also comparing gemcitabine in combination with erlotinib and gemcitabine in combination with capecitabine.

Whilst both studies reported broadly similar incremental improvements in health of approximately 0.25 QALYs, when comparing FOLFIRNOX to gemcitabine the reported lifetime incremental costs were double in one study compared to the other. These resulted in the studies concluding differently as to the cost effectiveness of FOLFIRINOX from a Canadian perspective. The committee acknowledged that the study that concluded that FOLFIRINOX was not cost effective incorporated the more realistic assumptions. They also noted that FOLFIRINOX was significantly more expensive in Canada (approximately by a factor of 10) where the oxaliplatin component is still on patent.

The committee acknowledged the low applicability of the studies given the differing perspective to that used by NICE although they agreed that the QALY values reported were believable in a NHS setting and were in line with the evidence from the clinical evidence review. With the lower costs associated with using FOLFIRINOX in a NHS setting it was strongly thought that FOLFIRINOX would be cost effective from a NHS+PSS perspective compared to gemcitabine alone. It was also noted that FOLFIRINOX is currently standard of care for eligible people and that this recommendation would be cost neutral.

Both gemcitabine with capecitabine and gemcitabine with erlotinib were health improving and more costly than gemcitabine alone. Given that the increase in QALYs were lower in this group compared to FOLFIRINOX, the committee found it more difficult to generalise these results to a NHS setting. Whilst the committee thought combination therapies were health improving compared to gemcitabine alone it would also be cost increasing through increased use of additional chemotherapies - although the committee did not think this cost would be significant. It was difficult to draw any conclusions from the evidence identified about cost effectiveness from a NHS+PSS perspective and a consider recommendation was made around combination therapies.

No published economic evidence was identified for the other interventions in the review question. The committee agreed that recommendations for second line treatment would probably cause an increase in costs as the current standard of care was best supportive

care. Given the relatively short life expectancy and limited number of people receiving second line treatment it was felt that any cost increases were unlikely to be significant.

The committee also agreed that the recommendations around LWMH were unlikely to have a significant resource impact as eligible people were already receiving this treatment as standard of care, although there would be some additional cost from delivering it prophylactically. Given that this intervention would reduce the complications of pancreatic cancer and emergency admissions it was possible this recommendation is cost neutral or saving.

11.2.8.5 Other considerations

The committee were aware that there was existing NICE guidance on the use of nab-paclitaxel (TA360) and liposomal irinotecan (TA440) in metastatic pancreatic cancer. Consequently and in line with NICE processes, the committee did not investigate the use of nab-paclitaxel or liposomal irinotecan in this population or make any recommendations on these interventions.

11.2.9 Research recommendation

8. A randomised phase II feasibility study should be undertaken comparing surgery/ablative treatment (in combination with chemotherapy) against chemotherapy in people with hepatic oligometastatic potentially resectable pancreatic cancer.

The role of surgery in controlling metastatic pancreatic cancer is of considerable interest. Debulking surgery is established in some other forms of advanced cancer and, combined with chemotherapy, helps to prolong life. No RCT evidence exists which evaluates the role of surgical resection of metastatic pancreatic cancer and compares it against standard non-surgical treatment. More data in this area my enable recommendations to be made about this intervention. Outcomes of interest are feasibility of recruitment, recurrence/progression free survival, quality of life and PROMS.

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12 Economic modelling: cost effectiveness of different types of stent for the management of biliary obstruction in people with unresectable pancreatic cancer

12.1 Introduction

Biliary obstruction causing obstructive jaundice is the most visible manifestation of pancreatic malignancy in the head of pancreas. The main symptom associated with the obstructive jaundice is an itch which can be severe and debilitating but is not present in all patients. Other symptoms that may be caused/exacerbated by biliary obstruction include early satiety and nausea. The visible signs of biliary obstruction include yellow sclera and skin and may be of most concern to the individual. Biliary obstruction leads to malabsorption of the fat soluble vitamins, resulting in a vitamin k deficiency if obstruction is prolonged and consequent derangement of blood clotting.

In people with unresectable pancreatic cancer causing biliary obstruction clarity is needed around the most cost effective stent to use in palliation of this blockage. Historically, inexpensive plastic stents (with a small diameter lumen) have been used for managing biliary obstruction. In the last few years more expensive self-expanding mesh metal stents (SEMS) have become widely available and there is a perception that use of these stents may cause less morbidity than plastic stents and may have a longer time to dysfunction. Therefore, they may be cost effective or cost saving through improved quality of life and reduced costs from reducing the need for further surgery following dysfunction and through reducing the need to treat other adverse events.

12.2 Methods

12.2.1 Interventions considered

12.2.1.1 Interventions and comparator

This economic model compared two stenting strategies for biliary obstruction in patients with unresectable pancreatic cancer:

- Initial stenting with plastic stents replaced with SEMS on dysfunction (Plastic/SEMS)
- Initial stenting with SEMS replaced with SEMS on dysfunction (SEMS/SEMS)

to a basecase of:

- Initial stenting with plastic stents replaced with plastic stents on dysfunction (Plastic/Plastic)

A strategy of initial stenting with metal stents replaced with plastic stents on dysfunction was not considered by the model as this was a strategy that was not deemed clinically appropriate as metal stents can be reused upon dysfunction and would be used again.

All people in the model would receive initial stenting for palliation of the bile duct blockage by insertion of the stent (either plastic or SEMS) during endoscopic retrograde cholangiopancreatography (ERCP). It is also assumed for the simplicity of modelling that the initial insertion attempt had been successful and that patients would enter the model at this

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point. Other placement methods are possible (e.g. percutaneous transhepatic cholangiography (PTC) but these were not considered by the economic model. ERCP is the most widely used method within the NHS for the insertion of biliary stents and was used by all but one study included in the accompanying clinical evidence review. Whilst the issue of method of insertion is not considered by the economic model it is considered more widely as part of the recommendations for this topic. Whilst there will be differences between the methods in terms of both costs and adverse events, the use of either SEMS or plastic stent would not influence this choice. Therefore, the costs of initial insertion, excluding the cost of the stent, are likely to be identical between the interventions considered and would not influence which strategy is cost effective. Whilst the model assumes otherwise, in a small proportion of cases multiple methods of insertion will be attempted or the same method used more than once in initial insertion when the original attempt has not been successful. Whilst this will ultimately mean the model will underestimate costs, no evidence was identified and it was deemed unlikely by the committee that the need for second or further procedures during initial stenting would differ between strategies. Therefore, this assumption would not have any effect upon the preferred strategy.

12.2.1.2 Type of stent

There are three broad types of SEMS: covered, uncovered and partially uncovered describing the extent to which the SEMS is covered by plastic. It is possible that the different types of covering have a different rate of migration and occlusion, with the plastic covering believed to reduce occlusion but potentially increase migration. The cost of these different broad stent types are almost identical and the choice of which type is preferable would be based on clinical factors, not economic and consequently this question is not addressed by this economic model.

For this model where parameters have been informed by the clinical evidence review the pooled estimates from studies including all types of SEMS has been used. To test the robustness of this assumption these estimates have been replaced with those estimates for solely covered and solely partially covered SEMS. Given the evidence that was identified by the clinical evidence review it was not possible to calculate estimates for solely uncovered metal stents and this analysis was not performed.

The clinical evidence review also identified randomised controlled evidence on paclitaxel-eluting SEMS. These, as well as other drug-eluting SEMS are relatively new and seldom used in an NHS setting. It is unclear currently how these would fit into the clinical pathway for this patient group and more discussion and research is needed in this area. Therefore drug eluting SEMS were not considered by this economic model.

Plastic stents are, by themselves, of insignificant cost and there is little variation in design amongst different variations and consequently unlikely to be any difference in effectiveness and costs between different manufacturers and types.

12.2.2 Model structure

A simple Markov model was created which included three states to try and estimate the number of stents received by the three different strategies considered. The Markov model has three displayed states: initial stent placement, subsequent stent placement and death. The model cohort remained in the initial stent placement state until they either experienced stent dysfunction and received a secondary stenting or died. In **Error! Reference source not found.** the '2nd insertion/subsequent' represents multiple states where patients can receive a third or in very limited cases fourth and fifth stentings. The model cohort can transit to the death state from any of these subsequent stenting states.

The Markov model had a cycle length of one month. When patients transitioned between a 1st and 2nd/sub stent insertion states (i.e. their stent became dysfunctional) there is one cycle

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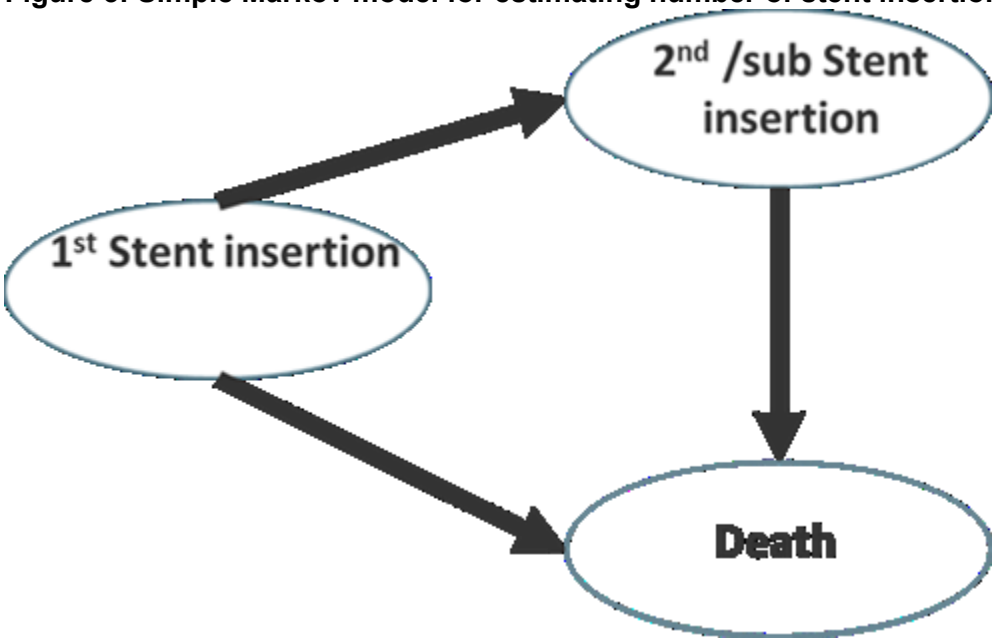
length, not depicted in the diagram, where patients would receive their diagnostic work-up and surgery to replace or reposition their stent. Whilst this allowed the simple Markov model to allow these transitions it also accurately mirrored clinical practice where the process of becoming symptomatic, having the diagnostic work up and scheduling surgery can take approximately 3-6 weeks or approximately one month.

Quality of life, adverse events, hospital stay and other important components of the estimates of costs and QALYs were not estimated through the Markov model and were added to the outcomes of the model directly. This was because given the short life expectancy of this patient group most of the evidence reported primary outcomes, such as death, and these did not need to be estimated, for the different strategies, through modelling. All modelling was performed in Microsoft Excel 2013.

Figure 3: Simple Markov model for estimating number of stent insertions



12.2.3 Population

The model covers all people with an increased bilirubin level and/or clinical symptoms of jaundice caused by an obstructive inoperable malignancy of the bile duct resulting from pancreatic cancer presenting in a NHS secondary care setting. The model only covers people of sufficient health for palliative stenting and the model assumes that all patients would receive a successful stenting.

12.2.4 Model parameters

12.2.4.1 Overall survival

In the accompanying clinical evidence review the hazard ratio for overall survival was 1.0 (95%CI 0.75-1.31) based on three RCTs (n=247) when comparing SEMS to plastic stents. This suggests that there is no difference in overall survival between the differing stenting interventions. Whilst this was based on low quality evidence, the committee considered it reasonable that there would be no difference in overall survival between the three interventions considered. Therefore, in our analysis survival was assumed identical between all interventions.

For the purposes of the model we used a mean overall survival for the model cohort of 109 days as reported in Walter et al. (2015) the most recent study reported in the clinical evidence review for patients with unresectable blockage. Walter et al. (2015) was a three armed RCT comparing two types of SEMS (uncovered and partially covered) to plastic stenting in 219 patients across 18 hospitals in The Netherlands. Only three quarters of patients had a blocking malignancy resulting from pancreatic cancer in this trial which may impact upon the accuracy of the estimate for overall survival for this patient group. Mixed populations were reported in all but one study (Travis & Nicholson 1997), which published two decades ago, identified for this patient group. It is difficult to tell which direction any bias resulting from these mixed populations would be as the type of other malignancies are not reported in detail. However, the committee agreed this was a reasonable estimate of life expectancy for this patient group. The model assumes a constant probability of survival at all time points.

Given this uncertainty, overall survival was varied during both deterministic and probabilistic sensitivity analysis (PSA). For the purposes of the PSA, overall survival was altered over the range of survivals reported in the clinical evidence review (108-149 days) using a uniform distribution.

12.2.4.2 Time to dysfunction

The clinical evidence review estimated a hazard ratio of dysfunction of plastic stents of 2.59 (95%CI 1.67-4.0) compared to SEMS when used as either a first or secondary stent. For the base case the economic model used a mean time to dysfunction of a primary plastic stent of 172 days and for a secondary stent of 170 days based on that reported by Walter et al. (2015) described above. These mean times were adjusted in the model, using the reported hazard ratio, to estimate corresponding times to dysfunction. Mean time to dysfunction was not adjusted for death in the Walter et al (2015) trial and was only counted in those patients who survived and consequently experienced a dysfunction. The mean time in the model will likely be shorter as a large proportion of the model cohort will die before dysfunction. The probability of dysfunction was assumed constant at all time points. When adjusting for relative risk a proportional hazard assumption was made throughout.

For PSA the hazard ratios were varied across their reported distribution using a Log Normal distribution. Time to dysfunction of plastic stents was varied across the 95% CI using a uniform distribution.

12.2.4.3 Adverse events

The economic model only included adverse events which occurred after the operative and peri-operative period. Adverse events of the placement of a stent can cause significant detriments in quality of life and can be costly to treat. These include, in particular, wound infection and wound perforation. In some cases the ERCP to place the stent can lead to procedural related mortality although this would be picked up by our survival estimates. There was no evidence identified that these differed by type of stent used and the committee thought it most likely be identical between stent type. As these costs and quality of life detriments would cancel out in this incremental analysis their inclusion in the model is very unlikely to alter the preferred option.

Pancreatitis, cholangitis, stent migration and stent occlusion were the only adverse events widely reported in the evidence review. Stent migration and stent occlusion are the two leading causes of stent dysfunction and consequently the need to reposition or reinsert a stent. Therefore, to prevent double counting alongside time to dysfunction, migration and occlusion were not individually considered in the economic model leaving only cholangitis and pancreatitis to be considered by the model. Other adverse events are possible from stent placement but are uncommon and no evidence was identified to estimate the differences between stent types.

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Both pancreatitis and cholangitis occur more frequently in people who have had a plastic stent placement. Compared to SEMS, people with a plastic stent placement have a relative risk of 1.52 (95%CI 0.51-4.59) of pancreatitis and a relative risk of 3.1 (95%CI 1.28-7.48) of cholangitis post placement. The relative risk of cholangitis were high for people with plastic stents when compared to partially covered and covered SEMS alone (Table 211). Baseline rates of pancreatitis and cholangitis for those with plastic stents were taken from the mean prevalence of all the studies included in the accompanying evidence review.

For the PSA the relative risks were varied across their reported distribution using a Log Normal distribution and the baseline probability of both pancreatitis and cholangitis varied across a beta distribution.

12.2.4.4 Time in hospital

Time in hospital was again identical between plastic and SEMS in the post-operative period and as these would cancel out during the incremental analysis and were likely to be picked up in the stenting costs, they were not included by the model. However, time in hospital for treating adverse events arising from stent placement are included. Total number of days in hospital were not reported in Walter et al. (2015) and were back calculated by dividing reported total costs of hospitalisation by unit costs to get an estimate of the unreported hospital days from the trial. This estimated that after discharge from the primary stenting people with plastic stents spend a mean 3.82 days in hospital compared to 3.48 days for SEMS. For patients with a secondary stenting this was 5.18 and 2.51 days for plastic and SEMS respectively again ignoring the immediate post-operative period.

The post-operative length of stay was not varied during PSA as this uncertainty would be picked up by the variation in costs of the stenting procedures and consequently would lead to an overstatement of this uncertainty. The length of stay in hospital was varied across a uniform distribution from zero to double the base case estimate during PSA.

