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Chemotherapy and radiotherapy for advanced pancreatic cancer (Review)

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[Intervention Review]

Chemotherapy and radiotherapy for advanced pancreatic cancer

Venessa Chin[1,2], Adnan Nagrial[1,3], Katrin Sjoquist[4,5], Chelsie A O'Connor[2,6,7], Lorraine Chantrill[8], Andrew V Biankin[9,10,11], Rob JPM Scholten[12], Desmond Yip[13,14]

[1]The Kinghorn Cancer Centre, Garvan Institute of Medical Research, Sydney, Australia. [2]St Vincent's Hospital, Sydney, Australia. [3]The Crown Princess Mary Cancer Centre, Westmead, Australia. [4]NHMRC Clinical Trials Centre, University of Sydney, Sydney, Australia. [5]Medical Oncology, Cancer Care Centre, St George Hospital, Kogarah, Australia. [6]Genesis Cancer Care, Sydney, Australia. [7]Macquarie University Hospital, Sydney, Australia. [8]Department of Pancreatic Cancer, The Kinghorn Cancer Centre, Garvan Institute of Medical Research, Sydney, Australia. [9]Institute of Cancer Sciences, University of Glasgow, Glasgow, UK. [10]South Western Sydney Clinical School, Faculty of Medicine, University of New South Wales, Liverpool, Australia. [11]West of Scotland Pancreatic Unit and Glasgow Royal Infirmary, Glasgow, UK. [12]Cochrane Netherlands, Julius Center for Health Sciences and Primary Care / University Medical Center Utrecht, Utrecht, Netherlands. [13]Department of Medical Oncology, The Canberra Hospital, Garran, Australia. [14]ANU Medical School, Australian National University, Acton, Australia

Contact address: Venessa Chin, The Kinghorn Cancer Centre, Garvan Institute of Medical Research, 384 Victoria Street Darlinghurst, Sydney, NSW, 2010, Australia. v.chin@garvan.org.au, venessa.t.chin@gmail.com.

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ABSTRACT

Background

Pancreatic cancer (PC) is a highly lethal disease with few effective treatment options. Over the past few decades, many anti-cancer therapies have been tested in the locally advanced and metastatic setting, with mixed results. This review attempts to synthesise all the randomised data available to help better inform patient and clinician decision-making when dealing with this difficult disease.

Objectives

To assess the effect of chemotherapy, radiotherapy or both for first-line treatment of advanced pancreatic cancer. Our primary outcome was overall survival, while secondary outcomes include progression-free survival, grade 3/4 adverse events, therapy response and quality of life.

Search methods

We searched for published and unpublished studies in CENTRAL (searched 14 June 2017), Embase (1980 to 14 June 2017), MEDLINE (1946 to 14 June 2017) and CANCERLIT (1999 to 2002) databases. We also handsearched all relevant conference abstracts published up until 14 June 2017.

Selection criteria

All randomised studies assessing overall survival outcomes in patients with advanced pancreatic ductal adenocarcinoma. Chemotherapy and radiotherapy, alone or in combination, were the eligible treatments.

Data collection and analysis

Two review authors independently analysed studies, and a third settled any disputes. We extracted data on overall survival (OS), progression-free survival (PFS), response rates, adverse events (AEs) and quality of life (QoL), and we assessed risk of bias for each study.

Main results

We included 42 studies addressing chemotherapy in 9463 patients with advanced pancreatic cancer. We did not identify any eligible studies on radiotherapy.

We did not find any benefit for chemotherapy over best supportive care. However, two identified studies did not have sufficient data to be included in the analysis, and many of the chemotherapy regimens studied were outdated.

Compared to gemcitabine alone, participants receiving 5FU had worse OS (HR 1.69, 95% CI 1.26 to 2.27, moderate-quality evidence), PFS (HR 1.47, 95% CI 1.12 to 1.92) and QoL. On the other hand, two studies showed FOLFIRINOX was better than gemcitabine for OS (HR 0.51 95% CI 0.43 to 0.60, moderate-quality evidence), PFS (HR 0.46, 95% CI 0.38 to 0.57) and response rates (RR 3.38, 95% CI 2.01 to 5.65), but it increased the rate of side effects. The studies evaluating CO-101, ZD9331 and exatecan did not show benefit or harm when compared with gemcitabine alone.

Giving gemcitabine at a fixed dose rate improved OS (HR 0.79, 95% CI 0.66 to 0.94, high-quality evidence) but increased the rate of side effects when compared with bolus dosing.

When comparing gemcitabine combinations to gemcitabine alone, gemcitabine plus platinum improved PFS (HR 0.80, 95% CI 0.68 to 0.95) and response rates (RR 1.48, 95% CI 1.11 to 1.98) but not OS (HR 0.94, 95% CI 0.81 to 1.08, low-quality evidence). The rate of side effects increased. Gemcitabine plus fluoropyrimidine improved OS (HR 0.88, 95% CI 0.81 to 0.95), PFS (HR 0.79, 95% CI 0.72 to 0.87) and response rates (RR 1.78, 95% CI 1.29 to 2.47, high-quality evidence), but it also increased side effects. Gemcitabine plus topoisomerase inhibitor did not improve survival outcomes but did increase toxicity. One study demonstrated that gemcitabine plus nab-paclitaxel improved OS (HR 0.72, 95% CI 0.62 to 0.84, high-quality evidence), PFS (HR 0.69, 95% CI 0.58 to 0.82) and response rates (RR 3.29, 95% CI 2.24 to 4.84) but increased side effects. Gemcitabine-containing multi-drug combinations (GEMOXEL or cisplatin/epirubicin/5FU/gemcitabine) improved OS (HR 0.55, 95% CI 0.39 to 0.79, low-quality evidence), PFS (HR 0.43, 95% CI 0.30 to 0.62) and QOL.

We did not find any survival advantages when comparing 5FU combinations to 5FU alone.

Authors' conclusions

Combination chemotherapy has recently overtaken the long-standing gemcitabine as the standard of care. FOLFIRINOX and gemcitabine plus nab-paclitaxel are highly efficacious, but our analysis shows that other combination regimens also offer a benefit. Selection of the most appropriate chemotherapy for individual patients still remains difficult, with clinicopathological stratification remaining elusive. Biomarker development is essential to help rationalise treatment selection for patients.

PLAIN LANGUAGE SUMMARY

The effects of anti-cancer therapies on advanced pancreatic cancer

Review question

This review aimed to answer the question, which therapies are the most effective for advanced pancreatic cancer?

Background

Pancreatic cancer (PC) is a serious, often fatal disease, and many people are not diagnosed until they have advanced tumours that cannot be removed with surgery. Symptoms include abdominal pain, weight loss, and yellowing of the skin and eyes. Up until recently, gemcitabine was the standard drug for treating advanced pancreatic cancer, but this gave people only a modest benefit.

Study characteristics

We looked for all studies in people with pancreatic cancer that could not be operated on (locally advanced) or that had already spread beyond the pancreas (metastatic). We found 42 clinical studies involving 9463 participants who were receiving their first therapy for PC. Our search is current to June 2017.

The studies compared one therapy against either best supportive care (symptom management only) or another type of therapy. Studies had to evaluate overall survival (or time to death). The study could be testing either chemotherapy (drugs that kill or slow the growth of cancer cells) or radiotherapy (X-ray treatment). We collected data on survival, tumour response rate, side effects and quality of life. The results of clinical studies addressing targeted/biological therapies, immunotherapies, second-line therapies and local treatments for locally advanced disease will be reported in a separate Cochrane Review.

Key results

This review has shown that in advanced disease, combination chemotherapy with FOLFIRINOX (5-fluorouracil, irinotecan, oxaliplatin combination); GEMOXEL (gemcitabine, oxaliplatin and capecitabine); cisplatin/epirubicin/5FU/gemcitabine; gemcitabine plus nab-paclitaxel; and gemcitabine plus a fluoropyrimidine agent, provide a survival advantage over gemcitabine alone. These combinations do increase side effects. Gemcitabine given slowly using a fixed rate of infusion may be more effective than giving it in the standard way, which is quickly over 30 minutes.

Quality of the evidence

The quality of the evidence varied greatly amongst comparisons. The highest quality evidence was for gemcitabine versus fixed dose rate gemcitabine and some of the gemcitabine combinations (fluoropyrimidine, topoisomerase, and taxane). We judged the studies for quality using factors like how well they were conducted, how well they reported results and whether they used a placebo.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Anti-cancer therapy versus best supportive care for advanced pancreatic cancer

Person or population: advanced pancreatic cancer
Setting: first-line therapy
Intervention: anti-cancer therapy
Comparison: best supportive care

Outcomes	Anticipated risk of death* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments	Toxicity and QoL
	Risk with best supportive care	Risk with anti-cancer therapy					
Overall survival	Study population		HR 1.08 (0.88 to 1.33)	298 (4 RCTs)	⊕⊕⊕◯ Moderate[a]	-	The analysis showed that toxicity data were inconsistently reported. Most studies reporting this outcome noted that gastrointestinal adverse events were the most frequent, occurring in between 15% to 31%. 1 study noted haematological toxicity was present in 81.5% of people. 2 out of the 3 studies that analysed QoL demonstrated a benefit with anti-cancer therapy. 1 study showed no difference between the 2 groups
	707 per 1000	734 per 1000 (660 to 804)					

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **HR**: hazard ratio; **RCT**: randomised controlled trial.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]Confidence interval include both benefit and harm; optimal information size not met.

BACKGROUND

Recently published global cancer statistics show that pancreatic cancer (PC) accounted for 184,400 deaths worldwide in 2012, with the highest incidence in men in high-income countries at 8.6 cases per 100,000 (Torre 2015). In Australia, although PC is relatively uncommon (incidence of 11 per 100,000), it is highly lethal, representing the fourth leading cause of death from cancer (Tracey 2010). The US National Cancer Institute has reported a five-year survival of 21.5% for those with localised disease (www.cancer.gov); however, a review of the Finnish Cancer Registry showed five-year survival of only 4.3% for those with localised disease and an overall five-year survival of 0.2% (Carpelan 2005).

PC is a notoriously insidious cancer, commonly presenting with vague, non-specific symptoms that classically consist of the triad of epigastric abdominal pain, weight loss and jaundice (Howard 1977; Warshaw 1992), which gradually worsen over time. Physical examination is often normal, with the commonest sign of an enlarged liver present in fewer than half of patients (Von Hoff 2005). Thus, most patients have advanced disease when they are diagnosed.

Approximately 10% of early stage pancreatic carcinomas are amenable to curative surgery (Siegel 2013). However, the risk of relapse after surgical resection is still quite high, with only 10% of patients surviving for five years (Conlon 1996; Shahrudin 1997). Although studies have reported a benefit for chemotherapy in advanced disease (Burris 1997; Heinemann 2008; Conroy 2011; Von Hoff 2013), the role of second and subsequent lines of chemotherapy remains controversial (Nagrial 2015). The benefits of radiotherapy, either alone or in combination, as a palliative treatment for advanced or relapsed disease, is uncertain (Sultana 2007). Hammel 2013 tested contemporary chemotherapy and radiotherapy techniques but did not demonstrate a survival benefit in locally advanced disease. Biological therapies are emerging in the treatment of pancreatic cancer and but have yet to find their place in routine clinical practice (Castellanos 2011).

There are other published meta-analyses that look at various aspects covered by this review. Li 2014 analysed eight studies that assessed randomised data using gemcitabine and fluoropyrimidine agents, finding a benefit using gemcitabine plus fluoropyrimidine. Petrelli 2014 analysed 29 studies that assessed gemcitabine monotherapy versus chemotherapy combinations, finding improved outcomes with the chemotherapy combinations. Two studies have used a Bayesian network meta-analysis to perform direct and indirect comparisons of chemotherapy combinations (Chan 2014; Gresham 2014). Chan 2014 concluded that FOLFIRINOX was likely to be the most efficacious regimen in the advanced stage. Two meta-analyses have assessed chemotherapy plus radiotherapy (Bernstein 2014; Chen 2013), both finding a small benefit to adding chemotherapy to radiation; however, neither included the recent study conducted by Hammel 2013.

Anti-cancer therapies in the metastatic setting ideally aim to improve people's quality and length of life, with tolerable side effects. This review will analyse both the anti-cancer effects and the adverse effects of treatments in patients with pancreatic cancer.

Description of the condition

Pancreatic ductal adenocarcinoma (PDAC) is a cancer arising from the ducts in the pancreas gland. It can be localised to the pancreas (local disease), locally advanced (still confined to the area around the pancreas but possibly involving lymph glands or other immediately adjacent structures) or metastatic (with cancer spread to distant areas).

This review includes studies in patients with locally advanced (not amenable to local therapies) or metastatic PC, formally defined as follows (Callery 2009).

1. Locally advanced or unresectable, defined by:
   i) greater than 180° of superior mesenteric vein encasement, any coeliac abutment;
   ii) unreconstructable superior mesenteric vein or portal occlusion;
   iii) aortic invasion or encasement;
   iv) nodal involvement beyond the field of resection.
2. Metastatic, defined by distant sites of disease.

Description of the intervention

Chemotherapy

Chemotherapy encompasses all cytotoxic or antineoplastic drug treatments, intravenous or oral, which work by killing or slowing the growth of cancer cells. Although the schedules differ between therapies, most are given on a four-weekly basis (one cycle) for up to six cycles.

Radiotherapy

Radiation therapy uses X-rays to destroy or injure cancer cells so they cannot multiply (Queensland Cancer Fund 2012). It is given in a number of different ways.

1. External beam radiotherapy: delivered over a number of sessions (fractions) utilising an external radiotherapy source emitting X-rays, gamma rays, electrons or heavy particles.
2. Stereotactic body radiation therapy: a highly conformal (targeted) technique for delivering external beam radiotherapy in a single fraction (stereotactic radiosurgery) or a number of fractions (stereotactic radiotherapy).
3. Brachytherapy: internal radiotherapy utilising a radioactive source placed into or adjacent to the pancreas and administered in a single fraction or number of fractions, given alone or in combination with external beam radiotherapy.

4. Intraoperative radiotherapy: administration of external source radiotherapy or brachytherapy at the time of surgery, given alone or in combination with external beam radiotherapy.

Best supportive care

Best supportive care in advanced disease is defined as anything other than chemotherapy. It may include symptom control by radiotherapy (not to the primary site), palliative surgery, biliary stent insertion, analgesia, blood transfusion, and psychological or social support.

How the intervention might work

The primary goal for all treatments for locally advanced or metastatic pancreatic cancer is to palliate symptoms and improve overall survival (see Appendix 1, 'Glossary of terms'). In general, chemotherapy and radiotherapy can potentially kill cancer cells in the body and reduce the severity of the disease. This can in turn, reduce symptoms and increase survival times. In the advanced setting, chemotherapy and radiotherapy do not offer a cure. Best supportive care is usually administered alongside chemotherapy and radiotherapy, but it can be the sole treatment given to some patients. All anti-cancer therapies can cause side effects, which commonly include fatigue, nausea, vomiting, low blood counts (haemoglobin, white cells and platelets) and diarrhoea. Radiotherapy can cause local pain, skin rash, fatigue, nausea and vomiting.

Why it is important to do this review

Given the poor prognosis of PC, evidence-based clinical decision-making is paramount in guiding patients through treatments. Performing a meta-analysis of studies will ensure that clinicians and patients have a reference to inform their clinical choices.

The meta-analysis published previously in Yip 2009 has been criticised for not using hazard ratios to assess survival (Sultana 2007). This update will use hazard ratios and also assess quality of life.

PC is a notoriously difficult cancer in which to perform clinical studies, and much controversy exists. Although there is evidence in the first line setting that supports the use of FOLFIRINOX (Conroy 2011), gemcitabine plus erlotinib (Moore 2007), gemcitabine plus fluoropyrimidine (Cunningham 2009), or nab-paclitaxel (Von Hoff 2013), questions remain with regard to toxicity, cost and survival benefits. There is conflicting evidence on the place for and schedule of chemoradiation as well as debate about the optimum drug and dose (Kim 2007; Philip 2011).

Previous meta-analyses have had narrow search criteria (Chan 2014; Li 2014; Petrelli 2014), or they have used only phase III randomised data (Gresham 2014). Here, we have attempted to synthesise and organise all available randomised data concerning patients having treatment for advanced pancreas cancer in order to help inform clinical decision-making and guide further research in this area.

OBJECTIVES

To assess the effect of chemotherapy, radiotherapy or both for first-line treatment of advanced pancreatic cancer. Our primary outcome was overall survival, while secondary outcomes include progression-free survival, grade 3/4 adverse events, therapy response and quality of life.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled studies, both published and unpublished, comparing one of the intervention types versus placebo, another intervention type or best supportive care.

Types of participants

People with a diagnosis of pancreatic adenocarcinoma established by either histological or cytological findings (investigations on body tissue or cells). Studies enrolling people with advanced, unresectable or recurrent disease were eligible for inclusion.

Types of interventions

Any type of chemotherapy, radiotherapy or combination of chemotherapy plus radiotherapy versus placebo, no treatment, best supportive care or another chemotherapy and/or radiotherapy treatment regimen.

Best supportive care in advanced disease may include symptom control by radiotherapy (not to the primary site), palliative surgery, biliary stent insertion, analgesia, blood transfusion and psychological or social support.

We looked for interventions falling into the following comparisons.

1. Any chemotherapy treatment versus placebo, no treatment or best supportive care.
2. Any chemotherapy treatment versus any other chemotherapy treatment.
3. Any radiotherapy treatment versus placebo, no treatment or best supportive care.
4. Any radiotherapy treatment versus any other radiotherapy treatment.

5. Any combination of radiotherapy and chemotherapy versus placebo, no treatment or best supportive care.
6. Any combination of radiotherapy and chemotherapy versus any other combination of radiotherapy and chemotherapy.

After searching was complete, the studies were organised into four specific comparisons.

1. Anti-cancer therapy versus best supportive care
2. Various types of chemotherapy versus gemcitabine
3. Gemcitabine combinations versus gemcitabine alone
4. Fluoropyrimidine combinations versus fluoropyrimidines alone

Types of outcome measures

Primary outcomes

Overall survival (OS) - survival until death from any cause

Secondary outcomes

1. Progression-free survival (PFS) - time to progression of disease on a given therapy. This is usually detected by an increase of the size or number of cancer lesions seen on a computer tomography scan (CT) using the Response Evaluation Criteria in Solid Tumours (RECIST) criteria (Nishino 2010).
2. Quality of life (QoL), measured with a validated instrument, such as the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire for cancer patients (QLQ-C30) (eortc.be/qol/).
3. Response rates - this relates to the shrinkage of a cancer in response to therapy and is usually measured on CT scans, with cancer shrinkage defined according to the RECIST criteria (Nishino 2010).
4. Grade 3/4 adverse events - adverse events are defined by the National Cancer Institute (cancer.gov) as an unfavourable and unintended sign or symptom associated with a medical treatment. Severity is graded. Grade 3 is classed as a severe or medically significant event but not immediately life threatening. Hospitalisation is indicated, and the effects limit the patients' ability to self care. Grade 4 is classed as a life-threatening event requiring urgent attention.

Search methods for identification of studies

The authors completed searches to identify all relevant published and unpublished randomised controlled studies. Articles published in any language were eligible for inclusion.

We searched the following electronic databases.

1. Cochrane Central Register of Controlled Trials (CENTRAL; 2017; Issue 6), which includes the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group Trials Register, in the Cochrane Library (searched 14 June 2017); Appendix 2.
2. MEDLINE (1946 to 14 June 2017); Appendix 3.
3. EMBASE (1980 to 14 June 2017); Appendix 4.
4. CANCERLIT (1999 to 2002). We did not undertake subsequent searches in CANCERLIT, as the database merged with MEDLINE in 2002.