12.2.4.5 Health related quality of life

The literature search for the clinical evidence review was conducted to identify any evidence comparing Health Related Quality of Life (HrQoL) in people with pancreatic cancer with an inoperable malignancy receiving either a plastic stent or SEMS. Only one study was identified during this search. (Walter et al. 2017)

This study of HrQoL was conducted in parallel with the Walter et al. (2015) study described above. Of the 219 patients in the original RCT, 140 patients completed two general health related QoL questionnaires (the EQ-5D-3L and QLQ-C30) alongside a disease specific one. The EQ-5D-3L gives a utility weighting up to 1 (representing perfect health) with a score of 0 assumed to be equal to death. In some cases the utility weighting score can be below zero representing health states worse than death. This utility weighting can be used to adjust life expectancy in an economic model, by multiplying the time lived in each health state by its utility weighting, to give quality adjusted life years (QALYs).

As the preferred measure of QoL in NICE economic modelling, the EQ-5D-3L took precedence for populating the model over the disease specific measures. The EQ-5D-3L is a non-disease specific survey assessing health related QoL across five health domains (mobility, self-care, daily activities, pain and anxiety/depression) with the severity rated on one of three levels (No Problems, Moderate Problems, Extreme Problems). This is given alongside a visual analogue scale ranging from ‘worst imaginable health’ and ‘best imaginable health’ with a 0 to 100 scale on which responders can rate their current health. These responses were amalgamated into a health profile and given a QoL score, between 0 and 1 based upon Dutch general population sample. NICE prefer EQ-5D scores valued using the UK general population sample but no QoL data was identified using this measure. QoL scores are likely to differ between countries through both a differing national way of valuing

health and through differing demographics leading to sampling differences. These Dutch population values may therefore differ from UK ratings. The committee however thought the values for QoL reported in the paper were consistent with their own clinical experience around treating this patient group.

The people who responded to the QoL questionnaires in the trial had a baseline EQ-5D-3L score of 0.6. Unsurprisingly, given the short life expectancy and debilitating nature of unresectable pancreatic cancer QoL in both the plastic and SEMS cohorts decreased over time with a near identical change (-0.1) between the two stent types for every 6 months of follow-up. This value was used in the base case and as no difference in either survival or QoL is assumed in the primary base case analysis in this model, the analysis becomes a de-facto cost minimisation.

This equal QoL score was inconsistent with the clinical experience of the committee who thought that quality of life, through both reduction in adverse events and through the longer time to dysfunction, would be higher (or at least decrease less rapidly) in people receiving SEMS. It was hypothesised that as a result of only having three levels of severity for each domain the EQ-5D-3L was not sensitive enough to identify any differences in QoL between the groups. The results of the more sensitive visual analogue scale show a similar baseline utility value of 0.53 with a change of -0.25 and -0.11 every six months for plastic stents and SEMS respectively. This shows a more pronounced difference between the two groups and although it is more consistent with the committee's clinical experience the difference does not become statistically significant (p-value=0.08). The VAS is known to be unreliable in the measurement of QoL values. It is also difficult to estimate the likely direction of any biases introduced by this method. Given these problems and better quality evidence being identified it was decided not to try to incorporate these values into the primary analysis even if it more closely matched the committee's clinical experience.

These values were used as part of a secondary analysis to account for an improved quality of life for SEMS. These changes were converted into monthly deteriorations assuming that the deterioration between the two points was constant. QoL was not reported separately by type of SEMS and therefore was not differed for the relevant secondary analyses. Quality of life was not stratified by whether a patient was receiving an initial or subsequent stent placement and therefore we assumed that the deterioration for patients in the plastic/SEMS strategy would follow the deterioration based on the type of stent they currently have inserted.

The rate of deterioration of QoL weights above were varied across a triangular distribution between the reported range during probabilistic sensitivity analysis. Baseline utilities were not varied as this parameter would not influence the preferred option.

12.2.4.6 Costs

All costs were taken from NHS Reference Costs (Department of Health 2016) unless otherwise stated. During PSA all costs were varied using their reported range and a Gamma distribution.

12.2.4.6.1 Stent insertion costs

The cost of initial stent insertion were taken from NHS reference costs. (NHS Reference Costs 2016) The model cohort was assumed to all have a complications and comorbidity (CC) score of 4+ given that the entirety of the cohort will have either unresectable or metastatic pancreatic cancer. This figure would include all pre-operative imaging, the unit costs of the stents, the insertion of the stent and any peri-operative treatment and hospital stay.

NHS Reference costs gave a difference in total insertion costs between insertion of SEMS and plastic stents of £760; slightly less than the difference in unit cost of the different stents as reported in the NHS Supply Catalogues of £820 (Table 211). The slightly lower cost is consistent with our modelling assumption that non-stent costs between patients receiving plastic stents or SEMS would be picked up by the difference in NHS reference costs. We would hypothesise that the difference between the costs in the insertion of SEMS over plastic stents would be the difference in stent costs minus the savings from a reduction in short term adverse events associated with SEMS.

Where the insertion of the stent is a secondary or later insertion the costs are assumed to be equal to those above apart from where a person is receiving a secondary SEMS stenting having previously received SEMS stenting (i.e. the SEMS/SEMS strategy). In this case the cost is assumed equal to that of receiving a plastic stent. This is because, unlike plastic stents, SEMS can be reused on migration or occlusion and thus the stent costs are not incurred again. During PSA the random number assigned for the distributions for the three insertion types were identical. This was to avoid widely different costs, during the random iterations, for operations which are broadly similar apart from the type of stent inserted.

12.2.4.6.2 Occlusion and migration costs

When occlusion or migration is suspected a patient would receive a diagnostic endoscopic procedure to investigate and confirm the suspicion and to rule out any other causes of the associated symptoms. Following this patients would receive their secondary or later stenting. This procedure was again costed using NHS Reference Costs.

12.2.4.6.3 Adverse events and hospitalisation costs

During the base case analysis hospital days were not costed. Hospital days were not costed as the reference costs for stent placement allow for some days in hospital and it was likely that costing the differences could lead to double counting of this cost.

Days in hospital above those in the perioperative period were costed in line with excess bed days for the procedure, as reported by NHS reference costs during PSA and varied across their reported range using a gamma distribution

In the base case analysis adverse events were not assigned a cost as it was assumed that these adverse events would often be treated as part of surgical treatment follow-up. A sensitivity analysis was carried out where adverse events were assigned a cost, again from NHS reference costs, in line with one consultant led outpatient appointment. Again this value was varied across its reported range using a gamma distribution.

12.2.4.6.4 Cost of death

Studies of resource use in cancer show a peak in costs towards the final months of life. This is likely to be true for this model cohort. However, as the model assumes no difference in survival between the interventions the preferred option would not change for any value for the cost of death. Therefore, this was not costed in the economic model.

12.2.4.7 Discounting

All health and cost outcomes were discounted at a rate of 3.5% per annum in line with the NICE guidelines manual. This was not varied during sensitivity analyses. Costs for the model were not inflated and as they were all reported and inputted in 2016 costs.

Table 211: List of parameters used in the economic model and PSA distribution

	Value	Source	PSA Distribution
Overall Survival (Days)			

	Value	Source	PSA Distribution
All stent types	109	Clinical Evidence Review	Uniform(108,149)
Time to dysfunction primary stenting (days)			
Plastic	172	Walter 2015	Uniform(126,219)
SEMS (Hazard Ratio)	2.59	Clinical Evidence Review	Log normal
Time to dysfunction primary stenting (days)			
Plastic	170	Clinical Evidence Review	Uniform(85,255)
SEMS (Hazard Ratio)	2.59	Clinical Evidence Review	Log normal
Adverse events			
Pancreatitis-plastic	2.6%	Clinical Evidence Review	BETA
Pancreatitis-Relative Risk	1.52	Clinical Evidence Review	Log normal
Cholangitis-plastic	6.7%	Clinical Evidence Review	BETA
Cholangitis-Relative Risk	3.10	Clinical Evidence Review	Log normal
Hospital Days			
Plastic Primary	3.8	Walter 2015	Uniform(0,7.6)
SEMS primary	3.5	Walter 2015	Uniform(0,7.0)
Plastic Secondary	5.2	Walter 2015	Uniform(0,10.4)
SEMS secondary	2.5	Walter 2015	Uniform(0,5.0)
Costs			
Insertion Plastic Stent	£7,176.47	NHS Reference Costs(YG05A)	Gamma
Insertion Metal Stent	£7,936.64	NHS Reference Costs(YG04A)	Gamma
Insertion Secondary Metal Stent	£7,176.47	NHS Reference Costs(YG05A)	Gamma
Diagnostic Endoscope	£770.51	NHS Reference Costs(FZ60Z)	Gamma
Adverse Event	£162.84	NHS Reference Costs(WF01A)	Gamma
Hospital day	£191.01	NHS Reference Costs(YG03A)	Gamma
Utility			
Baseline EQ-5D	0.60	Walter 2017	Not varied
Baseline EQ-5D VAS	0.53	Walter 2017	Not varied
Change Quality of Life (180 days)			
EQ-5D VAS Plastic	-0.25	Walter 2017	Triangular(-0.39,-0.11)
EQ-5D VAS metal	-0.11	Walter 2017	Triangular(-0.19,-0.03)
Discount (per annum)			
Costs		NICE	Not varied
QALYs		NICE	Not varied

12.3 Results

12.3.1 Deterministic base case results

In the base case analysis where overall survival and quality of life were assumed equal across the different strategies (a de-facto cost-minimisation) SEMS/SEMS was the least costly strategy with a cost saving, over the lifetime of one person of over £1,500 when compared to the plastic/plastic strategy (Table 212). Given the assumptions of the model all costs are driven by the surgical procedure to insert/adjust the stent and the diagnostic work up prior to the operation. The SEMS/SEMS strategy reduced the number of surgical operations by 0.32 per patient, saving one additional operation for every three patients needing biliary drainage. This is slightly lower than the number of subsequent surgeries prevented reported in Walter et al. (2015) although their estimated hazard ratio for stent dysfunction was of a larger magnitude than the one estimated in the clinical evidence review. Considering all patients must receive at least one stenting, a SEMS/SEMS strategy more than halves the number of subsequent insertions. Less than 1% of insertions were 3rd or subsequent operations and these did not significantly contribute towards costs. As expected given the relative risks included in the model both pancreatitis and cholangitis was less common in the SEMS/SEMS strategy.

Table 212: Deterministic Base Case Results

	Mean Number Insertions	Pancreatitis (%)	Cholangitis (%)	Total Costs	Incremental Cost
Plastic/Plastic	1.57	2.6	6.7	£11,697	Reference
Plastic/SEMS	1.48	2.6	6.7	£11,267	-£ 430
SEMS/SEMS	1.25	1.7	2.2	£10,117	-£ 1,580

12.3.2 Stochastic base case results

When the stochastic results (means of the iterations of the probabilistic sensitivity analysis) are considered the same conclusion can be drawn with the SEMS/SEMS strategy again being dominant (Table 213). Total costs are greater for all strategies. This is as a result of a probabilistic distribution around survival which is skewed towards increased survival and the inclusion of hospital and adverse event costs.

Table 213: Stochastic Base Case Results

	Total Costs	Incremental Cost	ICER
Plastic/Plastic	£13,836	Reference	
Plastic/SEMS	£12,828	-£ 1,009	Dominant†
SEMS/SEMS	£11,286	-£ 2,551	Dominant

†Whilst Plastic/SEMS dominated Plastic/Plastic it was dominated by the SEMS/SEMS approach. QALYs were assumed equal between the groups.

12.3.3 Deterministic one way sensitivity analysis

A number of one way sensitivity analyses were conducted, where the impact of a change on one variable, to the overall conclusion of the model is assessed (Table 214). During all deterministic sensitivity analyses the SEMS/SEMS strategy remains the preferred or least costly option.

One threshold analysis was conducted around overall survival. For the plastic/plastic strategy to become the preferred option overall survival in the patient group needed to be less than 24 days.

Table 214: One Way Deterministic Sensitivity Analysis Results

Parameter	Change Made	Lowest lifetime costs
Stent Functional time days- Plastic Primary	Lower 95% Confidence Interval=126 days	SEMS/SEMS
	Higher 95% Confidence Interval=219 days	SEMS/SEMS
Stent Functional time Relative Risk- Plastic Secondary	Lower 95% Confidence Interval=85 days	SEMS/SEMS
	Higher 95% Confidence Interval=255 days	SEMS/SEMS
Stent Functional Relative Risk – SEMS Primary	Lower 95% Confidence Interval=1.67	SEMS/SEMS
	Higher 95% Confidence Interval=4.00	SEMS/SEMS
Stent Functional Relative Risk – SEMS Secondary	Lower 95% Confidence Interval=1.67	SEMS/SEMS
	Higher 95% Confidence Interval=4.00	SEMS/SEMS
Adverse Events Pancreatitis Plastic	Lower 95% Confidence Interval=1.5%	SEMS/SEMS
	Higher 95% Confidence Interval=4.0%	SEMS/SEMS
Adverse Events Pancreatitis SEMS Relative Risk	Lower 95% Confidence Interval=0.51	SEMS/SEMS
	Higher 95% Confidence Interval=4.59	SEMS/SEMS
Adverse Events Cholangitis Plastic	Lower 95% Confidence Interval=7.2%	SEMS/SEMS
	Higher 95% Confidence Interval=11.7%	SEMS/SEMS
Adverse Events Cholangitis SEMS	Lower 95% Confidence Interval=1.28	SEMS/SEMS
	Higher 95% Confidence Interval=7.48	SEMS/SEMS
Cost Insertion Plastic	Lower 95% Confidence Interval=£6,813	SEMS/SEMS
	Higher 95% Confidence Interval=£7,066	SEMS/SEMS
Cost Insertion SEMS	Lower 95% Confidence Interval=£7,214	SEMS/SEMS
	Higher 95% Confidence Interval=£8,857	SEMS/SEMS
Adverse Event Cost added	=£163	SEMS/SEMS
Hospital Day Cost added	=£191 per day	SEMS/SEMS
EQ-5D VAS change 180 days plastic	Lower 95% Confidence Interval=-0.39	SEMS/SEMS

Parameter	Change Made	Lowest lifetime costs
	Higher 95% Confidence Interval=-0.11	SEMS/SEMS
EQ-5D VAS change 180 days SEMS	Lower 95% Confidence Interval=-0.19	SEMS/SEMS
	Higher 95% Confidence Interval=-0.03	SEMS/SEMS

12.3.4 Secondary Analysis including VAS Quality of Life Values

When scoring from the EQ-5D VAS was included in the secondary analysis the SEMS/SEMS strategy also led to the largest amount of QALYs with an additional 0.0245 QALYS compared to plastic/plastic. It was also cost saving and health improving compared to the plastic/SEMS strategy making it dominant compared to all other strategies considered in the base case analysis.

Table 215: Secondary Analysis Results Including VAS Quality of Life Values

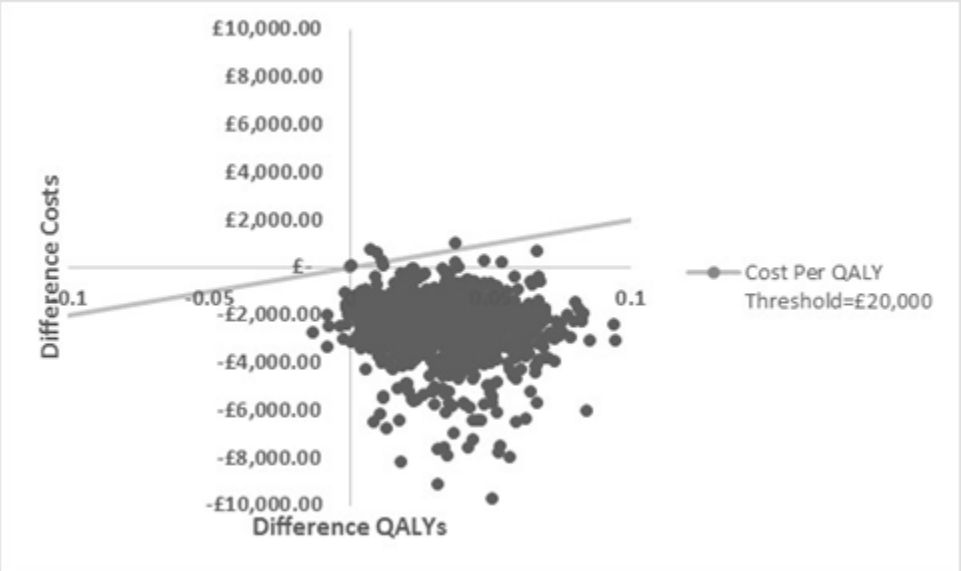
	Total Costs	Total QALYs	Incremental Cost	Incremental QALY	ICER
Plastic/Plastic	£11,696.79	0.093	Reference	Reference	
Plastic/SEMS	£11,266.63	0.106	-£430	0.0128	Dominant†
SEMS/SEMS	£10,117.00	0.118	-£1,580	0.0245	Dominant

†Whilst Plastic/SEMS dominated Plastic/Plastic it was dominated by the SEMS/SEMS approach.