To identify randomised controlled studies, we applied phases one, two and three of the Cochrane highly sensitive search strategy, as described in the *Cochrane Handbook for Reviews of Interventions* (Higgins 2011).

Electronic searches

We handsearched reference lists from studies and review articles from the electronic searching to identify further relevant studies. We also handsearched published abstracts from the following conference proceedings.

1. American Gastroenterological Association (AGA) (1994 to 2014).
2. American Society of Clinical Oncology (ASCO) (1996 to 2016).
3. American Association of Cancer Research (AACR) (1957 to 2014).
4. American Pancreatic Association (APA) (2001 to 2014).
5. Digestive Disease Week (DDW) (1994 to 2014).
6. European Cancer Conference (ECCO) (1997, 1999, 2001, 2003, 2005, 2007, 2009, 2011, 2013).
7. European Society of Medical Oncology (ESMO) (1998, 2000, 2002, 2004, 2006, 2008, 2010, 2012, 2014).
8. Joint ECCO/ESMO meeting (2009, 2010, 2011, 2013).
9. European Pancreatic Club (EPC) (2000 to 2014).
10. Gastrointestinal Cancers Symposium (2007 to 2015).
11. United European Gastroenterology Week (UEGF) (1960 to 2014).

We searched the following information resources.

1. National Cancer Institute Physician Data Query.
2. UK Co-ordinating Committee on Cancer Research.

We also searched the following study registers.

1. Australian and New Zealand Clinical Trials Registry.
2. National Research Register.
3. Medical Research Council.
4. Clinicaltrials.gov.
5. Current Controlled Trials.
6. Trialscentral.
7. Center Watch.

Searching other resources

We searched the Internet using the Google search engine. In addition, we contacted members of the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group and other experts in the field and ask them to provide details of outstanding clinical studies and any relevant unpublished materials that were known to them.

Data collection and analysis

Selection of studies

We scanned titles of studies from the electronic search, removing duplicates. Two independent review authors (VC and AN) then considered the titles and abstracts to exclude clearly ineligible studies. We retrieved the full text of all remaining records, and two review authors (VC and AN) independently assessed them against inclusion criteria for the review, resolving disagreements with adjudication by a third review author (DY) according to the process outlined in Chapter 7.2.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We documented reasons for excluding studies according to Higgins 2011.

Data extraction and management

Two independent review authors (VC and AN) extracted data, recording the inclusion/exclusion criteria, number of participants and treatment arms for each study. For survival outcomes, we recorded hazard ratios (HRs) for OS and PFS from the published data where possible. If not reported, then we extracted time-to-event data and derived the HRs using the methods described in Tierney 2007. We also extracted median survival times. For response rates and adverse events (AEs), we recorded the number of people who had experienced an event of interest and the total number of people evaluated for that event to determine the risk ratio (RR). We extracted details on QoL in a descriptive fashion as published.

Assessment of risk of bias in included studies

Two review authors used the Cochrane 'Risk of bias' tool to independently assess risk of bias in the studies, with a a third independent review author settling disputes (Higgins 2011).
We summarised the results in a 'Risk of bias summary' graph. We interpreted the results of meta-analyses in light of the findings of the risk of bias assessments.

Measures of treatment effect

For survival data, we used the HR with 95% confidence intervals (CI) and median survival times. For dichotomous data (response rates and grade 3/4 AEs), we used the risk ratio (RR) with a 95% CI. We report quality of life in a descriptive, tabulated fashion.

Unit of analysis issues

For studies that compared more than one treatment arm with a control arm in the same meta-analysis, we divided the number of participants in the control group by the number of treatment arms. There were no other unit of analysis issues.

Dealing with missing data

When we could not extract data from the text, or when statistics were missing, we attempted to contact the authors of the original article to obtain the necessary information.

Assessment of heterogeneity

We assessed heterogeneity by visual inspection of the forest plots and statistically with the Chi^2 test for homogeneity and the I^2 statistic for inconsistency.

Assessment of reporting biases

Had we included comparisons with more than 10 included studies, we would have constructed funnel plots to assess reporting bias.

Data synthesis

We used the generic inverse variance method for all meta-analyses according to the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Due to the heterogeneity of the interventions and comparators, we used a random-effects model in all instances. We performed all analyses using Review Manager 5 (RevMan 5) software (RevMan 2014), following an intention-to-treat principle when data permitted.

Subgroup analysis and investigation of heterogeneity

We did not perform any subgroup analyses.

Sensitivity analysis

We planned to perform sensitivity analyses by excluding studies at high risk of bias from the meta-analysis, but due to the small number of studies in the various comparisons, we were unable to do so.

Summary of findings table

We created four summary of findings tables describing the primary outcome measure of OS for participants. We included a narrative summary of the toxicity and QoL data in the comments section of the table. We calculated the median 12-month survival rate for the control arm to calculate the assumed risk for each comparison. We used the percentage of people alive at 12 months if it was available, otherwise we extracted the data from the Kaplan-Meier curves. We then applied the summary HR to this rate to give an anticipated effect on the rate of death with the intervention versus the comparator, expressed as number of events per 1000 people. We used the 6-month survival rate if all control arm participants had died by 12 months.
We used the GRADE approach to assess the quality of the body of evidence for the outcome OS as described by the GRADE Working Group and in the GRADE Handbook (Guyatt 2011; Schünemann 2013).

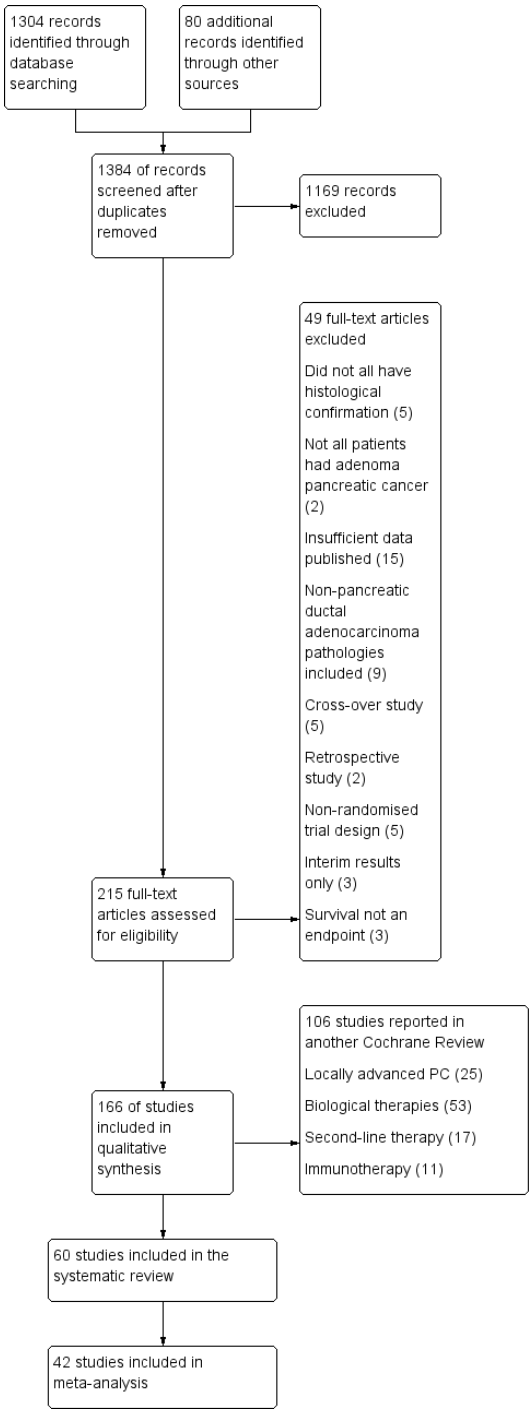
RESULTS

Description of studies

Results of the search

Figure 1 presents the study flow chart. We identified 1304 studies through electronic searches and an additional 80 studies through handsearching. After removing duplicates and studies that were clearly not eligible for inclusion, we assessed 215 full-text articles. Of these, we excluded 155, including 49 that did not meet the inclusion criteria for the review, and 106 that will be reported in a separate Cochrane Review.

Figure 1. 1 Study flow diagram.



Included studies

The original published protocol had wide inclusion criteria. Due to the large number of studies identified, we decided to split the review. Therefore, we will report studies addressing biological agents, immunotherapy, second-line therapies and local therapies for locally advanced disease separately. This report focuses on studies of either chemotherapy or radiotherapy in the advanced setting only. We included sixty studies assessing the effects on chemotherapy in advanced PC (Characteristics of included studies). We did not identify any studies that addressed radiotherapy in the advanced setting. Of the included studies, we were able to include 42 with data on 9463 participants in a meta-analysis.

We categorised these studies into five main categories.

1. Any anti-cancer treatment versus best supportive care (6 studies: Andren-Sandberg 1983; Frey 1981; Glimelius 1996; Huguier 2001,Takada 1998; Xinopoulos 2008).
2. Various types of chemotherapy versus gemcitabine (8 studies: Burris 1997; Cheverton 2004; Conroy 2011; Poplin 2009; Poplin 2013; Singhal 2014; Smith 2003; Tempero 2003).
3. Gemcitabine combination versus gemcitabine alone (7 studies addressing platinum plus gemcitabine: Colucci 2002; Colucci 2010; Heinemann 2006; Li 2004; Louvet 2005; Viret 2004; Wang 2002; 10 studies addressing fluoropyrimidine plus gemcitabine: Berlin 2002; Cunningham 2009; Di Costanzo 2005; Herrmann 2007; Lee 2017; Ohkawa 2004; Ozaka 2012; Riess 2005; Scheithauer 2003; Ueno 2013; 3 studies addressing topoisomerase inhibitors plus gemcitabine: Abou-Alfa 2006; Rocha Lima 2004; Stathopoulos 2006; 1 study addressing taxane plus gemcitabine: Von Hoff 2013; 2 studies addressing multidrug combinations including gemcitabine: Petrioli 2015; Reni 2005; and 4 studies of other agents combined with gemcitabine: Gansauge 2002; Meng 2012; Oettle 2005; Ueno 2013 - EPA study).
4. Fluoropyrimidine-based studies (4 studies: Ducreux 2004; Kovach 1974; Maisey 2002; Moertel 1979).
5. Single studies addressing unique treatment comparisons (13 studies: Afchain 2009; Boeck 2008; Bukowski 1983; Corrie 2017; Hirao 2011; Kelsen 1991; Kulke 2009; Levi 2004; Lohr 2012; Lutz 2005; Moertel 1977; Reni 2012; Topham 1991).