12.3.5 Probabilistic sensitivity analyses

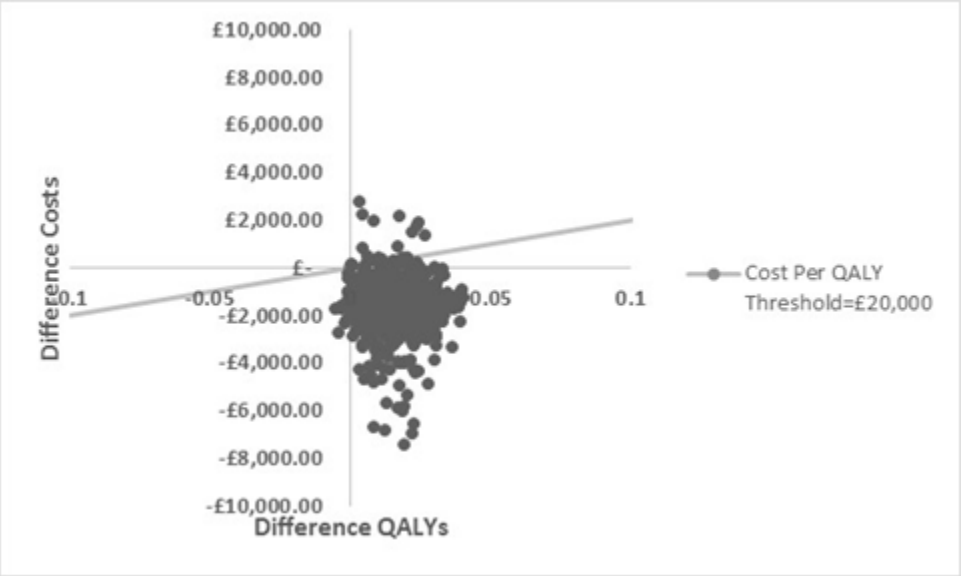
Figure 4 shows the cost effectiveness plane for the SEMS/SEMS strategy compared to a plastic/plastic strategy. Where no difference in survival or quality of life is assumed the SEMS/SEMS strategy is cost saving in 98.8% of iterations. When a difference between quality of life is included in less than 1% of iterations is the SEMS/SEMS strategy health decreasing. When a willingness to pay per QALY threshold is assumed of £20,000 per QALY, NICE's conventionally held threshold for approving technologies, over 99% of iterations would be cost effective.

Figure 4: Cost Effectiveness Plane: Plastic/Plastic vs SEM/SEM



A similar conclusion can be drawn for when a plastic/SEMS strategy is compared to plastic plastic strategy (Figure 5**Error! Reference source not found.**). In this comparison the results are less strong with 95.0% of iterations being cost saving. Again when differences in survival and quality of life are considered, less than 1% of iterations shows the plastic/SEMS strategy being health decreasing.

Figure 5: Cost Effectiveness Plane: Plastic/Plastic vs Plastic/SEMS



When comparing a SEMS/SEMS strategy to a plastic/SEMS strategy the SEMS/SEMS strategy is cost saving in over 97% of iterations. At a £20,000 willingness to pay threshold over 99% of iterations are cost-effective (Figure 6).

Figure 6: Cost Effectiveness Plane: Plastic/SEMS vs SEMS/SEMS

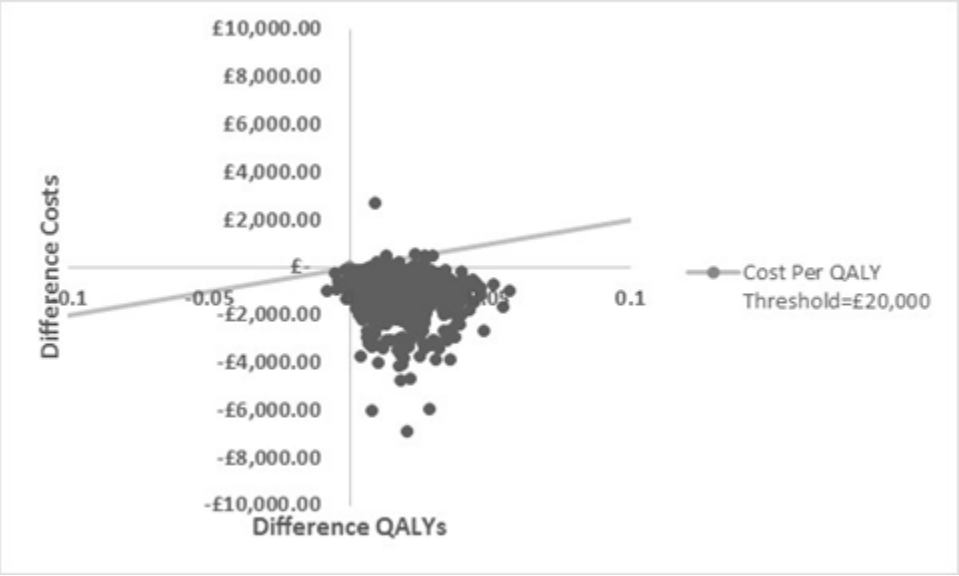


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Figure 7: Cost Effectiveness Acceptability Curve

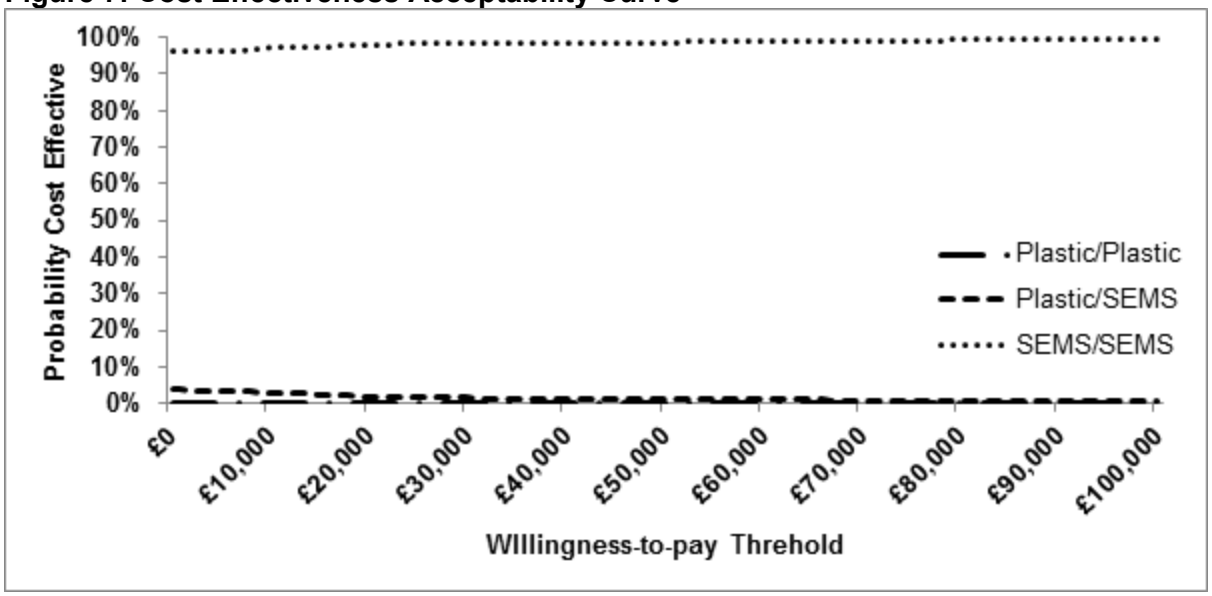

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Figure 6: Cost Effectiveness Plane: Plastic/SEMS vs SEMS/SEMS

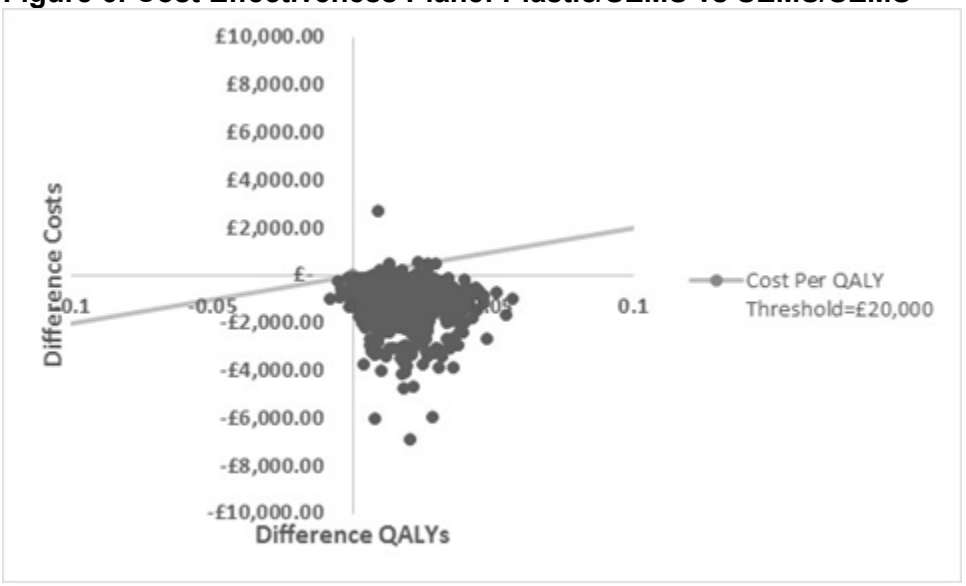

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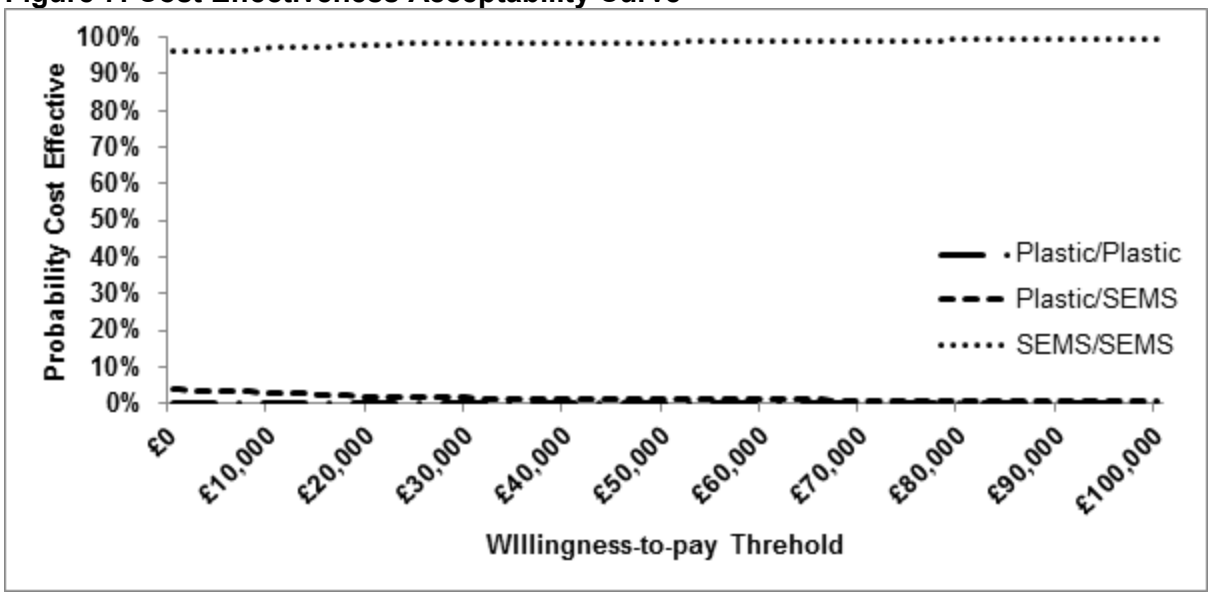
Figure 7: Cost Effectiveness Acceptability Curve



The above conclusions for a SEMS/SEMS strategy are strongly supported by the Cost Effectiveness Acceptability Curve (Figure 7**Error! Reference source not found.**) which shows the SEMS/SEMS strategy having a greater than 98% probability of being cost saving (the preferred option).

12.4 Discussion

A strategy of SEMS/SEMS was the preferred option in the base case results for both deterministic and stochastic results. When no difference in survival between the different strategies was considered a SEMS/SEMS strategy was cost saving through reducing the number of surgeries for subsequent placement or adjustment of stents. Despite the best available evidence identified around quality of life showing no difference between the different strategies when a more sensitive instrument although with large biases (EQ-5D VAS) was used a SEMS/SEMS strategy also appeared to be health improving.

This conclusion was robust to both one way deterministic sensitivity analyses and probabilistic sensitivity analysis. SEMS/SEMS was the preferred option in all deterministic sensitivity analyses apart from when plastic stent or SEMS insertion were varied to their lower and upper confidence interval respectively when plastic/plastic becomes the preferred option. Given the similarity of the two procedures this wide variation in costs is unlikely to represent any plausible difference in cost which may be observed. The robustness of these results are further highlighted by the probabilistic sensitivity analysis where a SEMS/SEMS strategy is cost saving in greater than 98% of iterations.

The results of this economic model were based on evidence from the clinical evidence review which was derived entirely from RCT evidence. The costings for the model were taken from UK NHS sources and quality of life from a European EQ-5D questionnaire given alongside an RCT. The results, conclusions and sensitivities are almost identical to the one economic evaluation identified by the review of the previous economic evidence (Arguedas et al. 2002). The conclusions of the model could be strengthened by finding UK-based quality of life evidence measured using a sensitive but validated scale (i.e. the EQ-5D-5L). However, even in these circumstances a SEMS/SEMS strategy will remain cost saving and it is likely, given the favourable clinical outcomes of a SEMS/SEMS strategy that it will remain health

improving. Therefore, it is unlikely that the conclusions of the model would change if this evidence was available.

12.5 References

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13 Network Meta-Analysis (Mixed Treatment Comparison) and Economic Model on treatment of unresectable locally advanced non-metastatic pancreatic cancer

13.1 Methods

13.1.1 Clinical data considered in the network meta-analyses

The Network Meta-Analysis (NMA) considered the effectiveness of treatments for unresectable locally advanced non-metastatic pancreatic cancer (LAPC). The NMA includes all studies, identified by the accompanying clinical evidence review, which are phase II or phase III randomised comparative trials that compared treatments which fit into the broad groups of:

- chemotherapy,
- chemoradiotherapy,
- combination of chemotherapy and chemoradiotherapy,
- radiotherapy
- biological therapies

with another treatment or to placebo, best supportive care or no treatment. Other local therapies (such as microwaves, radiofrequency ablation) were not considered in the NMA although it was unlikely that randomised evidence would be identified to allow inclusion. Treatments not in these broad groups (as well as the excluded interventions) were only considered if they provided indirect evidence to the network via a closed loop of treatment effects for included interventions. Studies in which all investigated treatments were not considered in any other study, and therefore could not be usefully statistically synthesised into either the main NMAs or a smaller alternative one were not considered in this analysis.

Only studies published in the year 2000 or later were included in the NMA as it was considered evidence published prior to this date would not adequately represent current practice. Studies were excluded from the NMA if they included cancers other than pancreatic cancer or included populations that had both locally advanced and metastatic disease and the locally advanced group were not analysed and reported separately. Studies which considered a previously treated patient group with responding or stable disease were also excluded from the NMA, unless they were randomised before receiving treatment, as it was considered that this patient group would have better outcomes than for studies which included treatment naïve patients.

All data were derived from trials identified in the accompanying systematic reviews.

13.1.2 Review Strategy and Evidence Synthesis

Inspection of the data in the accompanying clinical evidence review identified 9 trials involving 1294 patients considering 12 different treatments. The only outcome reported in all these trials was overall survival (OS). It was therefore decided that the primary NMA would consider OS. OS was inputted into the model in the form of a hazard ratio comparing the intervention to the control. Where hazard ratios had not been reported in the original paper

these were calculated using methods outlined in Parmar et al. (2008). Consequently outcomes were also reported in terms of hazard ratio using gemcitabine as the control. This was because gemcitabine was the most widely used control treatment in the studies identified. It is also widely used within England for the treatment of LAPC and is covered by TA25 for use in the treatment of both locally advanced unresectable and metastatic pancreatic cancer.

Inspection of the other outcome measures reported, identified both progression-free survival (PFS) and objective response (complete response or partial response) as outcomes that would form usefully sized networks although these would be smaller (less participants and interventions) and would be considered as secondary NMAs. The NMA for PFS considered 7 studies looking at 10 treatments involving 1125 patients. The NMA for objective response looked at 6 studies involving 706 patients. As with OS, PFS was included in the NMA in the form of hazard ratios. Again where hazard ratios had not been reported these were calculated using the same methods as for OS. Outcomes were again reported in terms of hazard ratio with gemcitabine as control. All studies included in the objective response NMA reported this information or it was able to be easily calculated from the partial response and complete response data. However, there were differences in studies between what criteria was used to assess resectability or this was not reported. It was therefore difficult to say how strictly comparable this outcome was between studies. This data was included in the NMA as count data. Outcomes from this secondary analysis were reported in terms of odds ratios, again with gemcitabine as the control.

Treatment related adverse events were also reported widely in the literature. However, due to the definitions used for recording these and uncertainty about whether an unreported event had not occurred or had not been included in the data, it was decided that an NMA looking at adverse events would not be useful. Therefore, this analysis was not performed. Other outcomes identified by the committee in the clinical evidence review protocol were either too sparsely or inconsistently reported to make any sort of evidence synthesis worthwhile. Minimally important differences were not considered in any of the NMAs as the results of both the primary and secondary analyses fed directly into a cost effectiveness model.

The following studies were included in the accompanying clinical evidence review but were excluded in both the primary or secondary NMAs (Table 216):

- Chung et al. (2014) and Rich et al. (2012): these studies only included interventions which were not considered by other studies. It was therefore not possible to include them in a useful way in any of the NMA analyses.
- Mukherjee et al (2013), Khan et al. (2016) and the 2nd randomisation in Hammel et al. (2016): these randomisations only considered previously treated patients with responding or stable disease.

Table 216: List of studies included in the Clinical Evidence review but excluded from the primary and secondary NMA analyses.

Study	Control	Intervention
Chung et al. (2004)	CRT(Gem) plus docetaxel	CRT(Paclitaxel) plus docetaxel
Hammel et al. (2016)†	Gem± erlotinib	CRT (Gem) ± erlotinib
Khan et al. (2016)	Cap or UFT plus radiotherapy	Cap or UFT plus cetuximab and radiotherapy
Mukherjee et al. (2013)	CRT(Gem)	CRT(Cap)
Rich et al. (2012)	CRT(Gem)+Paclitaxel	CRT(Gem)+paclitaxel+tipifarnib

†Only the second randomisation from Hammel et al. (2016) was excluded from the analysis
CRT=Chemoradiotherapy Gem=Gemcitabine Cap=Capecitabine

Of the studies included in the primary analysis only Shinchi et al. (2001) was not included in any of the secondary analyses as both PFS and objective response were not reported. The list of studies included in the primary and secondary analyses are reported in Table 217. Where hazard ratios or counts have been inputted as not reported (NR) these studies have not been included in the corresponding secondary analysis. The sole reason for studies not being included in the secondary analysis was that the outcome of interest was not reported in the study.

Table 217: List of studies included in the primary NMA and where sufficient data has been reported the relevant secondary NMAs

Study	Control	Intervention	N (control)	N (intervention)	HR OS (SD)	HR PFS (sd)	Objective response Control	Objective response Intervention
Cantore et al. (2004)	Gemcitabine	FLEC	67	71	0.75 (0.1569)	NR	6.0%	14.1%
Chauffert et al. (2008)	Chemorad(5-fu)+Cisplatin	Gemcitabine	59	60	0.69 (0.2562)	0.72(0.2521)	NR	NR
Hammel et al. (2016)	Gemcitabine	Gemcitabine+Erlotinib	223	219	1.19 (0.1008)	1.12 (0.0911)	NR	NR
Heinemann et a. (2013)	Gemcitabine	Gemcitabine+400mg Upamostat Gemcitabine+ 200mg Upamostat	31	33 31	0.75(0.2181) 0.90(0.1954)	0.87(0.1334) 0.92(0.1270)	3.8%	7.1% 12.9%
Herman et a. (2013)	Chemorad(5-fu)	Chemorad(5-fu)+TNFerade	90	187	0.90(0.1552)	0.96(0.1625)	8.2%	12.0%
Li et al. (2003)	Chemorad(Gem)	Chemorad(5-fu)	18	16	1.33(0.3138)	1.87(0.3523)	50.0%	12.5%
Loehrer et al. (2011)	Gemcitabine	Chemorad(Gem)	37	34	0.58(0.2354)	1.16(0.2436)	5.4%	5.9%
Shinchi et al. (2002)	Best Supportive Care	Chemorad(5-fu)	16	15	0.78(0.4930)	NR	NR	NR
Wilkowski et al. (2009)	Chemorad(5-fu)	Chemorad (Gem) + cisplastin X 2 Chemorad (Gem) + cisplastin	31	31 32	0.82(0.2351) 0.81(0.2090)	0.75(0.1907) 0.85(0.1802)	19.4%	12.9% 21.9%

13.1.32 Network meta-analysis Model structure

The network for the primary and two secondary NMAs including studies which did not connect to the main network are shown in Figure 8 to Figure 10**Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.**. The area of the nodes are in proportion with the number of patients, in the NMAs, receiving that treatment.

Figure 8: Network for overall survival

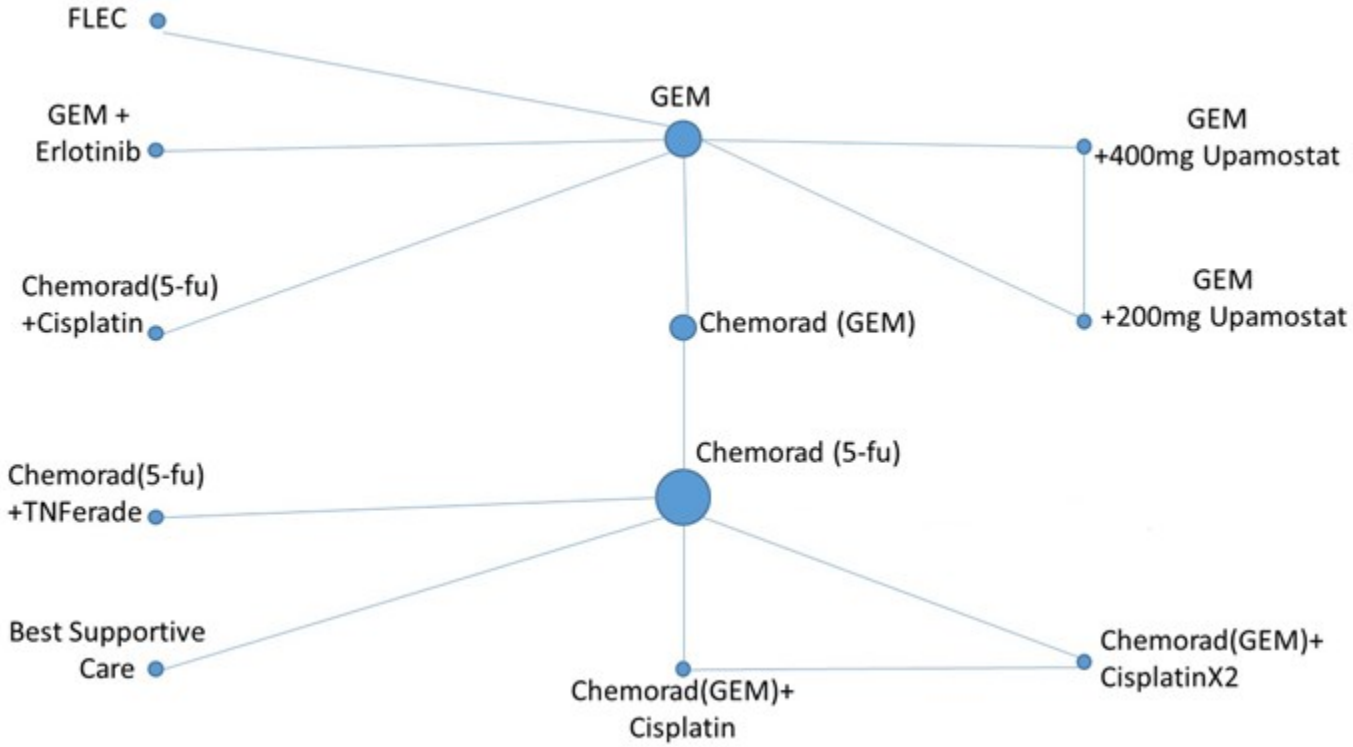

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Figure 9: Network for Progression Free Survival

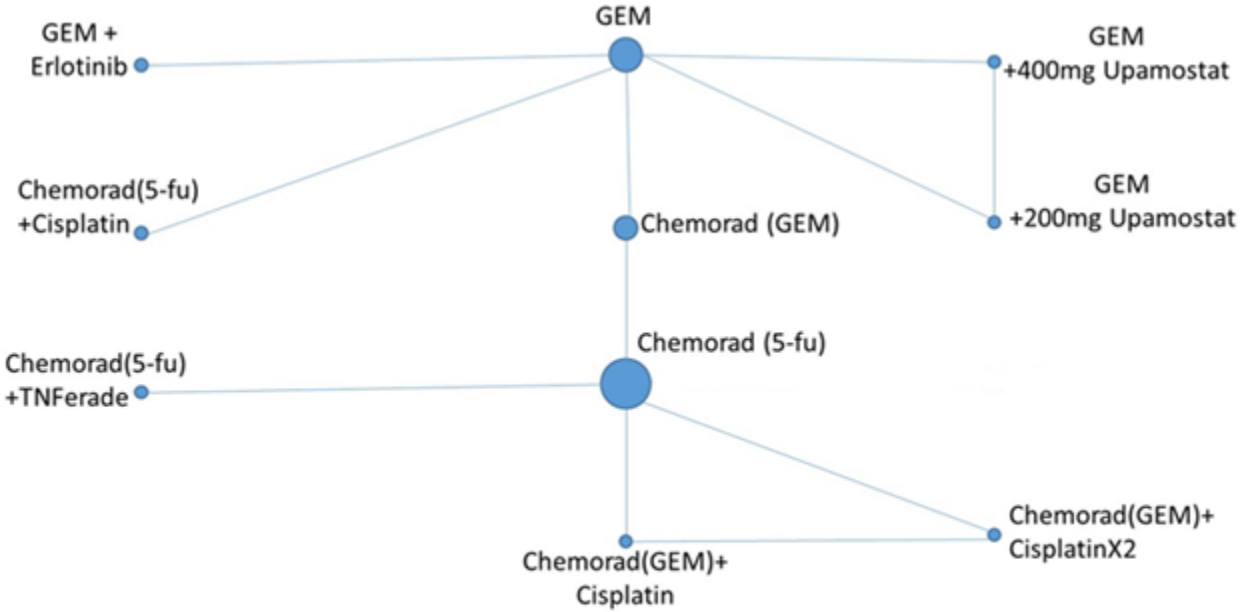
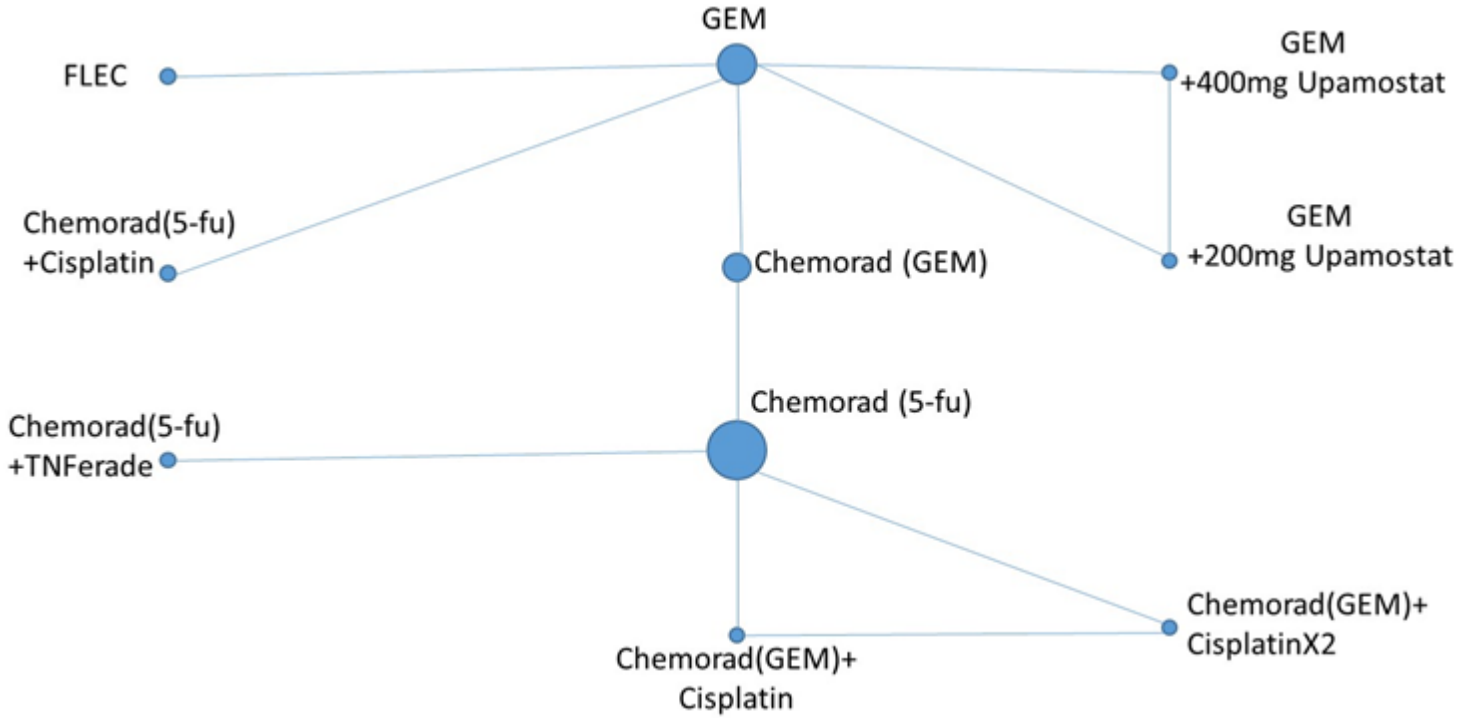


Figure 10: Network for Objective response



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Fixed effects models were run for all 3 NMAs considered. It was not possible to run an alternative random effects model, to compare goodness of fit, as no two trials in the NMA compared the same interventions and both random and fixed effect models would give identical results. The fixed effects model was created to estimate the hazard ratio for OS and PFS and the odds ratio for overall response compared to the reference treatment gemcitabine for use in the economic model.

For the OS and PFS models the log hazard ratio for each trial j comprised a normal likelihood:

$$\gamma_{ik} \sim N(\theta_{ik}, se_{ik}^2)$$

Where γ_{ik} represents the log hazard ratio of treatment k relative to the control arm of trial i, se_{ik} represents the standard error of the log hazard ratios and θ_{ik} represents the trial-specific log hazard ratio. As the data used in the NMA is relative to other treatments, no baseline values can be predicted and the linear predictor is reduced to:

$$\theta_{ik} = \delta_{i,bk}$$

Where $\delta_{i,bk}$ is the trial specific log hazard ratio for treatment k compared to a control of treatment b in trial i . As fixed effects are assumed then:

$$\delta_{i,bk} = d_{12}$$

Where d12 is the log hazard ratio of treatment 2 compared to a baseline of treatment 1.

For the objective response model, the data for each trial j comprised a binomial likelihood:

$$r_{jk} \sim \text{Bin}\ (p_{jk}, n_{jk})$$

where p_{jk} is the probability of an objective response in trial j under treatment k, r_{jk} is the number of people experiencing the event in trial j under treatment k, and n_{jk} is the total number of people at risk of the event in trial j under treatment k.