1 Anti-cancer therapy versus best supportive care

Six studies compared a type of anticancer therapy with best supportive care (BSC). Andren-Sandberg 1983 (N = 47) compared 5FU/CCNU plus vincristine (n = 25) versus BSC (n = 22). Frey 1981 included 152 participants with unresectable PC and assessed 5-fluorouracil (5FU) plus chloroethylcyclohexylnitrosurea (CCNU). Glimelius 1996 studied people with advanced PC or biliary tract cancer; of the 53 participants with PC, 29 were given 5FU/LV, with or without etoposide, and 24 received BSC. Huguier 2001 included 45 participants with unresectable PC; the treatment arm was cisplatin plus 5FU plus leucovorin (LV). Takada 1998 included 83 people with unresectable PC; the treatment arm was 5FU plus doxorubicin plus mitomycin C (MMC). Xinopoulos 2008 included 49 people with locally advanced PC; the treatment arm was gemcitabine.

2 Various types of chemotherapy versus gemcitabine

Eight studies compared various types of chemotherapy versus gemcitabine.

2.1 5FU versus gemcitabine

There was one study in this group involving 126 people with symptomatic advanced PC; 63 were given 5FU and 63 gemcitabine chemotherapy (Burris 1997).

2.2 FOLFIRINOX versus gemcitabine

Conroy 2011 tested FOLFIRINOX in 342 people, and Singhal 2014 in 310 people, with metastatic PC.

2.3 CO-101 versus gemcitabine

One study in 367 participants with metastatic PC compared CO-101 (lipid conjugate form of gemcitabine) versus gemcitabine (Poplin 2013).

2.4 ZD9331 versus gemcitabine

One study addressed this comparison (Smith 2003), including 55 participants with locally advanced (LA) or metastatic PC. The treatment arm was ZD9331 (thymidylate synthase inhibitor).

2.5 Fixed-dose rate gemcitabine versus standard infusional gemcitabine

Two studies were available for analysis: Poplin 2009 and Tempero 2003. Both had slightly different schedules: Poplin 2009 involved 824 participants with LA or metastatic PC and compared gemcitabine at 1000 mg/m² given over 30 min weekly for 7 out of 8 weeks then 3 out of 4 weeks versus gemcitabine given at 1500 mg/m² over 150 min 3 out of 4 weeks. Tempero 2003 involved 92 people with LA or metastatic PC and compared a dose-dense regimen of gemcitabine 2200 mg/m² weekly, 3 out of 4 weeks versus gemcitabine 1500 mg/m² given at 10 mg/m²/min, weekly, 3 out of 4 weeks.

2.6 Exatecan (DX-8951f) versus gemcitabine

One study addressed this comparison (Cheverton 2004), including 339 chemotherapy-naive participants with LA or metastatic PC. The treatment arm was exatecan (a hexacyclic, water-soluble, topoisomerase-1 inhibitor).

3 Gemcitabine combination studies

3.1 Gemcitabine plus a platinum agent versus gemcitabine alone

Seven studies compared gemcitabine plus a platinum agent versus gemcitabine alone (Colucci 2002; Colucci 2010; Heinemann 2006; Li 2004; Louvet 2005; Viret 2004; Wang 2002). Louvet 2005 used oxaliplatin, while the rest used cisplatin. All studies had gemcitabine alone as the control arm and gemcitabine plus a platinum agent in the treatment arm. Colucci 2002 (N = 107), Colucci 2010 (N = 400), Heinemann 2006 (N = 195). Li 2004 (N = 46) and Louvet 2005 (N = 326) all included people with LA or metastatic PC, while Viret 2004 (N = 83) and Wang 2002 (N = 42) included participants with stage III/IV PC.

3.2 Gemcitabine plus fluoropyrimidine versus gemcitabine alone

Ten studies compared gemcitabine plus fluoropyrimidine versus gemcitabine alone (Berlin 2002; Cunningham 2009; Di Costanzo 2005; Herrmann 2007; Lee 2017; Ohkawa 2004; Ozaka 2012; Riess 2005; Scheithauer 2003; Ueno 2013).

- Two studies assessed infusional 5FU in 567 participants with with LA/metastatic PC (Di Costanzo 2005; Riess 2005), and one study tested bolus 5FU in 322 participants with unresectable PC (Berlin 2002).
- Four studies used capecitabine in: 533 people with LA/metastatic PC (Cunningham 2009), 319 people with inoperable/metastatic PC (Herrmann 2007), 214 people with LA/metastatic PC (Lee 2017), and 83 people with metastatic PC (Scheithauer 2003).
- Two studies used oral tegafur (S1) in LA/metastatic PC: Ozaka 2012 included 112 participants and Ueno 2013 832. Ueno 2013 was a multi-armed study that compared gemcitabine versus S1 versus gemcitabine plus S1.
- One study assessed tegafur-uracil (UFT) in 19 participants (Ohkawa 2004).

3.3 Gemcitabine plus toposiomerase inhibitor versus gemcitabine alone

Three studies compared gemcitabine plus a toposiomerase inhibitor versus gemcitabine alone in participants with LA or metastatic PC (Abou-Alfa 2006; Rocha Lima 2004; Stathopoulos 2006). Rocha Lima 2004 (N = 360) and Stathopoulos 2006 (N = 130) tested irinotecan, and Abou-Alfa 2006 (N = 349) used exatecan.

3.4 Gemcitabine plus taxane versus gemcitabine alone

Only one study, in 861 participants with metastatic PC, was suitable for analysis (Von Hoff 2013).

3.5 Gemcitabine plus other combinations of chemotherapy versus gemcitabine alone

Two studies assessed gemcitabine plus other combinations of chemotherapy: Petrioli 2015 included 67 people with metastatic PC and combined oxaliplatin plus capecitabine plus gemcitabine (GEMOXEL). Reni 2005 assessed 99 people with LA/metastatic PC and used a combination cisplatin-epirubicin-5FU-gemcitabine.

3.6 Gemcitabine in combination with other agents versus gemcitabine alone

Four studies examined different agents in combination with gemcitabine: Gansauge 2002 looked at 90 participants with unresectable PC and used Ukrain (herbal medicine), Meng 2012 assessed 76 people with unresectable PC and used huachansu (Chinese herbal medicine), Oettle 2005 included 565 people with LA/metastatic PC and used pemetrexed, and Ueno 2013 - EPA study included 66 people with advanced PC and used eicosapentaenoic acid supplement (EPA).

4 Fluoropyrimidine combinations versus fluoropyrimidine alone

Four studies compared fluoropyrimidine combinations versus fluoropyrimidine alone (Ducreux 2004; Kovach 1974; Maisey 2002; Moertel 1979). Ducreux 2004 was a three-armed study in 63 participants with LA or metastatic PC, and Kovach 1974 included 82 participants with unresectable PC and compared 5FU versus bis-chloroethylnitrosurea (BCNU) alone versus 5FU plus BCNU. Maisey 2002 analysed 209 participants with LA or metastatic PC and compared 5FU versus 5FU plus mitomycin C (MMC). Moertel 1979 involved 176 people with metastatic PC and used streptozocin in the treatment arm. We were unable to include Cullinan 1985 and Cullinan 1990 in the meta-analysis, as they were multi-armed studies in which the control arm could not be split.

5 Single studies addressing unique treatment comparisons

Many studies addressed unique comparisons, so we could not group them with other studies.

- Boeck 2008 studied capecitabine plus oxaliplatin (n = 61) versus capecitabine plus gemcitabine (n = 64) versus modified gemcitabine plus oxaliplatin (n = 63).
- Kulke 2009 was a multi-armed study comparing fixed dose rate gemcitabine (n = 64) versus infusional gemcitabine plus cisplatin (n = 66) versus infusional gemcitabine plus docetaxel (n = 65) versus infusional gemcitabine plus irinotecan (n = 60).
- Afchain 2009 compared standard gemcitabine plus oxaliplatin (n = 20) versus a simplified gemcitabine plus oxaliplatin protocol (n = 37).
- Bukowski 1983 compared mitomycin C plus 5FU (MF) (n = 73) versus streptozocin plus MMC plus 5FU (SMF) (n = 72).
- Hirao 2011 looked at gemcitabine given on a three-week schedule (n = 45) versus gemcitabine given on a four-week schedule (n = 45).
- Kelsen 1991 compared streptozocin plus MMC plus 5FU (SMF) (n = 42) versus cisplatin plus ara-C plus caffeine (CAC) (n = 40).
- Levi 2004 studied 5FU given either as a constant or chronomodulated infusion, with (n = 52) versus without (n = 55) cisplatin.
- Lutz 2005 compared gemcitabine plus docetaxel (n = 49) versus cisplatin plus docetaxel (n = 47).
- Moertel 1977 looked at streptozocin plus 5FU (n = 40) versus streptozocin plus cyclophosphamide (n = 48).
- Reni 2012 compared capecitabine plus cisplatin plus gemcitabine plus docetaxel (PDXG) (n = 53) versus capecitabine plus cisplatin plus gemcitabine plus epirubicin (PEXG) (n = 48).
- Finally, Topham 1991 looked at epirubicin (n = 32) versus 5FU plus epirubicin plus MMC (n = 30).

Excluded studies

We excluded 155 studies. Other Cochrane Reviews will cover the 53 studies addressing biological agents, the 11 assessing immunotherapies, the 25 looking at local therapies in locally advanced disease and the 17 focusing on second-line therapies. We excluded the remaining 49 studies for the following reasons.

- Five studies did not mandate histological confirmation in the study protocol (Abdel Wahab 1999; Johnson 2001; Mallinson 1980; Nakai 2012; Palmer 1994).
- Two studies included some participants who did not have advanced stage PC (Andersen 1981; Lygidakis 1995).
- Fifteen studies did not provide sufficient data (Baker 1976; Cohen 2010; GITSG 1985; Kim 2011; Oberic 2011; Queisser 1979; Ramanathan 2011; Sakata 1992; Senzer 2006; Shapiro 2005; Sultana 2009; Sun 2011; Tagliaferri 2013; Trouilloud 2012; Van Cutsem 2013).
- Nine studies included people with non-PDAC histologies (Ducreux 2002; GITSG 1988; Lokich 1979; Mizuno 2013; Moertel 1981; Oster 1986; Schein 1978; Sudo 2014; Takada 1994).
- Five were cross-over studies (Berglund 2010; Dahan 2010; Heinemann 2013 (GUT); Horton 1981; Javle 2011).
- Two were retrospective studies (Nio 2010; Reni 2009).
- Five had a non-randomised study design (Bukowski 1993; Gong 2007; Mitry 2006; Yongxiang 2001; Zemskov 2000).
- Three studies published only interim results (GITSG 1979; Topham 1993; Tuinmann 2008).
- Survival was not an endpoint in three studies (Ardalan 1988; Meyer 2008; Schmitz-Winnenthal 2013).

Risk of bias in included studies

Figure 2 and Figure 3 summarise the risk of bias of all included studies. Many studies did not publish sufficient details to make a judgement on selection bias. Of those that did, all were judged to be at a low risk of bias because they used centralised randomisation techniques. Only one study was double-blind and placebo controlled (Meng 2012), and we judged it to be at low risk for performance bias. We assessed the remainder of the studies to be at a high risk of bias. We considered studies that used OS as the primary endpoint to be at a low risk for detection bias (Abou-Alfa 2006; Berlin 2002; Cheverton 2004; Colucci 2010; Conroy 2011; Cullinan 1985; Cullinan 1990; Cunningham 2009; Frey 1981; Gansauge 2002; Glimelius 1996; Heinemann 2006; Herrmann 2007; Huguier 2001; Kulke 2009; Lee 2017; Levi 2004; Li 2004; Lohr 2012; Louvet 2005; Oettle 2005; Poplin 2009; Poplin 2013; Riess 2005; Rocha Lima 2004; Singhal 2014; Smith 2003; Stathopoulos 2006; Takada 1998; Tempero 2003; Ueno 2013; Von Hoff 2013; Xinopoulos 2008). If tumour assessments were needed to assess the primary outcome (e.g. RR or PFS), we assigned a low risk of bias only if an independent reviewer or by a blinded radiologist conducted the assessments (Ducreux 2004; Reni 2005; Reni 2012; Scheithauer 2003). We judged all other studies to be at a high risk of bias. We deemed studies that reported the intention-to-treat population (all participants randomised on the study regardless if they received any treatment or not) to be at a low risk of attrition bias, while we considered studies that did not report all randomised patients to be at a high risk of bias (Bukowski 1983; Cullinan 1985; Ducreux 2004; Kelsen 1991; Louvet 2005; Moertel 1977; Ozaka 2012). We detected selective reporting bias in only two studies (Bukowski 1983; Moertel 1979), the former because only the participants with measurable disease were reported in detail and the latter because the toxicity data were not comprehensively reported.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

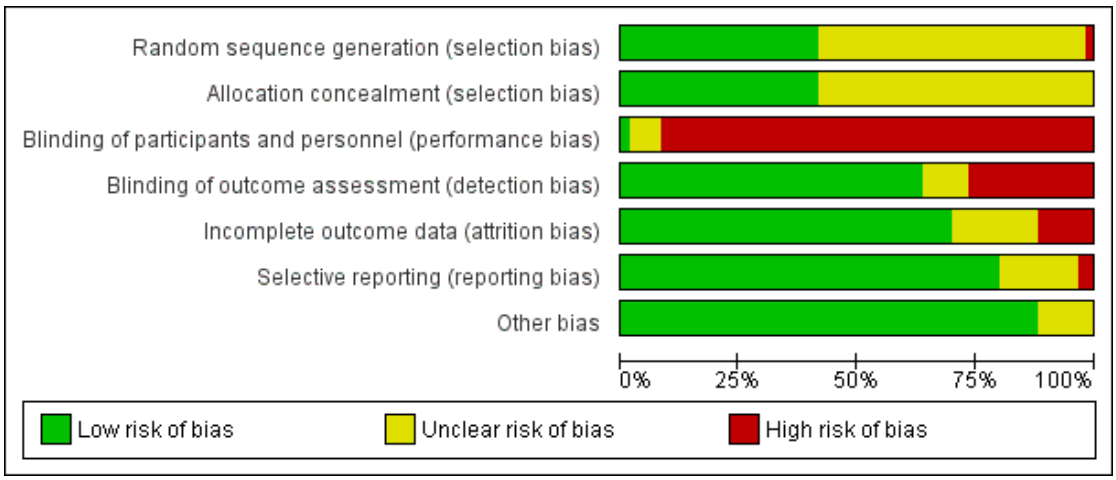
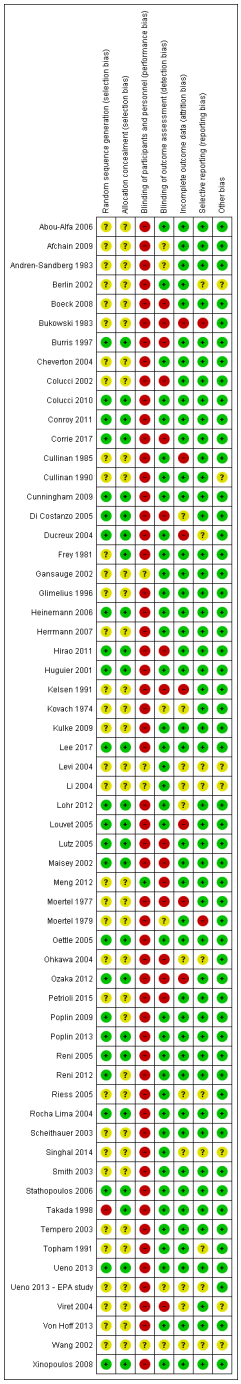


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



We describe details of the risk of bias of the included studies in the Effects of interventions section.

Effects of interventions

See: **Summary of findings for the main comparison** Anti-cancer therapy versus best supportive care for advanced pancreatic cancer; **Summary of findings 2** Various types of chemotherapy versus gemcitabine for advanced pancreatic cancer; **Summary of findings 3** Gemcitabine combinations versus gemcitabine alone for advanced pancreatic cancer; **Summary of findings 4** Fluoropyrimidine combinations versus fluoropyrimidine alone for advanced pancreatic cancer

1 Anti-cancer therapy versus best supportive care (BSC)

Six studies addressed any anti-cancer therapy versus best supportive care (Andren-Sandberg 1983; Frey 1981; Glimelius 1996; Huguier 2001, Takada 1998; Xinopoulos 2008). The main potential source of bias in these studies came from their non-blinded design; however, we did not feel this significantly affected the results for overall survival (Figure 2; Figure 3). In three studies the risk of selection bias was unclear due to insufficient reporting (Andren-Sandberg 1983; Glimelius 1996; Xinopoulos 2008).

Four of the six studies provided data in sufficient detail to derive hazard ratios (HR) for OS, with 298 people analysed. Pooled data of four studies in 298 people showed an HR of 1.08 (95% CI 0.88 to 1.33; Analysis 1.1). There was no statistical heterogeneity between studies (I^2 = 0%). Median survival ranged from 3.0 to 8.6 months in the anti-cancer therapy group and 2.5 to 7.0 months in the BSC group. The difference in median survival times ranged from 0.9 months in favour of BSC to 3.5 months in favour of anticancer therapy (Table 1).

Three studies reported quality of life (Table 1). Andren-Sandberg 1983 did not find a difference in Karnofsky performance status (KPS) score. In Glimelius 1996, the EORTC QLQ-C30 results favoured the treatment group; however, there was a high rate of dropouts in the later time points. The third study (Xinopoulos 2008) demonstrated a superior QoL (EORTC QLQ-C30) in the gemcitabine group during the first month (P = 0.028), but there was no difference in months two to four, and the BSC group had a superior QoL in months five (P = 0.010) and six (P = 0.0003).

Trials either did not study or did not adequately report PFS and response rates, with the exception of Takada 1998. This study reported complete or partial response in one person in the anti-cancer therapy group versus none in the BSC group.

With respect to adverse effects or toxicity in the anti-cancer therapy group, Frey 1981 reported that 31% of participants experienced at least one toxicity, with the most common being gastrointestinal. Huguier 2001 reported that the most common toxicities were haematological and gastrointestinal (each seen in 15% of people). Takada 1998 showed that the commonest grade 3/4 adverse events (AEs) were anorexia, which occurred in in 15/28 participants and nausea/vomiting, in 5/24 participants. Haematological toxicities were the most common in Xinopoulos 2008, with leucopenia occurring in 81.5% of participants.

2 Various types of chemotherapy versus gemcitabine

Eight studies compared various types of chemotherapy versus gemcitabine (Burris 1997; Cheverton 2004; Conroy 2011; Poplin 2009; Poplin 2013; Singhal 2014; Smith 2003; Tempero 2003), analysing a total of 1844 participants in six treatment subgroups. Due to the heterogeneity of the investigational agents, we did not pool the results. Five studies provided PFS data (Burris 1997; Conroy 2011; Poplin 2009; Singhal 2014; Smith 2003). The main potential source of bias in these studies came from the non-blinded study design. We were unable to comprehensively assess selection bias in some studies (Cheverton 2004; Singhal 2014; Smith 2003; Tempero 2003), and there was a high risk of detection bias noted in Burris 1997, Poplin 2013 and Smith 2003; however, we did not consider that it significantly affected results for overall survival.