Since the parameters of interest, p_{jk}, are probabilities and therefore can only take values between 0 and 1, a transformation (link function) was used that mapped these probabilities into a continuous measure between plus infinity and minus infinity. Also, since this was a binomial likelihood the logit link function was used. The probabilities of success p_{jk} were modelled on the logit scale as:

$$\text{logit}(p_{ik}) = \mu_i + d_{12} \text{ x } I_{\{k \neq 1\}}$$

where

$$I_{\{u\}} = \begin{cases} 1 & \text{if u is true} \\ 0 & \text{otherwise} \end{cases}$$

In the fixed effects model the between-trial heterogeneity σ^2 was set to 0 which was equivalent to assuming homogeneity of the underlying true treatment effects.

The analysis was undertaken following Bayesian statistical principles. The goodness of fit of the models was tested using the total residual deviance in the model. All models were created in WinBUGS 14 and the code for the OS and PFS models is provided in Table 218 and the objective response model in Table 219. All code was based on that reported by Dias et al. (2016).

Table 218: WinBUGS code used to estimate the hazard ratio for overall survival and progression free survival for all treatment options compared to gemcitabine for people with LAPC – fixed effects model

```
# Normal likelihood,
# Trial-level data given as Hazard Ratios
# Fixed effects model for multi-arm trials
model{                                                    # *** PROGRAM STARTS
for(i in 1:ns2) {                                         # LOOP THROUGH 2-ARM STUDIES
   y[i,2] ~ dnorm(delta[i,2],prec[i,2])                   # normal likelihood for 2-arm trials
#Deviance contribution for trial i
   resdev[i] <- (y[i,2]-delta[i,2])*(y[i,2]-delta[i,2])*prec[i,2]
 }
for(i in (ns2+1):(ns2+ns3)) {                             # LOOP THROUGH THREE-ARM STUDIES
   for (k in 1:(na[i]-1)) {                               # set variance-covariance matrix
      for (j in 1:(na[i]-1)) {
         Sigma[i,j,k] <- V[i]*(1-equals(j,k)) + var[i,k+1]*equals(j,k)
       }
    }
   Omega[i,1:(na[i]-1),1:(na[i]-1)] <- inverse(Sigma[i,,])   #Precision matrix
                                                          # multivariate normal likelihood for 3-arm trials
   y[i,2:na[i]] ~ dmnorm(delta[i,2:na[i]],Omega[i,1:(na[i]-1),1:(na[i]-1)])
                                                          #Deviance contribution for trial i
   for (k in 1:(na[i]-1)){  # multiply vector & matrix
      ydiff[i,k]<- y[i,(k+1)] - delta[i,(k+1)]
      z[i,k]<- inprod2(Omega[i,k,1:(na[i]-1)], ydiff[i,1:(na[i]-1)])
    }
   resdev[i]<- inprod2(ydiff[i,1:(na[i]-1)], z[i,1:(na[i]-1)])
 }
for(i in 1:(ns2+ns3)){                                    #   LOOP THROUGH ALL STUDIES
    for (k in 2:na[i]) {                                  #  LOOP THROUGH ARMS
      var[i,k] <- pow(se[i,k],2)                          # calculate variances
      prec[i,k] <- 1/var[i,k]                             # set precisions
      delta[i,k] <-  d[t[i,k]] - d[t[i,1]]
    }
 }
totresdev <- sum(resdev[])                                #Total Residual Deviance
d[1]<-0                                                   # treatment effect is zero for reference treatment
                                                          # vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }

                                                  # pairwise HRs and LHRs for all possible pair-wise comparisons
for (c in 1:(nt-1)) {  for (k in (c+1):nt) {

LHR[c,k] <- (d[k] - d[c])
HR[c,k] <- exp(d[k] - d[c])
    }
}

# ranking
for (k in 1:nt) {
  rk[k] <- rank(d[],k)                                                    # assumes events are "bad"
  best[k] <- equals(rk[k],1)                              #calculate probability that treatment k is best
best3[k] <- equals(rk[k],3) + equals(rk[k],2) + equals(rk[k],1)     #Calculate probability that treat K is top 3
}

}                          # *** PROGRAM ENDS
```

Table 219: WinBUGS code used to estimate the odds ratio for objective response for all treatment options for people with LAPC – fixed effects model

```
# Binomial likelihood, logit link, MTC
# Fixed effect model
model{                                                  # *** PROGRAM STARTS
for(i in 1:ns){                                          # LOOP THROUGH STUDIES
  mu[i] ~ dnorm(0,.0001)                                  # vague priors for all trial baselines
  for (k in 1:na[i]) {                                   # LOOP THROUGH ARMS
    r[i,k] ~ dbin(p[i,k],n[i,k])                         # binomial likelihood
    logit(p[i,k]) <- mu[i] + d[t[i,k]]-d[t[i,1]]          # model for linear predictor
    rhat[i,k] <- p[i,k] * n[i,k]                         # expected value of the numerators
    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))          #Deviance contribution
       + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
  }
  resdev[i] <- sum(dev[i,1:na[i]])              # summed residual deviance contribution for this trial
}
totresdev <- sum(resdev[])                      #Total Residual Deviance
d[1]<- 0                                        # treatment effect is zero for reference treatment
for (k in 2:nt)  { d[k] ~ dnorm(0,.0001) }       # vague priors for treatment effects

# pairwise ORs and LORs for all possible pair-wise comparisons
for (c in 1:(nt-1)) {  for (k in (c+1):nt) {
      or[c,k] <- exp(d[k] - d[c])
      lor[c,k] <- (d[k]-d[c])
     }
}

# ranking
for (k in 1:nt) {
  rk[k] <- nt+1-rank(d[],k)                 # assumes events are "good"

  best[k] <- equals(rk[k],1)                #calculate probability that treat k is best

best3[k] <- equals(rk[k],3) + equals(rk[k],2) + equals(rk[k],1)                #Calculate probability that treat K is top 3



}

# *** PROGRAM ENDS
```

13.2 Network Meta-analysis Results

13.2.1 Estimated Hazard Ratios and Odds Ratios

Table 220 to Table 222 show the results of the three NMAs compared to gemcitabine as the reference case. In all three analyses only one treatment, chemoradiotherapy with gemcitabine, reported a hazard ratio or odds ratio, which had a 95% credible interval that did not pass the line of no effect. This effect would have been completely driven by one trial, Loehrer et al. (2012). Table 223 shows the direct trial results and the NMA indirect results in the form of a matrix. Given that there were no independent closed loops in the NMA and only one trial identified for each comparison, where both indirect and direct evidence is available the HR is identical although inverted.

The results presented for progression free survival in Table 221 may seem counterintuitive with PFS being most favourable for the gemcitabine and gemcitabine and upamostat therapies. This is despite them performing relatively more poorly in the OS NMA. It may be expected that interventions which delay progression in cancer also lead to an increase in overall survival and there is strong evidence in advanced pancreatic cancer of a strong correlation between OS and PFS (Hamada 2016). The great uncertainty with the PFS NMA

should be noted in that all of the 95% credible intervals for all interventions in this NMA passed the line of no effect and could all plausibly have higher or lower PFS than the reference treatment gemcitabine.

Table 220 Estimated Hazard Ratios and Credible Intervals for overall survival compared to gemcitabine

Treatment	median (HR)	2.5%CrI	97.5%CrI	sd
Chemorad (GEM)	0.58	0.37	0.92	0.14
Chemorad (Gem) + Cisplatin	0.62	0.26	1.50	0.33
Chemorad (Gem) +CisplatinX2	0.63	0.26	1.56	0.34
Chemorad(5-fu)+TNFerade	0.69	0.30	1.59	0.34
Gem+400 Upamostat	0.75	0.49	1.15	0.17
FLEC	0.75	0.55	1.02	0.12
Chemorad(5-fu)	0.77	0.36	1.67	0.34
Gem+ 200 Upamostat	0.90	0.61	1.32	0.18
Best Supportive Care	0.99	0.29	3.41	0.84
Gemcitabine	1	Reference		
Gemcitabine + Erlotinib	1.19	0.98	1.45	0.12
Chemorad(5-fu) + Cisplatin	1.45	0.88	2.39	0.39

Table 221 Estimated Hazard Ratios and Credible Intervals for progression free survival compared to gemcitabine.

Treatment	median (HR)	2.5%CrI	97.5%CrI	sd
Gem+400 Upamostat	0.75	0.49	1.15	0.17
Gem+ 200 Upamostat	0.90	0.61	1.32	0.18
Gemcitabine	1.00	Reference		
Chemorad (Gem) +CisplatinX2	1.16	0.49	2.75	0.59
Chemorad (GEM)	1.16	0.72	1.87	0.30
Gemcitabine + Erlotinib	1.19	0.98	1.45	0.12
Chemorad (Gem) + Cisplatin	1.31	0.56	3.09	0.66
Chemorad(5-fu)+TNFerade	1.39	0.60	3.21	0.68
Chemorad(5-fu) + Cisplatin	1.45	0.88	2.39	0.39
Chemorad(5-fu)	1.54	0.71	3.37	0.69

Table 222 Estimated Odds ratio and Credible Intervals for objective response.

Treatment	median (OR)	2.5%CrI	97.5%CrI	sd
Gem+ 200 Upamostat	4.97	0.57	157.00	1394
FLEC	2.73	0.84	10.82	3
Gem+400 Upamostat	2.35	0.17	82.64	552
Chemorad (GEM)	1.10	0.11	10.85	64
Gemcitabine	1	Reference		
Chemorad (Gem) + Cisplatin	0.15	0.01	3.55	26
Chemorad(5-fu)	0.13	0.01	2.31	13
Chemorad(5-fu)+TNFerade	0.09	0.00	1.93	11
Chemorad (Gem) +CisplatinX2	0.08	0.00	1.91	12

1 **Table 223: Indirect and direct comparisons for overall survival.**

Gemcitabine	0.84(0.69,1.02)			1.33(0.98,1.81)	1.73(1.09,2.74)					1.11(0.76,1.63)	1.33(0.87,2.04)
0.84(0.69,1.02)	**Gemcitabine + Erlotinib**						0.69(0.42, 1.14)				
1.3(0.6,2.82)	1.54(0.69,3.44)	**Chemorad(5-fu)**	1.11(0.82, 1.51)		0.9(0.71, 1.14)	0.78(0.3, 2.04)		1.23(0.82,1.86)	1.22(0.77,1.94)		
1.44(0.63,3.32)	1.71(0.73,4.04)	1.11(0.82,1.51)	**Chemorad(5-fu)+TNFerade**								
1.33(0.98,1.81)	1.59(1.1, 2.29)	1.03(0.45,2.36)	0.93(0.38, 2.24)	**FLEC**							
1.73(1.09,2.74)	2.05(1.24,3.39)	1.33(0.72,2.46)	1.2(0.6,2.38)	1.29(0.74,2.26)	**Chemorad (GEM)**						
1.01(0.29,3.48)	1.21(0.34,4.2)	0.78(0.3,2.04)	0.7(0.26,1.92)	0.76(0.21,2.7)	0.59(0.19,1.84)	**Best Supportive Care**					
0.69(0.42,1.14)	0.82(0.48,1.41)	0.53(0.21,1.34)	0.48(0.18, 1.27)	0.52(0.29,0.93)	0.4(0.2,0.79)	0.68(0.18,2.59)	**Chemorad(5-fu) + Cisplatin**				
1.6(0.67, 3.84)	1.9(0.77, 4.67)	1.23(0.82,1.86)	1.11(0.67, 1.85)	1.2(0.48, 3.04)	0.93(0.44,1.95)	1.58(0.56,4.52)	2.32(0.84, 6.37)	**Chemorad (Gem) + Cisplatin**	0.7(0.26,1.87)		
1.58(0.64,3.89)	1.88(0.75,4.73)	1.22(0.77,1.94)	1.1(0.63,1.91)	1.19(0.46,3.08)	0.92(0.42,1.98)	1.56(0.54,4.55)	2.29(0.81, 6.45)	0.99(0.64,1.53)	**Chemorad (Gem) +CisplatinX2**		
1.11(0.76,1.63)	1.32(0.86,2.03)	0.86(0.36,2.03)	0.77(0.31, 1.92)	0.83(0.51,1.36)	0.64(0.35,1.17)	1.1(0.3,4.02)	1.61(0.86, 3.03)	0.69(0.27,1.81)	0.7(0.26,1.87)	**Gem+ 200 Upamostat**	1.2(0.8,1.8)
1.33(0.87,2.04)	1.59(0.99,2.54)	1.03(0.42,2.48)	0.93(0.36, 2.35)	1(0.59,1.69)	0.77(0.41,1.45)	1.32(0.36,4.88)	1.93(1,3.74)	0.83(0.31,2.21)	0.84(0.31,2.29)	1.2(0.8,1.8)	**Gem+400 Upamostat**

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Lower half displays indirect NMA results. Upper half displays direct results from included studies. Results, read horizontally, show the Hazard ratio for experimental vs control for indirect results and control vs experimental for direct results. Results in bold show results where the 95% credible intervals do not pass 1.

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13.2.2 Model Fit

The goodness of model fit, evaluated using total residual deviance, for the OS NMA was 12.01 almost identical to the number of data points. The same is seen with the PFS NMA (9.003 for 9 data points) this suggested a good model fit. For the objective response NMA the residual deviance (16.08) is much larger than the number of data points suggesting a poor model fit. Given this and the wide credible intervals (given the large number of zero or small number of events in the data) around the estimates it would be difficult make any strong conclusions around this NMA.

13.3 Economic Model

13.3.1 Interventions Considered

An economic model was created to consider the interventions identified by and connected in the primary network meta-analysis for overall survival described above. Given its wide use across England in NHS settings for the treatment of LAPC, FOLFIRINOX was also included in a secondary economic analysis despite no evidence being identified which matched the inclusion criteria for it to be included in any of the NMAs or the clinical evidence review. Gemcitabine was chosen as the comparator for the included interventions in the economic model for identical reasons for using it as the comparator in the NMAs.

Best supportive care was not considered by the economic model. Where there are already established treatments for a disease it is not deemed appropriate to recommend a no treatment strategy based on cost effectiveness alone. If best supportive care is deemed to be the optimal treatment strategy, on clinical effectiveness grounds, it is likely to be both cost saving as well as health improving making the need for economic modelling redundant. Interventions which had components of TNFerade and Upamostat were also not considered in the analysis. This is because they were seldom or never used in the NHS for any condition and did not appear in either the BNF or EMIT database of drug prices. The review of the costing literature failed to identify any costs for these two interventions for any condition in any country. It was therefore agreed that any meaningful estimate of cost effectiveness would be near impossible and of little use in making recommendations. Given both these drugs are ‘on patent’ they are likely to be associated with drug costs much higher than other drug interventions considered in this analysis. These interventions are therefore unlikely to have strong evidence of cost effectiveness without strong evidence of clinical effectiveness. This was not provided by the accompanying NMA.

Interventions in patients with stable and responding disease having been previously treated were explicitly excluded from the NMA. However, subsequent different (or further) treatment of patients with stable and responding disease form a vital part of treatment and widely happens in practice for treatment of LAPC across the NHS. Therefore, a secondary analysis was included in the economic model to compare treatments for stable disease. Three interventions (chemoradiotherapy (gemcitabine), chemoradiotherapy (capecitabine) and continued gemcitabine) were considered for this economic model. This covered all interventions that were investigated in studies which were solely excluded from the NMA on account of being in people with responding or stable disease. The model was configured so that change in treatment happened 12 weeks into the model. This analysis was performed using the same methodology as for all other interventions but treatment was only altered in patients with disease that had not progressed during initial treatment. Given a paucity of evidence around the topic the outcomes of this secondary analysis were independent of the initial treatment received. For the purposes of modelling this secondary analysis was performed in people with stable disease from the gemcitabine alone group although given

the assumptions made above the results would be identical for any initial treatment. Continued gemcitabine was used as the basecase comparative treatment in this analysis

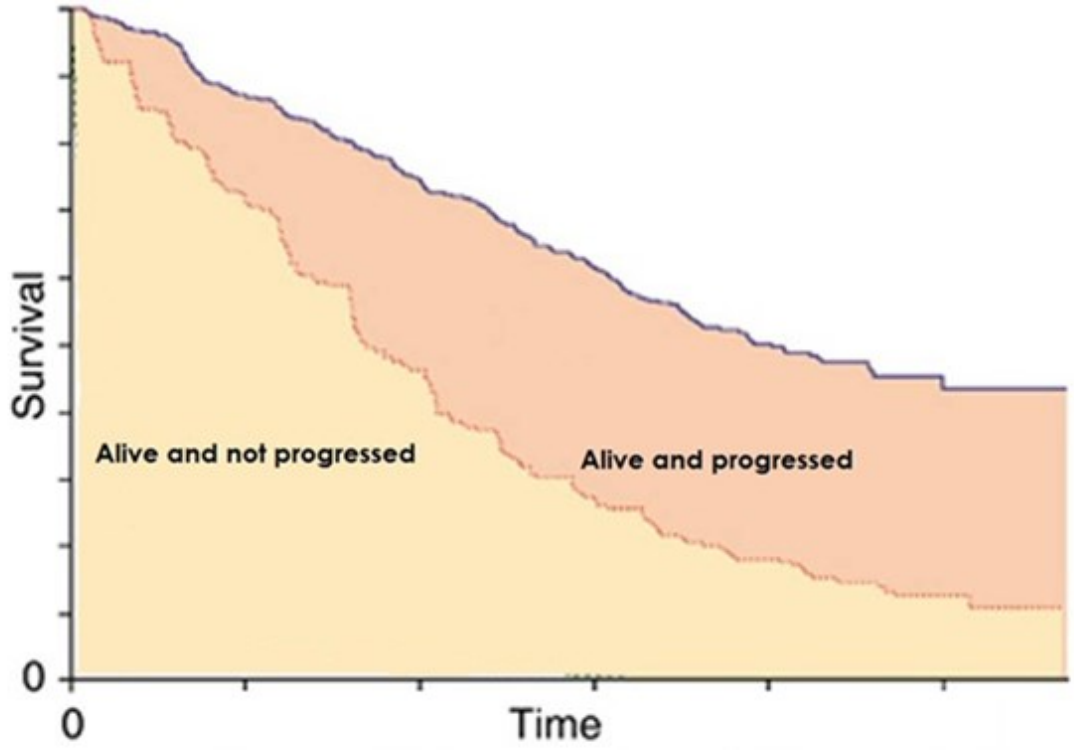
13.3.2 Model Structure

A partitioned survival analysis was developed to estimate the expected life time quality adjusted life years (QALYs) and costs associated with the competing interventions in the patient population. A partitioned survival analysis divides the model cohort between different health states based on the parametric survival functions derived in the NMAs for OS and PFS. The expected OS and PFS are then calculated from the area under the respective curves. For our model three mutually exclusive health states were derived for the cohort to be partitioned into:

- Alive without progressed disease (equal to the difference between area under the PFS curve)
- Alive with progressed disease (equal to the area between the PFS curve and OS curve)
- Death (area above the OS curve)

An illustrative example of the structure of the partitioned survival analysis is shown in Figure 11**Error! Reference source not found.**.

Figure 11: Illustrative example of partitioned survival analysis



A partitioned survival analysis approach was chosen over other modelling approaches, for example a state transition model. This approach is not widely used in models of the cost-effectiveness of oncology interventions. A review of recent oncology NICE Technology Appraisals found that this approach was used in 73% of submissions (Woods 2017). This approach was chosen given the properties of the accompanying NMAs. As both hazard ratios for OS and PFS were estimated in separate mutually exclusive NMAs these values were independent of each other. Consequently, as the survival functions of the included interventions in the model are informed by these hazard ratios the survival curves were also

independent of each other. In the absence of evidence of the relationship between OS and PFS a partitioned survival analysis approach allowed for these estimates to feed directly into the model. Given the modelling assumptions made about other events in the model, such as adverse events and receiving resection, do no impact upon OS and PFS, the curves do not need to account for these factors. Such events are a potential source of bias in partitioned survival analysis.

Whilst not a consideration in choosing the most appropriate modelling approach, a partitioned survival analysis is a more intuitive modelling approach for LAPC. Evidence from trials and observational studies where survival is a key outcome are almost exclusively reported as median overall and progression free survival with accompanying hazard ratio and Kaplan Meier survival curves. As these are the primary inputs for partitioned survival analysis the inputs can be easily compared with those observed in the included trials and other external sources.

A partitioned survival analysis was performed for each intervention considered in the economic evaluation and total time spent in each health state for the model cohort was recorded. Each health state was assigned a quality of life weighting so that QALYs could be calculated.

A proportion of the cohort (informed by the secondary NMA) will have an objective response to treatment and will have a probability of becoming eligible for and receive resection of the pancreas with curative intent. This will incur costs associated with the surgical procedure. Surgery will have no impact upon health outcomes in the model as any benefit of surgery would have been picked up in the OS and PFS of the studies included in the NMA and thus any inclusion in the economic model will lead to double counting and overestimation of the costs and effectiveness of treatments.

Independently of the partitioned survival analysis the model cohort also has a probability of having treatment-related adverse events. The model considered four adverse events which were the most widely reported in the clinical evidence used to inform the NMA and economic model. These were neutropenia, thrombocytopenia, diarrhoea and fatigue. Adverse events were only considered by the model if they were either rated grade III or grade IV as these were considered the severity in which significant costs and quality of life (QoL) detriments were likely to occur. People in the cohort with treatment-related adverse events were given both quality of life detriment and cost at the start of the model. It was acknowledge by the committee that other adverse events were likely to be associated with both QoL detriments and costs, however as these were not consistently reported across the literature it was difficult to include in the model. However, sensitivity analysis was performed to test the robustness of this structural assumption.

The economic component of the model was built and run in Microsoft Excel 2013.

13.3.3 Model Parameters

13.3.3.1 Overall and Progression Free Survival

OS and PFS hazard ratios used in the economic model were estimated in the NMA. As the outcomes of the NMA were reported as relative and not absolute values, an assumption had to be made around absolute overall survival and progression free survival for one of the interventions. As gemcitabine is the reference treatment in both the NMA and economic evaluation it was deemed most appropriate to assign an absolute value of OS and PFS for this treatment. OS and PFS hazard ratios used in the economic model were estimated in the NMAs. As the outcomes of the NMA were reported as relative and not absolute values, an assumption had to be made around absolute overall survival and progression free survival for one of the interventions. As gemcitabine is the reference treatment in both the NMA and economic evaluation it was deemed most appropriate to assign an absolute value of OS and

PFS for this treatment. For the base case analysis a survival curve was fitted based on the summary Kaplan Meier curves reported in Hammel 2016. This trial was chosen for modelling the baseline OS and PFS as it was both the most recent and largest trial reporting OS and PFS for gemcitabine treatment in patients with LAPC. The curve was fitted using methods detailed in Hoyle 2011. The curves were fitted in R Statistical package using code made publicly available by the authors. The shape and scale parameters were taken directly from the R package results and added to the excel model. The covariance for these parameters were also calculated in the form of a Cholesky Decomposition Matrix and used to inform the probabilistic sensitivity analysis (PSA). These parameters are summarised in Table 224. Weibull and exponential models were considered using Akaike Information Criteria with weibull distribution estimated to be the best fit for both the OS and PFS data.

OS and PFS for the interventions were calculated from the hazard ratios reported in the NMA relative to the survival for gemcitabine. The usual proportional hazard assumptions were made about the hazard ratios for both OS and PFS. During PSA these hazard ratios were drawn at random from the iterations of the NMA to reflect uncertainty. PFS was constrained in the model so that it could not be greater than OS and cause a logistical inconsistency. Whilst this might constrict the range of PFS, potentially underestimating the true endpoint for PFS, this logical inconsistency happens in only a tiny number of cases and is unlikely to impact upon the conclusions of the model.

Where PFS was not reported for an intervention and therefore could not be calculated in the NMA it was assumed to be identical to PFS for gemcitabine in the absence of the alternative. As no values for OS and PFS for FOLFIRINOX had been calculated by the NMAs, excluded papers from the clinical evidence were searched for the best available evidence to inform this parameter. In the absence of randomised comparative evidence in a pure LAPC population, observational data was considered. From this, one systematic review and patient level meta-analysis of the use of FOLFIRINOX in people with LAPC was identified (Suker et al. 2016). The study identified 13 studies of 653 patients, 355 of which had LAPC. No studies were identified which were both randomised and comparative. The meta-analysis reported a median OS of 24.2 months (95% CI 21.7-26.8) and a median PFS of 15.0 months (95% CI 13.8-16.2). As FOLFIRINOX was the only intervention considered in this meta-analysis no comparative analysis was performed with any other intervention and therefore a hazard ratio was not and could not be calculated. FOLFIRINOX was therefore incorporated into the secondary analysis using the summary Kaplan Meier curves reported in Suker 2016. Identical methods were used for estimating the survival curves for FOLFIRINOX as used for gemcitabine and again a Weibull distribution was estimated to be the most appropriate fit for both OS and PFS. Shape, scale and Cholesky Decomposition Matrix parameters are reported in Table 227.

The shape and scale of both the OS and PFS curves for gemcitabine and FOLFIRINOX were varied during PSA using the estimated Cholesky Decomposition Matrices calculated above. This uncertainty is again estimated using methods discussed in Hoyle 2011.

The model used a time horizon of 5 years at which point over 99% of the cohort had died. This meant the survival curves were extrapolated out past three years reported by both Hammel 2016 and Suker 2016 using the shape and scale parameters estimated. It is difficult to say how accurate this extrapolation is in the absence of longer term follow-up data although any uncertainty should be picked up in the PSA. The extrapolation is only relevant to a small proportion of the trial cohort so the impact of any inaccuracy should be limited.

13.3.3.2 Proportion Adverse Events

The proportion of treatment related adverse events were taken from the accompanying clinical evidence review using the combined estimate for adverse events from the summary forest plots. Where the adverse events considered by the model were not reported in the clinical evidence they were assumed to be equal to that of gemcitabine. The proportion of

adverse events for FOLFIRINOX were taken from Suker et al (2016). During probabilistic sensitivity analysis, adverse events were varied using a binomial distribution when reported by the evidence. Where adverse events where not reported they were given a wide uniform distribution between 0% and 100% to reflect the large uncertainty.

13.3.3.3 Proportion receiving resection

The model assumed that a patient would go on to receive resection if their cancer had had an objective response to treatment. Given the difficulties discussed above with different criteria being used to estimate objective response it was difficult to give any weight to the absolute estimates of objective response estimated by the model and these were disregarded by the committee as they had little face validity. Therefore, the proportion of patients receiving gemcitabine becoming eligible for resection was assumed to be 3% based upon the committee's clinical opinion. The resection rate for other treatments were then estimated using the Odds Ratios estimated in the objective response NMA. During PSA these hazard ratios were drawn at random from the iterations of the NMA to reflect uncertainty. Where an intervention was not included in the objective response NMA it was assumed to have an objective response rate equal to that of gemcitabine but was varied over a uniform distribution between 0% and 6% during PSA.

The proportion receiving resection following FOLFIRINOX was again taken from Suker et al (2016). During probabilistic sensitivity analysis the proportion receiving resection was randomly drawn from the iterations of the NMA. Where this had not reported a wide uniform distribution was assigned around this variable ranging from 0% to 25%. The estimates for FOLFIRINOX were varied along a beta distribution.

Whilst it was acknowledge that the results of initial treatment may influence further treatment; not only with resection but also by chemotherapy and radiotherapy these were not considered in the base case analysis. The economic model considers chemoradiotherapy (gemcitabine), chemoradiotherapy (capecitabine) and continued treatment with gemcitabine in patients with stable and responding disease although the model will assume the effectiveness of this is independent of the previous treatment received. It will be the case that those patients receiving interventions with greater effectiveness will be more likely to receive further treatment downstream whether considered by the model or not. The model will underestimate both effectiveness and costs for the interventions. There is a paucity of evidence around 2nd and 3rd line treatments and the relationship with first line treatment, therefore any relationship between the two could not be accurately modelled and was therefore not considered in the analysis. As the bias will be in both costs and health outcomes it is not possible to say in which direction the bias will be on the overall cost effectiveness. Given the relatively short life expectancy of the cohort and the small number of patients able to receive 2nd and 3rd line treatments, in practice the more effective treatments will likely be given without consideration of future treatment.

13.3.4 Costs

13.3.4.1 Treatment costs

All chemotherapy and radiotherapy were costed in line with the trial protocols identified in the accompanying clinical evidence review. These are presented in the clinical evidence review. Patients were assumed to have a body surface area of 1.79m^2 based on a retrospective study of 3,613 adult cancer patients in the UK (Sacco et al, 2010). All patients in the cohort were assumed to complete the regimens as per the trial protocols. Given the relatively low life expectancy of the model cohort, the high probability of progression and the potential for serious adverse events this assumption was likely to be an unrealistic assumption. However it was likely to bias against interventions with the lower adverse events and higher OS and PFS for example, the more clinically effective interventions.

The cost of chemotherapy drugs were taken from the Drugs and Pharmaceutical Electronic Market Information Tool (eMIT). All regimens were costed assuming no wastage. Where the cost of the chemotherapy regimens were not available on eMIT the drugs were costed using the BNF (BNF 72). It was noted that this was likely to overestimate the true cost paid by the NHS for these drugs. The costs of drug procurement and administration were based on NHS reference costs. Chemotherapy regimens which required a longer infusion were costed at the higher complex tariff.

Radiotherapy and surgery were also costed using NHS reference costs. For radiotherapy the model cohort were assumed to complete the regimen specified in the trial protocols. The cost for radiotherapy included an initial set-up cost followed by a cost per fraction administered. Two costs are presented in the NHS reference costs for resection surgery, for surgeries with and without complications. The cost of surgery was estimated assuming a probability of complications of 39.6% based on the value estimated, from the literature, of a previous costing for a UK economic evaluation of preoperative biliary drainage in pancreatic cancer (Morris et al. 2014).

Total resource use, in line with the trial protocols are reported in Table 227. These were not varied during the PSA. All treatment costs were varied using a gamma distribution and the reported standard deviations during the PSA.

Table 224: Total resource use assumed by the model for each intervention considered.

	Total Resource Use Treatment Protocol
Gemcitabine	1 initial chemotherapy appointment, 11 subsequent chemotherapy appointments 20760mg gemcitabine
FOLFIRINOX	1 initial chemotherapy appointment, 11 subsequent chemotherapy appointments 176.46mg oxaliplatin 8304mg leucovorin 3736.8mg irinotecan 58128mg fluoracil
Chemorad (Gem)	1 initial chemotherapy appointment, 11 subsequent chemotherapy appointments 20760mg gemcitabine 28 fraction radiotherapy
Chemorad (Gem) + Cisplatin	1 initial chemotherapy appointment, 11 subsequent chemotherapy appointments 20760mg gemcitabine 28 fractions radiotherapy 346mg cisplatin
Chemorad (Gem) +CisplatinX2	1 initial chemotherapy appointment, 11 subsequent chemotherapy appointments 20760mg gemcitabine 28 fractions radiotherapy 692mg cisplatin
Chemorad(5-fu)	1 initial chemotherapy appointment, 11 subsequent chemotherapy appointments 58128mg fluoracil 28 fractions radiotherapy
Chemorad(5-fu) + Cisplatin	1 initial chemotherapy appointment, 11 subsequent chemotherapy appointments

	Total Resource Use Treatment Protocol
	20760mg gemcitabine 346mg cisplatin 28 fractions radiotherapy
FLEC	1 initial complex chemotherapy appointment, 7 subsequent chemotherapy appointments 8304mg epirubicin 8304mg leucovorin 4152mg carboplatin 58128mg fluoracil
Gemcitabine + Erlotinib	1 initial chemotherapy appointment, 11 subsequent chemotherapy appointments 20760mg gemcitabine 12 tablets erlotinib

13.3.4.2 Cost of adverse events.

No UK costs were identified for the specific adverse events considered by the economic model. In the absence of this evidence it was assumed that the adverse events could be treated during one face-to-face consultant follow-up meeting and was costed as such using NHS reference costs. Only one cost was assumed for any combination of the four considered adverse events included as part of the model structure. Again this assumption was likely to bias against treatments with a lower proportion of adverse events. The cost of adverse events was varied during PSA using a gamma distribution.

13.3.4.3 Cost of death

Studies of resource use in cancer show a peak in costs towards the final months of life. Given that over 99% of the model cohort died during the time horizon of the model no terminal cost was assigned to death in the model as this cost was likely to be borne by all patients regardless of intervention received. As costs after year one in the model are discounted this assumption again is likely to bias against the clinically effective interventions with the higher OS.

13.3.5 Quality of Life

As above three different, mutually exclusive health states were created in the partitioned survival analysis:

- Alive without progressed disease
- Alive with progressed disease
- Death

Each of these health states were given a quality of life (QoL) weighting based on those reported in a previous economic evaluation of LAPC (Murphy et al. 2012). This study used expert opinion to estimate a utility weight of 0.68 for patients without progressed disease. Based on a review of the literature a detriment of 0.12 was estimated for disease progression. This gave an estimate of 0.56 for patients with progressed disease. As these estimates were based on expert opinion and were considered very low quality evidence for informing this parameter, QoL weightings were given a large uniform distribution during sensitivity analysis, under the assumption that the QoL without progressed disease was higher or equal to that of progressed disease.