2.1 5FU versus gemcitabine

Burris 1997 (N = 126) was the only study to compare 5FU with gemcitabine, showing an HR for OS of 1.69 (95% CI 1.26 to 2.27, P < 0.001; Analysis 2.1). The difference in median survival was 1.3 months in favour of gemcitabine (Table 2). The analysis of PFS showed an HR of 1.47 (95% CI 1.12 to 1.92, P = 0.005; Analysis 2.2). There were better outcomes for both OS and PFS with gemcitabine, and this group also showed more treatment response (0 in the 5FU arm versus 3 in the gemcitabine arm; risk ratio (RR) 0.14, 95% CI 0.01 to 2.71, P = 0.19). On the other hand, the gemcitabine arm showed a higher risk of most types of grade 3/4 toxicity: anaemia (0 in the 5FU arm versus 6 events in the gemcitabine arm: RR 0.08, 95% CI 0.0 to 1.34, P = 0.08; Analysis 2.5); neutropenia (3 events versus 16 events: RR 0.19, 95% CI 0.06 to 0.61, P = 0.006; Analysis 2.6); thrombocytopenia (1 event versus 6 events: RR 0.17, 95% CI 0.02 to 1.34, P = 0.09; Analysis 2.7); and nausea (3 events versus 8 events: RR 0.38, 95% CI 0.10 to 1.35, P = 0.13; Analysis 2.8). Diarrhoea was the exception (3 events in the 5FU arm versus 1 event in the gemcitabine arm: RR 3.00, 95% CI 0.32 to 28.07, P = 0.34; Analysis 2.9). Clinical benefit was superior in the gemcitabine arm compared with the 5FU arm, with a higher clinical benefit response (23.8% versus 4.8%), shorter median time to clinical benefit response (3 weeks versus 7 weeks) and longer duration of clinical benefit response (18 weeks versus 13 weeks) (Table 2).

2.2 FOLFIRINOX versus gemcitabine

Two studies in 652 people assessed the effects of FOLFIRINOX versus gemcitabine (Conroy 2011; Singhal 2014). The FOLFIRINOX group generally outperformed gemcitabine, showing improved OS (HR 0.51, 95% CI 0.43 to 0.60, P < 0.001; I^2 = 29%; Analysis 2.1), longer median survival (4.3 months versus 3.4 months; Table 2), longer PFS (HR 0.46, 95% CI 0.38 to 0.57, N = 652, P < 0.001; I^2 = 0%; Analysis 2.2), longer time to degradation of QoL (HR 0.46, 95% CI 0.35 to 0.61, P < 0.001; I^2 = 0%; Analysis 2.3; Table 2), and more treatment responses (54 responses versus 16 responses: RR 3.38, 95% CI 2.01 to 5.65, P < 0.001; Analysis 2.4). On the other hand, FOLFIRINOX also showed more grade 3/4 haematological toxicity for: anaemia (13 events versus 10 events: RR 1.30, 95% CI 0.59 to 2.88, P = 0.52; Analysis 2.5), neutropenia (75 events versus 35 events: RR 2.14, 95% CI 1.52 to 3.01, P < 0.001: Analysis 2.6), and thrombocytopenia (15 events versus 6 events: RR 2.50, 95% CI 0.99 to 6.29, P = 0.05; Analysis 2.7).

2.3 CO-101 versus gemcitabine

Poplin 2013 tested CO-101 in 367 people. Outcomes were not different for participants in either arm. The HR for OS was 1.07 (95% CI 0.86 to 1.34, P = 0.68; Analysis 2.1). Median survival was similar in both groups, 5.2 months for CO-101 and 6.0 months for gemcitabine (Table 2). The trial did not report PFS. The RR for response was 0.67 (95% CI 0.43 to 1.04, P = 0.08; Analysis 2.4). We could neither prove nor rule out differences in various types of grade 3/4 toxicity (Analysis 2.5; Analysis 2.6; Analysis 2.7).

2.4 ZD9331 versus gemcitabine

Smith 2003 compared ZD9331 versus gemcitabine in 55 people. There was no difference in survival for participants in either arm. The HR for OS was 0.86 (95% CI 0.42 to 1.76, P = 0.68; Analysis 2.1) and for PFS, it was 0.78 (95% CI 0.46 to 1.32, P = 0.36; Analysis 2.2). Median survival was 5.0 months and 3.6 months, respectively (Table 2). The RR for response was 0.42 (95% CI 0.04 to 4.33, P = 0.46, Analysis 2.4). We could neither prove nor rule out differences in various types of grade 3/4 toxicity (Analysis 2.5; Analysis 2.6; Analysis 2.7; Analysis 2.8; Analysis 2.9).

2.5 Fixed dose rate gemcitabine (FDR-gem) versus standard infusional gemcitabine

Two studies assessed the effects of FDR-gem in 644 people (Poplin 2009; Tempero 2003). OS was improved in the FDR-gem group (HR 0.79, 95% CI 0.66 to 0.94, P = 0.009, I^2 = 0%; Analysis 2.1). In the two studies, median survival was 1.3 months and 3.0 months longer in the FDR-gem group (Table 2). Only Poplin 2009 (N = 552) reported PFS, finding no significant difference between groups (HR 0.88, 95% CI 0.77 to 1.01, P = 0.06, Analysis 2.2). There were more responses seen in the FDR-gem group (30 responses versus 19 responses), but this was not significant (RR 1.59, 95% CI 0.91 to 2.79, P = 0.10; Analysis 2.4). Analyses also showed more grade 3/4 toxicity in the FDR-gem group: anaemia (62 events versus 35 events: RR 1.79, 95% CI 1.22 to 2.63, P = 0.003; Analysis 2.5), neutropenia (183 events versus 100 events: RR 1.85, 95% CI 1.53 to 2.23, P < 0.001; Analysis 2.6), thrombocytopenia (107 events versus 39 events: RR 2.77, 95% CI 1.99 to 3.86, P < 0.001; Analysis 2.7), and nausea (37 events versus 25 events: RR 1.52, 95% CI 0.94 to 2.46, P = 0.09; Analysis 2.8). Diarrhoea was the exception (5 events versus 12 events: RR 0.44, 95% CI 0.16 to 1.23, P = 0.12; Analysis 2.9).

2.6 Exatecan (DX-8951f) versus gemcitabine

Cheverton 2004 demonstrated that exatecan had an inferior effect on OS compared with gemcitabine (HR 1.27, 95% CI 0.96 to 1.68, P = 0.093). Median survival in the two respective groups was 5 months versus 6.6 months; 6-month survival rates were 44.1% versus 51.1%; and 12-month survival rates, 17.9% versus 22.1%. There were insufficient data to include this study in the PFS analysis; however, median PFS was 2.8 months versus 4.4 months. Response rates were available in 276 people (1 response versus 10 responses: RR 0.10, 95% CI 0.01 to 0.78, P = 0.03; Analysis 2.4). Toxicity data were available in 330 people and showed that both agents performed similarly for grade 3/4 anaemia (10 events versus 10 events: RR 1.00, 95% CI 0.43 to 2.34, P = 1.00; Analysis 2.5), neutropenia (32 events versus 32 events: RR 1.00, 95% CI 0.64 to 1.55, P = 1.00; Analysis 2.6), thrombocytopenia (12 events versus 16 events: RR 0.75, 95% CI 0.37 to 1.54, P = 0.43; Analysis 2.7) and nausea (7 events versus 4 events: RR 1.75, 95% CI 0.52 to 5.86, P = 0.36; Analysis 2.8). QoL analysis showed that time to worsening of clinical benefit was longer in the gemcitabine arm, with 3.7 months to worsening of pain in the exatecan group versus 7.9 months in the gemcitabine group (P = 0.049). The gemcitabine group also showed a longer time to worsening KPS (3.4 months versus 4.6 months; P = 0.011) and to weight loss (2.3 months versus 3.8 months; P = 0.020). Global and pancreas-specific QoL questionnaires failed to elicit significant differences between the two groups. (Table 2).

3 Gemcitabine combination studies

We identified six subgroups in this comparison, and we pooled results in the subgroups only and not overall.

3.1 Gemcitabine plus a platinum agent versus gemcitabine alone

The HR for OS based on six studies in 1140 participants showed no difference between the treatment groups, 0.94 (95% CI 0.81 to 1.08, P = 0.38; Analysis 3.1). There was some statistical heterogeneity (I^2 = 15%). Four studies in 1015 participants reported

PFS and showed some improvement in the gemcitabine + platinum group, giving an HR of 0.80 (95% CI 0.68 to 0.95, P = 0.01; Analysis 3.2). There was high statistical heterogeneity (I^2 = 46%). The median survival times are listed in Table 3.

All studies (N = 1186) reported response rates favouring the combined treatment arm (100 responses versus 67 responses: RR 1.48, 95% CI 1.11 to 1.98, P = 0.007, I^2 = 0%; Analysis 3.3). Data from all studies (N = 1156) contributed to meta-analyses for grade 3/4 anaemia (62 events in the gemcitabine plus platinum group versus 45 events in the gemcitabine alone group: RR 1.41, 95% CI 0.87 to 2.31, P = 0.17; Analysis 3.4) and neutropenia (122 events versus 97 events: RR 1.34, 95% CI 0.90 to 1.97, P = 0.14; Analysis 3.5), with similar rates between groups. For other adverse events, data in 1110 participants from six studies showed more grade 3/4 AEs in the combination group: thrombocytopenia (78 events versus 35 events: RR 1.96, 95% CI 1.00 to 3.84, P = 0.05; Analysis 3.6) and nausea (52 events versus 22 events: RR 2.28, 95% CI 1.40 to 3.71, P = 0.001; Analysis 3.7), although for diarrhoea, we could not rule out the possibility that these results were due to chance (23 events versus 14 events: RR 1.48, 95% CI 0.62 to 3.53, P = 0.38; Analysis 3.8).

Four studies reported QoL data. Colucci 2010 measured QoL using the EORTC QLQ C30 questionnaires in multiple areas. Scores were from a scale of 0-100. The mean difference (MD) between baseline scores and scores after 4 weeks of treatment were measured. The study did not find a significant MD in global QoL scores between those taking gemcitabine alone (MD 6.20) versus gemcitabine plus platinum (MD 0.09), P = 0.07. Heinemann 2006 found no difference between the treatment groups in either the Spitzer index or pain intensity score, nor did Viret 2004 find any difference in the EORTC-QLQ C30 results between treatment groups. Li 2004 reported finding no difference in clinical benefit but better quality of life outcomes in the gemcitabine alone arm (3.8 months versus 5.6 months in QoL-adjusted life months gained P < 0.001; Table 3).

In the one study that we could not include in the meta-analysis (Li 2004), there were no differences between the control and treatment groups for OS (4.6 months versus 5.6 months) or PFS (2.8 months versus 2.8 months; Table 3).

The main source of bias identified in these studies was their non-blinded study design. There was a high risk of attrition bias in Louvet 2005 and insufficient details in Viret 2004 and Wang 2002 reports to make a comprehensive assessment of risk of bias.

3.2 Gemcitabine plus fluoropyrimidine versus gemcitabine alone

Ten studies reported OS in 2718 participants. A benefit for adding fluoropyrimidine to gemcitabine was detected (HR 0.88, 95% CI 0.81 to 0.95, P = 0.001; Analysis 3.1), with no statistical heterogeneity (I^2 = 0%). Eight studies reported PFS in 2608 participants and abenefit for the combination arm was also shown (HR 0.79, 95% CI 0.72 to 0.87, P < 0.001). There was moderate statistical heterogeneity with an I^2 of 34% (Analysis 3.2). The median survival times ranged from 5.4 months to 8.8 months in the gemcitabine alone group and from 6.7 months to 13.7 months in the combination group (Table 3). Ueno 2013 was a multi-armed study that compared gemcitabine alone versus S1 alone versus gemcitabine plus S1. The analysis in this review includes only the gemcitabine alone and gemcitabine plus S1 arms.

Nine studies reported response rates in 2176 participants. Responses were more common in the combination group (228 responses in the combination group versus 124 responses in the gemcitabine alone group), RR 1.78 (95% CI 1.29 to 2.47, P < 0.001; Analysis 3.3), with high statistical heterogeneity (I^2 = 52%). Eight studies reported grade 3/4 AEs in 2158 participants in the combination group versus the gemcitabine alone group, with the combination treatment group tending to experience more AEs: anaemia (97 events versus 89 events: RR 1.11, 95% CI 0.84 to 1.45, P = 0.47; Analysis 3.4), neutropenia (353 events versus 234 events: RR 1.53, 95% CI 1.34 to 1.74, P < 0.001; Analysis 3.5), thrombocytopenia (122 events versus 81 events: RR 1.48, 95% CI 1.00 to 2.18, P = 0.05; Analysis 3.6), nausea (61 events versus 47 events: RR 1.27, 95% CI 0.87 to 1.84, P = 0.22; Analysis 3.7), and diarrhoea (55 events versus 23 events: RR 2.16, 95% CI 1.34 to 3.47, P = 0.002; Analysis 3.8).

Five studies recorded QoL data. Cunningham 2009 used the Memorial pain assessment card, EORTC QLQ C30 and ESPAC QoL questionnaires. Di Costanzo 2005 recorded mean disturbed days and the mean days the person would like to cancel treatment. Herrmann 2007 used a linear-analogue self-assessment (LASA) indicators for clinical benefit response (CBR). Scheithauer 2003 recorded a combination of pain, KPS and weight, and Ueno 2013 recorded quality adjusted life years (QALYs). Cunningham 2009 did not find any significant differences in QoL between treatment groups. Likewise, Di Costanzo 2005 did not show any differences in QoL outcomes. Herrmann 2007 did not show a difference in either CBR or QoL (measured by LASA); however, in those people who did have a CBR, the duration was longer in the combination arm (9.5 weeks versus 6.5 weeks, P < 0.02). Scheithauer 2003 demonstrated an improvement in pain response and KPS but not weight gain in the combination arm, and Ueno 2013 showed a statistically significant improvement in QALYs in the combination group: 0.401 versus 0.525, P < 0.001 (Table 3).

The main source of bias identified in this comparison was due to the non-blinded study design. The risk of selection bias was unclear in Berlin 2002; Herrmann 2007; Ohkawa 2004; Riess 2005 and Scheithauer 2003, but we did not consider that this significantly affected the results.

3.3 Gemcitabine plus topoisomerase inhibitor versus gemcitabine alone

Three studies reported OS data in 839 participants, giving an HR

of 1.01 (95% CI 0.87 to 1.16, P = 0.92; Analysis 3.1), indicating no difference between groups. There was no heterogeneity (I^2 = 0%). Two studies reported similar PFS in 709 participants (HR 0.91, 95% CI 0.78 to 1.07, P = 0.26, I^2 = 0%; Analysis 3.2). The median survival times were very similar between the two groups (Table 3). All studies reported response rates, with data on 729 participants (49 responses in the combined treatment group versus 22 responses in the gemcitabine alone group: RR 1.50, (95% CI 0.92 to 2.46, P = 0.11, I^2 = 0%; Analysis 3.3). The combination arms were shown to be more toxic with data for grade 3/4 AEs in 797 participants: anaemia (41 events versus 37 events: RR 1.09, 95% CI 0.72 to 1.66, P = 0.68; Analysis 3.4), neutropenia (132 events versus 88 events: RR 1.54, 95% CI 1.04 to 2.30, P = 0.03; Analysis 3.5), thrombocytopenia (63 events versus 31 events: RR 2.28, 95% CI 0.97 to 5.36, P = 0.06; Analysis 3.6), nausea (36 events versus 23 events: RR 1.55, 95% CI 0.94 to 2.55, P = 0.09; Analysis 3.7) and diarrhoea (36 events versus 6 events: RR 3.47, 95% CI 0.74 to 16.33, P = 0.12; Analysis 3.8).

Rocha Lima 2004 was the only study to record QoL data (FACT-Hep questionnaire) and reported no significant differences between the two groups (Table 3).

The main source of bias identified in this comparison was due to the non-blinded study design, but we did not consider that this affected the results.

3.4 Gemcitabine plus taxane versus gemcitabine alone

Von Hoff 2013 was the only study in this group, and trialists analysed all 861 participants for OS, PFS and response rate. A benefit in survival outcomes was demonstrated in the combination arm. For OS, the HR was 0.72 (95% CI 0.62 to 0.84; P < 0.001; Analysis 3.1), and for PFS, HR was 0.69 (95% CI 0.58 to 0.82; P < 0.001; Analysis 3.2). The median survival time was 8.5 months in the combination group versus 6.7 months in the gemcitabine control (Table 3). There was a higher response rate in the combination arm (99 responses versus 30 responses: RR 3.29, 95% CI 2.24 to 4.84, P < 0.001; Analysis 3.3). Data on grade 3/4 AEs were available for 793 participants and overall, toxicity was more common in the combination arm: anaemia (53 events versus 48 events: RR 1.06, 95% CI 0.73 to 1.52, P = 0.76; Analysis 3.4), neutropenia (153 events versus 103 events: RR 1.42, 95% CI 1.16 to 1.75, P < 0.001; Analysis 3.5), thrombocytopenia (52 events versus 36 events: RR 1.38, 95% CI 0.93 to 2.07, P = 0.11; Analysis 3.6), neuropathy (70 events versus 3 events: RR 22.35, 95% CI 7.10 to 70.40, P < 0.001; Analysis 3.9) and fatigue (70 events versus 27 events: RR 2.48, 95% CI 1.63 to 3.79, P < 0.001; Analysis 3.10). The studies did not report on QoL.

Corrie 2017 was a unique study that we could not include in this analysis, addressing nab-paclitaxel plus gemcitabine versus the same agents given in a sequential dosing schedule. Here the standard arm had similar results to the nab-paclitaxel plus gemcitabine arm of Von Hoff 2013, with a median survival of 7.9 months, median PFS of 4.0 months and response rate of 33%.

Likewise, we could not include Lohr 2012 in the analysis as it was a multi-armed study. It showed that overall survival for the gemcitabine alone arm was 6.8 months, compared to 8.1 months in combination with liposomal paclitaxel 11 mg/m², 8.7 months in combination with liposomal paclitaxel 22 mg/m² and 9.3 months in combination with liposomal paclitaxel 44 mg/m². When comparing each combination arm with gemcitabine alone the HRs all crossed the line of null effect: for concomitant doses of 11 mg/m²: HR 0.93 (95% CI 0.60 to 1.43); for 22 mg/m²: HR 0.69 (95% CI 0.44 to 1.07); and for 44 mg/m²: HR 0.66 (95% CI 0.43 to 1.03). PFS in the gemcitabine alone group was 2.7 months compared with each of the combination arms: 4.1 months, 4.6 months and 4.4 months (11 mg/m², 22 mg/m² and 44 mg/m², respectively). When comparing each experimental arm with gemcitabine alone for PFS, the HRs were 0.84 (95% CI 0.44 to 1.28), 0.58 (95% CI 0.38 to 0.90) and 0.74 (95% CI 0.49 to 1.13), respectively. The number of responses were similar in all groups (14%, 14%, 14% and 16%, respectively). Neutropenia and fatigue were the commonest AEs and occurred at similar rates across the four groups. The trials did not report QoL. Toxicity was more common in the combination arm with a dose dependent increase in thrombocytopenia, chills and pyrexia.

Although there were insufficient details to make an assessment of selection bias, overall we assessed the study as being at low risk of bias, the main source being due to the non-blinded study design, which we considered to not affect the results.