No evidence was identified around adverse events and they were therefore difficult to accurately build into the model. These adverse events were relatively easy to treat and only

occurred for a short period of time and therefore the overall impact on QoL was likely to be small. Therefore, in the base case analysis no QoL detriment was assigned to adverse events. The committee acknowledged however that such adverse events are not negligible for patients receiving treatment for LAPC and some effort should be made to capture these in the QoL measures. Therefore, during probabilistic sensitivity analysis a 0.1 QoL weight detriment was assigned to all adverse events. During PSA this value was varied along a uniform distribution between this value and zero.

13.3.6 Discounting

All health outcomes were discounted at a rate of 3.5% per annum in line with the NICE guidelines manual. The way the model is structured no costs are consider after year one. Therefore no discounting is necessary around costs.

13.3.7 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was also conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that are utilised in the base case are replaced with values drawn from distributions around the mean values. The distributions used are presented in Table 225

13.3.8 Net Monetary Benefit

All results are presented as incremental net monetary benefit (INMB). INMB is a representation of cost effectiveness where incremental QALY gains, compared to the comparator intervention, are converted into a monetary value by multiplying by a willingness to pay per QALY. For example if an intervention had a QALY gain of 0.5 compared to the comparator and the willingness to pay per QALY was £20,000, the monetary value of the QALY gain would equal £10,000. INMB is then calculated by subtracting total incremental cost from this incremental monetary value of the QALYs gained. For our analysis the 'willingness to pay' per QALY is set equal to £20,000 the cost per QALY below which NICE conventionally recommends interventions and £50,000, a higher willingness to pay which NICE consider for interventions which increase life expectancy by at least three months in people in their final 24 months of life relative to current treatment. Interventions which report a positive INMB are cost effective compared to the comparator (gemcitabine) with those reporting a negative value not being cost effective. The 'preferred' intervention would be the one which reports the highest INMB.

Table 225 List of parameters used in the economic model and PSA distribution

	Value	Source	PSA Distribution
Overall Survival (Weibull Function)			
Gemcitabine Intercept	2.89	Hammel 2016	Cholesky
Gemcitabine Log Scale	-0.43	Hammel 2016	Cholesky
FOLFIRINOX Intercept	3.25	Suker 2016	Cholesky
FOLFIRINOX Log Scale	-0.75	Suker 2016	Cholesky
Hazard ratio (vs Gemcitabine)		See NMA results	NMA
Progression Free Survival (Weibull Function)			
Gemcitabine Intercept	2.38	Hammel 2016	Cholesky
Gemcitabine Log Scale	-1.15	Hammel 2016	Cholesky
FOLFIRINOX Intercept	2.99	Suker 2016	Cholesky
FOLFIRINOX Log Scale	-0.30	Suker 2016	Cholesky

	Value	Source	PSA Distribution
Hazard ratio (vs Gemcitabine)		See NMA Results	NMA
Proportion Adverse Events			
Gemcitabine	39.5%	Clinical Evidence Review	BETA(88,135)
FOLFIRINOX	60.4%	Suker et al (2016)	BETA(296,194)
Chemorad (Gem)	79.4%	Clinical Evidence Review	BETA(27,7)
Chemorad (Gem) + Cisplatin	51.6%	Clinical Evidence Review	BETA(16,15)
Chemorad (Gem) +CisplatinX2	63.0%	Clinical Evidence Review	BETA(17,10)
Chemorad(5-fu)	35.6%	Clinical Evidence Review	BETA(32,58)
Chemorad(5-fu) + Cisplatin	61.0%	Clinical Evidence Review	BETA(36,59)
FLEC	47.9%	Clinical Evidence Review	BETA(34,37)
Gemcitabine + Erlotinib	39.7%	Clinical Evidence Review	BETA(87,132)
Proportion Resection			
FOLFIRINOX	25.9%	Suker et al (2016)	BETA(81,313)
Other Interventions		See NMA Results	
Proportion Complications Resection	39.6%	Morris 2014	BETA(98,167)
Costs			
Total intervention Costs		EMIT, BNF, NHS Reference Costs	
Gemcitabine	£4,963.34		Gamma (individual components)
FOLFIRINOX	£7,172.59		Gamma (individual components)
Chemorad (Gem)	£8,342.37		Gamma (individual components)
Chemorad (Gem) + Cisplatin	£10,867.62		Gamma (individual components)
Chemorad (Gem) +CisplatinX2	£13,418.24		Gamma (individual components)
Chemorad(5-fu)	£5,686.62		Gamma (individual components)
Chemorad(5-fu) + Cisplatin	£8,211.87		Gamma (individual components)
FLEC	£6,618.30		Gamma (individual components)
Gemcitabine + Erlotinib	£5,493.00		Gamma (individual components)
Other Costs			
Adverse Event	£162.84	NHS Reference Costs	Gamma(162,6.0)
Cost resection no complications	£8,117.84	NHS Reference Costs	Gamma(8118,11.0)
Cost resection complications	£10,576.46	NHS Reference Costs	Gamma(10,576,13.3)
Utility (Month)			

	Value	Source	PSA Distribution
Stable Disease	0.057	Morris 2014	Uniform(0.023,0.080)
Disease Progression	0.047	Morris 2014	Uniform(0.023,0.080)
Death	0		Not Varied
Discount (per annum)			
Costs	3.5%	NICE	Not varied
QALYs	3.5%	NICE	Not varied

13.4 Results Economic Model

13.4.1 Overall and Progression Free Survival

Figure 12 and Figure 13 show the estimated OS and PFS estimated by the model for the interventions considered. FOLFIRINOX has greater OS up to 27 months and greater PFS throughout. This result is expected given the greater median OS and PFS reported by Suker 2016. The committee did not expect OS to be higher at any time point for the non-FOLFIRINOX interventions. This may be because the proportional hazard assumptions made for survival may not hold for the tail end of the survival curves. Of the other interventions considered in the primary analysis of interventions included in the NMA, chemoradiotherapy with gemcitabine had the greatest OS and gemcitabine the greatest PFS. This is consistent with the magnitude of the hazard ratios estimated by the NMAs.

Figure 12: Estimated Overall Survival for all interventions in the model

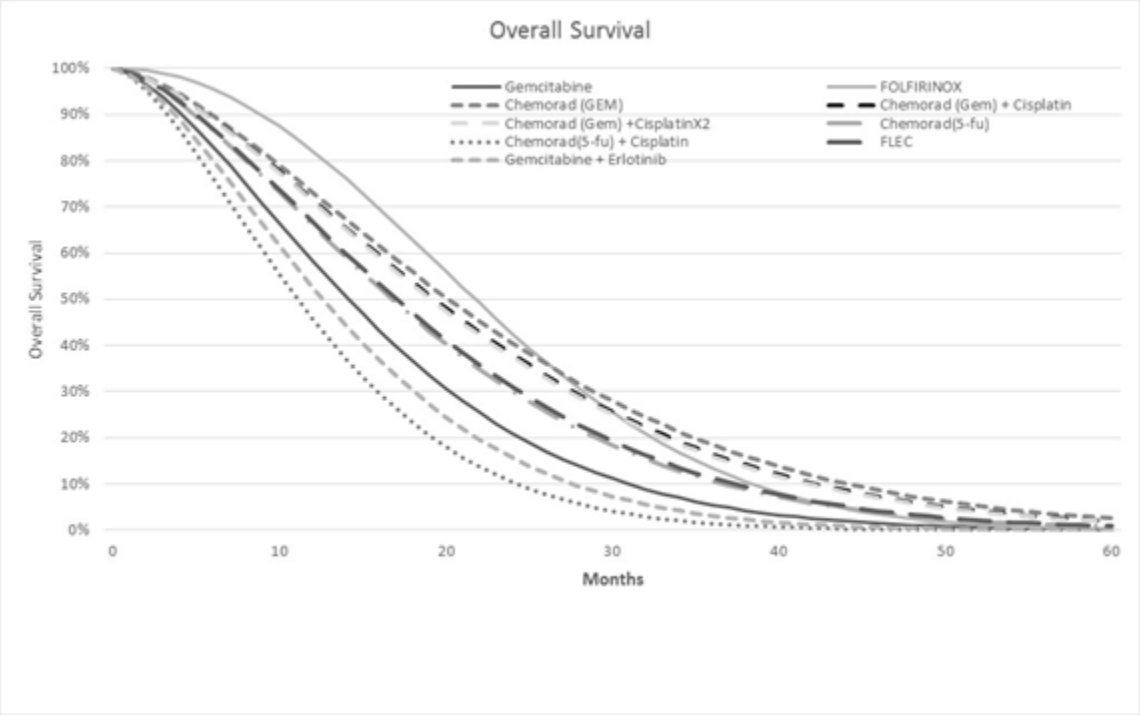
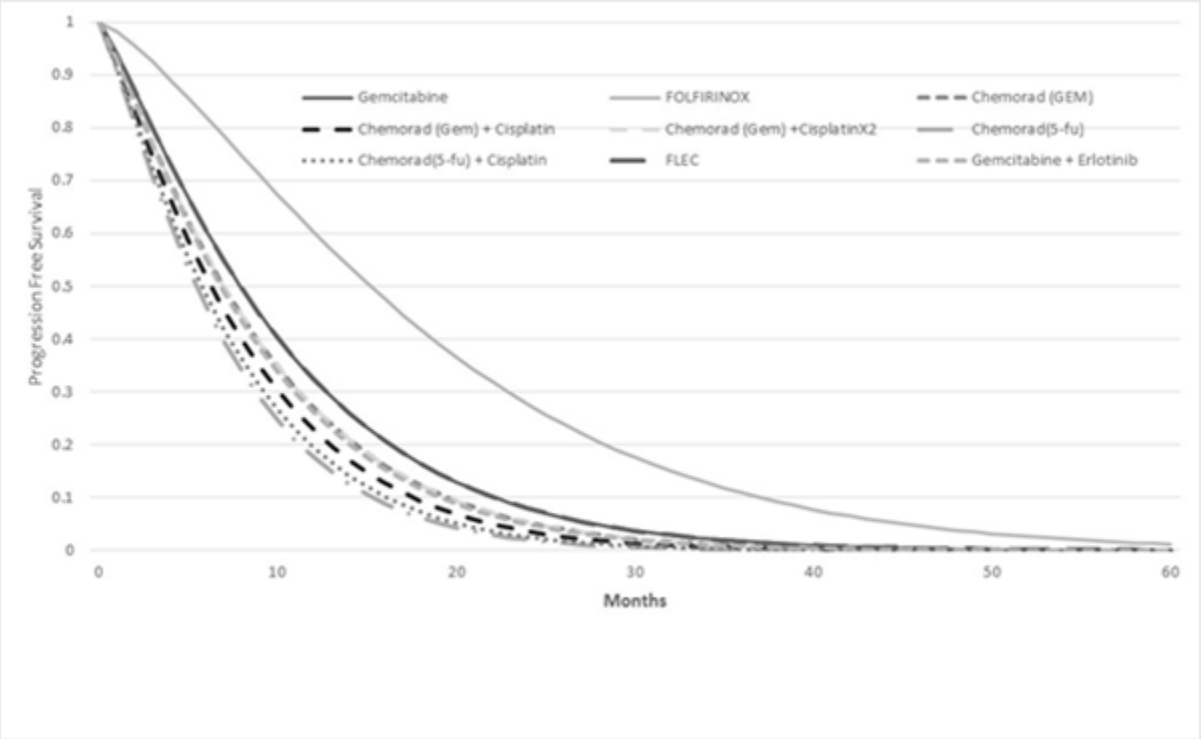


Figure 13: Estimated Progression Free Survival for all interventions in the model



13.4.2 Deterministic Base Case Results

13.4.2.1 Clinical Outcomes

As expected given the magnitude of the hazard ratios estimated in the accompanying NMAs, chemoradiotherapy with gemcitabine had the largest mean OS and gemcitabine the largest mean PFS (Table 226). FLEC was estimated to have identical PFS to gemcitabine in the basecase analysis however given no evidence was identified to include FLEC in the PFS NMA this was directly as a result of the assumptions made in the model. The mean OS and PFS values are larger than the median values reported in the clinical evidence. Given the tails of the survival curves this is not unexpected.

FLEC resulted in the largest percentage of patients going on to receive resection, although these figures should be interpreted with caution given the large uncertainty and other weaknesses associated with the OR NMA highlighted above.

Table 226: Primary Base Case Analysis Results- Clinical Outcomes

	Mean PFS (Months)	Mean OS (Months)	Percentage receiving resection
Gemcitabine	9.6	15.0	3.0%
Chemorad (Gem)	8.4	19.9	3.3%
Chemorad (Gem) + Cisplatin	7.6	19.3	0.5%
Chemorad (Gem) +CisplatinX2	8.4	19.2	0.2%
Chemorad(5-fu)	6.6	17.4	0.4%

	Mean PFS (Months)	Mean OS (Months)	Percentage receiving resection
Chemorad(5-fu) + Cisplatin	6.9	12.0	3.0%
FLEC	9.6	17.6	8.0%
Gemcitabine + Erlotinib	8.2	13.5	3.0%

13.4.2.2 Economic Outcomes

Table 227 shows the base case results for the different interventions for LAPC considered by both the NMA and economic model. At the higher £50,000 per QALY threshold all interventions with a positive incremental QALY compared to gemcitabine returned a positive INMB and therefore could be considered cost effective compared to gemcitabine alone. Chemoradiotherapy with gemcitabine was the preferred option with an INMB of £7,299 per patient or a cost per QALY of £16,378 compared to gemcitabine alone. At a £20,000 per QALY threshold chemoradiotherapy with gemcitabine still remained the preferred option although of the interventions considered in the NMA. Using the means of the probabilistic results rather than deterministic results did not impact significantly upon the results and did not change the conclusions.

Table 227: Primary Base Case Analysis Results Economic Outcomes

	Total Cost	Total QALY	Incremental Cost	Incremental QALYs	INMB £20k per QALY	INMB £50k per QALY
Gemcitabine	£3,157	0.80	Reference	Reference	Reference	Reference
Chemorad (Gem)	£6,713	1.01	£3,556	0.22	£786	£7,299
Chemorad (Gem) + Cisplatin	£6,397	0.98	£3,240	0.18	£374	£5,794
Chemorad (Gem) +CisplatinX2	£6,554	0.98	£3,397	0.18	£251	£5,724
Chemorad(5-fu)	£6,336	0.88	£3,179	0.08	-£1,601	£767
Chemorad(5-fu) + Cisplatin	£6,651	0.63	£3,494	-0.17	-£6,875	-£11,946
FLEC	£6,310	0.92	£3,152	0.12	-£753	£2,846
Gemcitabine + Erlotinib	£10,373	0.71	£7,216	-0.08	-£8,861	-£11,330

13.4.3 Deterministic one way sensitivity analysis

A number of one way sensitivity and scenario analyses were carried out to test the robustness of the model (Table 228). Broad scenarios were chosen for sensitivity analysis over individual sensitivity analyses as these are difficult to interpret for a large number of interventions and uncertainty is better displayed by the probabilistic results.

Chemoradiotherapy with gemcitabine remained the preferred option in the majority of scenarios. Importantly it was robust to assumptions around PFS and baseline OS.

Resection rates account for a large cost in the model with interventions with a large resection rate likely to have relatively larger costs. It was also acknowledged that estimates from the objective response NMA had great uncertainty and point estimates should be interpreted with caution. However, when resection rates and consequently costs are equal across all interventions the preferred intervention remained the same.

Only a handful of scenario analyses resulted in a different preferred therapy to the basecase. Halving the progressed disease state QALY resulted in gemcitabine becoming the preferred option. This is due largely to its point estimate performing well, comparative to other treatments, in the PFS NMA. Again these point estimates should be interpreted with caution given the large uncertainty and potentially counterintuitive results they produced.

When a one off QALY detriment of 0.1 is added for adverse events, chemoradiotherapy with gemcitabine and cisplatin becomes the preferred option at a £20,000 willingness to pay threshold, reflecting its lower number of adverse events reported in the accompanying clinical evidence review. FLEC becomes the preferred option when treatment administration costs are not included although FLEC is a relatively complex chemotherapy to administer attracting higher tariffs, so it is not clear how realistic this scenario is.

Table 228: One Way Deterministic Sensitivity Analysis Results

Parameter	Change Made	Cost Effective £20,000 QALY	Cost Effective £50,000 QALY
Survival	Gemcitabine OS upper 95%	Chemorad(Gem)	Chemorad(Gem)
	Gemcitabine OS lower 95%	Chemorad(Gem)	Chemorad(Gem)
	PFS same proportion as gemcitabine for all interventions	Chemorad(Gem)	Chemorad(Gem)
Resection Rate	Equal 3% all intervention	Chemorad(Gem)	Chemorad(Gem)
Adverse Events	Equal 40% all interventions	Chemorad(Gem)	Chemorad(Gem)
Quality of Life	Life years used instead of QALYs	Chemorad(Gem)	Chemorad(Gem)
	Progression QALY halved	Gemcitabine	Gemcitabine
	0.05 QALY detriment from adverse events	Chemorad(Gem)	Chemorad(Gem)
	0.1 QALY detriment from adverse events	Chemorad(Gem)	Chemorad(Gem)+Cisplatin
Costs	Chemo and radiotherapy administration costs remove	FLEC	Chemorad(Gem)
	No adverse event costs	Chemorad(Gem)	Chemorad(Gem)
	25% reduction in cost of gemcitabine	Chemorad(Gem)	Chemorad(Gem)
	50% reduction in cost of gemcitabine	Chemorad(Gem)	Chemorad(Gem)
	75% reduction in cost of gemcitabine	Chemorad(Gem)	Chemorad(Gem)

13.4.4 Secondary analysis of treatment for patients with stable or responding disease

In the secondary analysis, based on the results of the two trials identified during the clinical evidence review, continued gemcitabine alone dominated chemoradiotherapy, with gemcitabine being both health improving and less costly. Chemoradiotherapy with capecitabine was cost effective at a willingness to pay per QALY of both £20,000 and

£50,000. Compared to continued treatment with gemcitabine it returned a cost per QALY of £13,052 again below both the £20,000 and £50,000 willingness to pay thresholds.

Table 229: Secondary analysis base case results

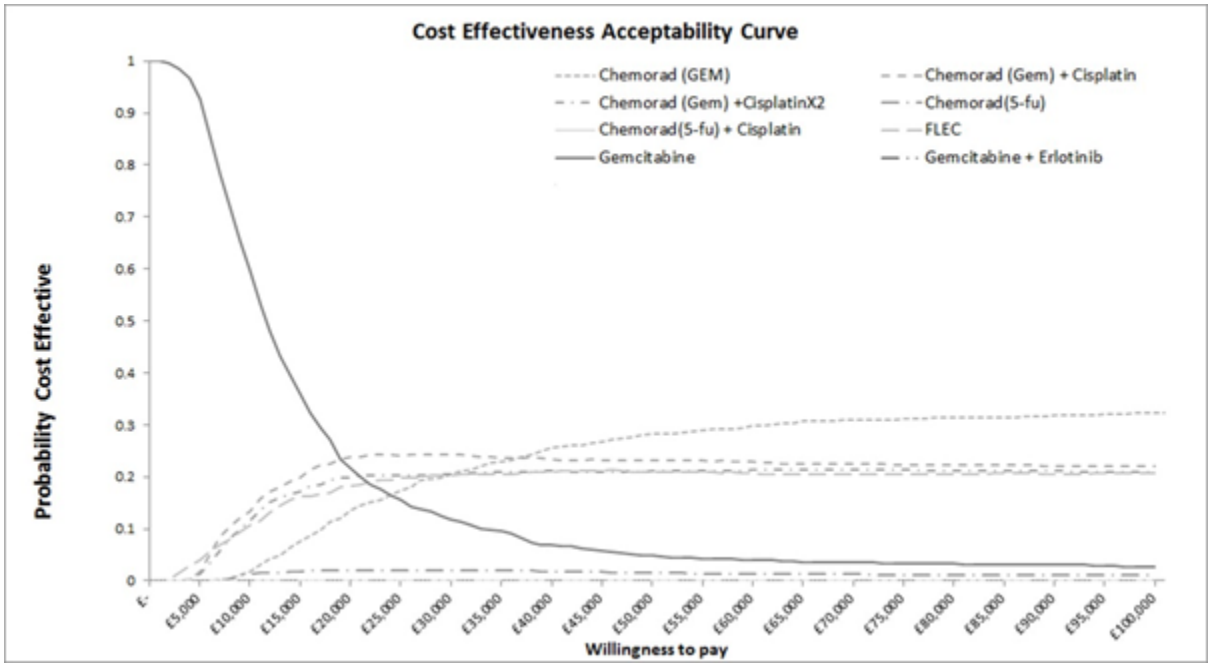
	Total Cost	Total QALY	Incremental Cost	Incremental QALYs	INMB £20k per QALY	INMB £50k per QALY
Gemcitabine	£3,992	0.73	Reference	Reference	Reference	Reference
Chemorad (Gem)	£6,342	0.71	£2,350	-0.02	-£2,750	£3,350
Chemorad (Cap)	£6,472	0.92	£2,480	0.19	£1,320	£7,020

13.4.5 Probabilistic Sensitivity Analysis

When only interventions included in the NMA are considered (Figure 14) chemoradiotherapy with gemcitabine and cisplatin becomes the preferred treatment option at the £20,000 per QALY threshold with a 24% chance of being the preferred option. Chemoradiotherapy with gemcitabine, the preferred choice in the deterministic analysis now has a 16% probability of being the most cost effective option. Gemcitabine alone had a 17% probability of being the preferred option in this scenario. As the only monotherapy in the analysis this corresponds to an 83% probability that some form of combination therapy is the most cost effective option.

At a £50,000 per QALY threshold chemoradiotherapy with gemcitabine becomes the preferred option with a 30% probability of being the most cost effective option. At this £50,000 per QALY threshold, gemcitabine has a 5% probability of being the preferred option corresponding to a probability of 95% that some form of combination therapy is the most cost effective option. The plateauing lines for all interventions suggests there is significant uncertainty around the clinical inputs for the model.

Figure 14: Cost effectiveness acceptability curve for all interventions included in the NMAs



13.4.6 Secondary Analysis Including FOLFIRINOX

13.4.6.1 Clinical Outcomes

Values for FOLFIRINOX in the economic model were taken from Suker 2016 and no modelling was performed around these clinical outcomes (Table 230). When FOLFIRINOX was included as part of the secondary economic analysis the values for median OS and PFS were greater than for any intervention in any trial reported in the NMA. It was therefore expected that FOLFIRINOX would also report a greater mean OS and PFS. The reported 25.9% of patients receiving resection was much higher than anything predicted by the NMAs and economic model.

Table 230: Secondary Analysis Results- Clinical Outcomes

	Mean PFS (Months)	Mean OS (Months)	Percentage receiving resection
Gemcitabine	9.6	15.0	3.0%
FOLFIRINOX	18.9	21.0	25.9%
Chemorad (Gem)	8.4	19.9	3.3%
Chemorad (Gem) + Cisplatin	7.6	19.3	0.5%
Chemorad (Gem) +CisplatinX2	8.4	19.2	0.2%
Chemorad(5-fu)	6.6	17.4	0.4%
Chemorad(5-fu) + Cisplatin	6.9	12.0	3.0%
FLEC	9.6	17.6	8.0%
Gemcitabine + Erlotinib	8.2	13.5	3.0%

13.4.6.2 Economic Outcomes

Table 231 shows the results of the secondary analysis which considers FOLFIRINOX as part of the secondary analysis. FOLFIRINOX has greater lifetime costs, other than gemcitabine with erlotinib, but also reports greater lifetime QALYs. FOLFIRINOX also becomes the preferred option for both a £20,000 and £50,000 per QALY willingness to pay thresholds.

Table 231: Secondary Analysis Results-Economic Outcomes

	Total Cost	Total QALY	Incremental Cost	Incremental QALYs	INMB £20k per QALY	INMB £50k per QALY
Gemcitabine	£3,157	0.80	Reference	Reference	Reference	Reference
FOLFIRINOX	**£7,718**	**1.58**	**£4,561**	**0.53**	**£5,992**	**£21,823**
Chemorad (Gem)	£6,713	1.01	£3,556	0.22	£786	£7,299
Chemorad (Gem) + Cisplatin	£6,397	0.98	£3,240	0.18	£374	£5,794
Chemorad (Gem) +CisplatinX2	£6,554	0.98	£3,397	0.18	£251	£5,724
Chemorad(5-fu)	£6,336	0.88	£3,179	0.08	-£1,601	£767

	Total Cost	Total QALY	Incremental Cost	Incremental QALYs	INMB £20k per QALY	INMB £50k per QALY
Chemorad(5-fu) + Cisplatin	£6,651	0.63	£3,494	-0.17	-£6,875	-£11,946
FLEC	£6,310	0.92	£3,152	0.12	-£753	£2,846
Gemcitabine + Erlotinib	£10,373	0.71	£7,216	-0.08	-£8,861	-£11,330

13.4.7 Threshold Sensitivity Analysis around FOLFIRINOX

Given the potential biases discussed around the data used to populate FOLFIRINOX (Table 232) a range of threshold sensitivity analyses were performed to try to capture at which values for FOLFIRINOX the intervention is no longer the preferred option in the secondary analysis. FOLFIRINOX remains the preferred option for OS and PFS much below that reported in Suker 2016. Even if the identified biases do lead to a large overestimate of these important parameters FOLFIRINOX may still be a cost effective option.

FOLFIRINOX remains the preferred choice for all values of adverse events. FOLFIRNOX is a relatively toxic chemotherapy. Even if treatment does lead to a large number of patients experiencing adverse events it is still likely to remain the preferred option.

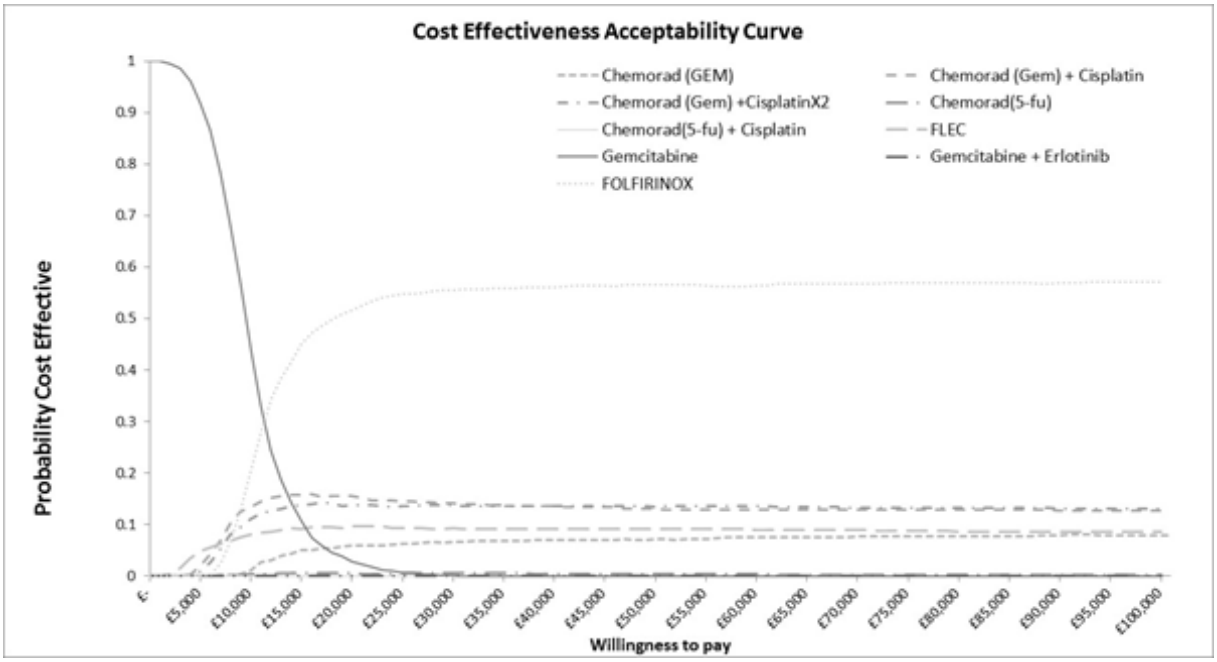
Table 232: Threshold sensitivity analyses for FOLFIRINOX

Variable	WTP £20k per QALY	WTP £50k per QALY
Overall Survival	<13.1 months	<11.3 months
Progression Free Survival	<9 months	<8.3 months
Adverse Events	All Values	All values
Total Drug Costs	£7,885	£18,322

13.4.8 Probabilistic Sensitivity Analysis

It can be seen from **Error! Reference source not found.**Figure 15 that the cost effective acceptability curve changes significantly when FOLFIRINOX is included as part of the analysis. FOLFIRINOX is now the most likely preferred option for all willingness to pay thresholds above £10,000 per QALY. The probability of FOLFIRINOX being the preferred option remains constant with a 51% and 56% chance of being cost effective at a willingness to pay per QALY of £20,000 and £50,000 respectively. At the same willingness to pay values there is only a few percentage points separating the other interventions (considered in the NMA) at both £20,000 and £50,000 with a less than 14% probability of any single intervention being the preferred option at both thresholds. Gemcitabine alone has a 3% and zero probability of being cost effective for a willingness to pay per QALY of £20,000 and £50,000 respectively. Again, this strongly suggests that a multimodal therapy approach is almost certainly the most cost effective treatment option.

Figure 15: Cost effectiveness acceptability curve for all interventions including FOLFIRINOX



13.5 Discussion

Of the interventions considered in the NMA chemoradiotherapy with gemcitabine was the preferred option during the deterministic base case results and, chemoradiotherapy with gemcitabine and cisplatin was the preferred option in the largest number of iterations in the PSA in line with the results of the NMA. However, it never had a greater than 25% probability compared to all other interventions at a willingness to pay per QALY values of £20,000 and £50,000 respectively. It was therefore difficult to strongly conclude for any intervention to be the preferred option from this group. The economic model suggested that gemcitabine alone only had a 17% probability of being the preferred option for any of the conventionally used willingness to pay thresholds suggesting strongly that multimodal therapy was likely to be cost effective.

FOLFIRINOX was the preferred option when added in the secondary analysis, being the preferred treatment in both the deterministic results and in over 50% of the iterations of the probabilistic sensitivity analysis. However, despite its prevalent usage for treatment of LAPC across England no direct, randomised comparative evidence was identified for this intervention solely in this patient group. The comparability of FOLFIRINOX to other interventions considered in the NMA and economic model is not strong. Whilst FOLFIRINOX was robust to the PSA, as the OS and PFS for FOLFIRINOX was reduced closer to those of other interventions in the NMA the strength of this conclusion was largely reduced. Comparative randomised evidence comparing FOLFIRINOX with other interventions in the NMA, would increase the comparability of this intervention and the strength of any conclusions drawn.

The plateauing of the lines in the CEACs suggest that most of the uncertainty around the model revolves around the clinical inputs. Additional randomised clinical trials which would strengthen and increase the power of the NMA would likely reduce this uncertainty and increase the strength of any recommendations made from the model.

The cost effectiveness evidence in TA25 compared 5-FU chemotherapy with gemcitabine chemotherapy. The two economic evaluations for this topic were largely based around one RCT (Burris et al. 1997) comparing gemcitabine monotherapy to 5-FU monotherapy in patients with either locally advanced or metastatic pancreatic cancer. The models submitted estimated a cost per QALY for gemcitabine compared to 5-FU of between £7,200 and £18,700.

It is difficult to draw comparisons with the NMA and economic model above given that 5-FU monotherapy was not used as a comparison in any of the identified evidence. Burris et al (1997) on which TA25 was based was not included as it was conducted before 2000 and had a mixed population of LAPC and metastatic cancer. Where evidence of 5-FU has been included in the NMA it is alongside radiotherapy, an intervention markedly different to 5-FU monotherapy. All regimens including 5-FU in the base case analysis are cost increasing and health decreasing compared to gemcitabine. This is mirrored by the PSA where again the 5-FU based regimens are rarely cost effective.

The costs of gemcitabine are also now likely to be much reduced compared to those considered in TA25 given that the treatment is now ‘off patent’ for this condition. The costs of gemcitabine and 5-FU are now likely to be very similar and that the total costs and costs per QALYs for gemcitabine are likely to be much lower than those reported in TA25 in 2001 even without taking account of inflation.

Despite the TA25 models not being strictly comparable to the bespoke economic model above the most pertinent difference is that gemcitabine monotherapy is now very unlikely to be the preferred option with the PSA estimating an almost 0% probability. This however is compared to regimens that were not considered by TA25. However, interventions that have a component of gemcitabine, in particular chemoradiotherapy with gemcitabine perform favourably in the bespoke economic model.

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