3.5 Gemcitabine plus other combinations of chemotherapy versus gemcitabine alone

Two studies reported OS data on 166 participants which showed improved survival in the combination group (HR 0.55, 95% CI 0.39 to 0.79, P = 0.001; Analysis 3.1). There was some statistical heterogeneity (I^2 = 24%). Both studies reported PFS and again showed a benefit to the combination arm, with an HR of 0.43 (95% CI 0.30 to 0.62, P < 0.001, I^2 = 17%; Analysis 3.2). Median survival times were only available for Petrioli 2015, who reported that the combined treatment group survived for a median of 11.9 months versus 7.1 months in the gemcitabine alone group (Table 3). Only Petrioli 2015 reported response rates in 67 participants (12 responses versus 6 responses: RR 1.94, 95% CI 0.83 to 4.56, P = 0.13; Analysis 3.3). The same study reported grade 3/4 AEs. Although AEs were more common in the combination arm, the small number of events makes it difficult to assess the real difference between the arms: anaemia (6 events versus 3 events: RR 1.94, 95% CI 0.53 to 7.13, P = 0.32; Analysis 3.4), neutropenia (8 events versus 4 events: RR 1.94, 95% CI 0.65 to 5.83, P = 0.24; Analysis 3.5), thrombocytopenia (10 events versus 5 events: RR 1.94, 95% CI 0.74 to 5.07, P = 0.11; Analysis 3.6) and nausea (5 events versus 0 events: RR 10.69, 95% CI 0.61 to 185.91, P = 0.10; Analysis 3.7).

Both studies reported QoL data. Petrioli 2015 used the EORTC QLQ C30 and McGill Melzack questionnaires, and Reni 2005 used the EORTC-QLQ Pan 26 questionnaire. Petrioli 2015 showed that global QoL was improved in the combined treatment group at two and four months. Reni 2005 stated that the sample size was insufficient to obtain statistical power to detect differences between the control and treatment groups. However, the treatment group had better average emotional functioning, overall QoL, cognitive measures, pain, fatigue, indigestion, dyspnoea, appetite loss and flatulence, while sexual function and body image were better in the control group (Table 3).

Petrioli 2015 did not publish enough data to make a full assessment of selection bias and had a high risk of performance and detection bias. Reni 2005 was a non-blinded study but otherwise had a low risk of bias.

3.6 Gemcitabine plus other agent(s) versus gemcitabine alone

Four studies assessed OS in 767 participants, with no differences in survival detected (HR 0.79, 95% CI 0.56 to 1.10, P = 0.16; I^2 = 62%; Analysis 3.1). Only Meng 2012 reported PFS data in 76 people, with no differences seen, HR 1.05 (95% CI 0.68 to 1.62, P = 0.83; Analysis 3.2). Median survival times in the gemcitabine group ranged from 5.2 months to 9.7 months and in the combination group from 5.2 months to 10.4 months (Table 3). Three studies reported response rates in 691 participants (61 responses versus 22 responses: with RR 3.66, 95% CI 1.04 to 12.82, P = 0.04; Gansauge 2002; Meng 2012; Oettle 2005; Analysis 3.3). Three studies reported haematological toxicity data for grade 3/4 events in 688 participants revealing more anaemia in the combination arm (Meng 2012; Oettle 2005; Ueno 2013 - EPA study): anaemia (49 events versus 12 events: RR 3.58, 95% CI 1.93 to 6.62, P < 0.001; Analysis 3.4), neutropenia (140 events versus 45 events: RR 2.02, 95% CI 0.88 to 4.66, P = 0.10; Analysis 3.5), and thrombocytopenia (55 events versus 23 events: RR 1.41, 95% CI 0.45 to 4.39, P = 0.56; Analysis 3.6). Four studies reported on nausea in 748 participants (17 events versus 11 events: RR 1.25, 95% CI 0.48 to 3.26, P = 0.64; Analysis 3.7).

Two studies reported on QoL: Meng 2012 used the FACT-G and MD Anderson Symptom Inventory questionnaires, and Oettle 2005 used the EORTC QLQ-C30 questionnaire. Meng 2012 did not find a difference in either of the scales used (FACT-G and MD Anderson Symptom Inventory questionnaire) at eight weeks. Oettle 2005 showed that people in the gemcitabine alone group had lower financial difficulties and better physical and cognitive functioning, but the combination arm had lower pain scores. There was no clear trend in QoL scores between the treatment groups, however (Table 3).

There was an unclear risk of selection bias in Gansauge 2002 and Meng 2012 due to insufficient details being published. Ueno 2013 - EPA study did not provide enough details to perform a comprehensive assessment.

4 Fluoropyrimidine combinations versus fluoropyrimidine alone

Four studies reported OS in 491 participants receiving either fluoropyrimidine combinations or fluoropyrimidine alone with no differences in survival detected (HR 0.84, 95% CI 0.61 to 1.15, P = 0.27; Analysis 4.1). There was high statistical heterogeneity with an I^2 of 66%. Ducreux 2004, which studied 5FU with or without oxaliplatin, showed a large benefit in the treatment group in contrast to the other three studies, which did not show much benefit with the combination arms. Only two studies reported PFS in 255 participants, and there were no differences (HR 0.52, 95% CI 0.19 to 1.38, P = 0.19; Analysis 4.2), again, with large statistical heterogeneity (I^2 = 89%). Median survival times ranged from 3.7 months to 6.5 months in the combination group and from 3.4 months to 5.25 months in the 5FU group (Table 4). All four studies reported response rates, but there were no differences between arms (32 responses versus 24 responses: RR 1.18, 95% CI 0.52 to 2.68, P = 0.10; I^2 = 52%; Analysis 4.3). Two studies (N = 255) reported rates of grade 3/4 anaemia, neutropenia, thrombocytopenia, nausea, and diarrhoea (Ducreux 2004; Maisey 2002). There were no significant differences between groups in: anaemia (8 events versus 11 events: RR 0.48, 95% CI 0.06 to 3.62, P = 0.16; Analysis 4.4); neutropenia (7 events versus 0 events: RR 5.70, 95% CI 0.73 to 44.46, P = 0.10; Analysis 4.5); thrombocytopenia (5 events versus 3 events: RR 1.40, 95% CI 0.34 to 5.80, P = 0.65; Analysis 4.6); nausea (7 events versus 5 events, RR 1.06, 95% CI 0.32 to 3.53, P = 0.93; Analysis 4.8); or diarrhoea (6 events versus 6 events: RR 0.92, 95% CI 0.31 to 2.78, P = 0.89; Analysis 4.9). Maisey 2002 reported similar rates of grade 3/4 fatigue in both arms (26 events versus 30 events: RR 0.91, 95% CI 0.58 to 1.43, P = 0.68; Analysis 4.7).

One study recorded QoL data (Maisey 2002), using the EORTC-QLQ C30 questionnaire, which did not demonstrate a difference between the two groups at baseline, 12 weeks or 24 weeks (Table 4).

The main source of bias was in the non-blinded study design. We assessed both Ducreux 2004 and Kovach 1974 as being at high risk of attrition bias, and this may have affected the results.

5 Single studies addressing unique treatment comparisons

Ten studies addressed unique comparisons that could not be categorised under the above-mentioned comparisons (Table 5).

Boeck 2008 showed that capecitabine plus gemcitabine had superior median survival (9.0 months) and response rate (25%) compared with 8.1 months/13% in the capecitabine/oxaliplatin group and 6.9 months/13% in the gemcitabine/oxaliplatin group.

Haematological AEs were more common in the gemcitabine-containing regimens.

Kulke 2009 showed a similar OS in all four treatment groups, ranging from 6.4 months to 7.1 months and response rates of 12% to 14%. AEs were similar across treatment arms, with neutropenia and fatigue being the most common.

Afchain 2009 found that a simplified gemcitabine/oxaliplatin regimen was superior to a standard gemcitabine/oxaliplatin regimen with an OS of 7.6 months versus 3.2 months and response rate of 27% versus 10%. Peripheral neuropathy was more common in the simplified arm, however.

Bukowski 1983 did not demonstrate a difference in OS for streptozocin/MMC/5FU (SMF) versus MMC/5FU (18 weeks versus 17 weeks); however, there was an increase in response rate of 34% versus 8%. There was more gastrointestinal and renal toxicity in the SMF arm.

Hirao 2011 showed a slight increase in OS for the three-week schedule of gemcitabine versus the four-week schedule (250 days versus 206 days), but there was a similar response rate (17.1% versus 14.2%). Thrombocytopenia was more common in the four-week schedule.

Kelsen 1991 found that the SMF arm had a longer OS than the cisplatin/ara-C/caffeine arm (10 months versus 5 months), but a similar response rate (10% versus 6%). Nausea and vomiting were more common in the caffeine-containing arm.

Levi 2004 showed that adding cisplatin to 5FU increased OS (8.3 months versus 5.4 months), but there was no difference between the continuous versus the chronomodulated arms (6.1 months versus 6.7 months). Cisplatin increased the rates of haematological AEs, and the chronomodulated regimen increased rates of mucositis.

Lutz 2005 did not demonstrate any striking differences between gemcitabine/docetaxel and cisplatin/docetaxel (OS 7.0 months versus 7.5 months); however, febrile neutropenia was more common in the cisplatin containing arm.

Moertel 1977 showed a slightly increased OS in the streptozocin/5FU arm compared with streptozocin/cyclophosphamide (13 weeks versus 9 weeks), with the cyclophosphamide arm experiencing more haematological AEs.

Reni 2012 showed a similar OS between capecitabine/cisplatin/gemcitabine/docetaxel (PDXG) and capecitabine/cisplatin/gemcitabine/epirubicin (PEXG) (10.7 months versus 11 months); however, there was a higher partial response rate in the PDXG group (58% versus 33%). The PEXG arm had more neutropenia.

Topham 1991 found a slightly higher one-year survival rate in the 5FU/epirubicin/MMC arm compared with epirubicin alone (23.2% versus 15.4%), and the AEs were similar in both arms.

ADDITIONAL SUMMARY OF FINDINGS [*Explanation*]

Various types of chemotherapy versus gemcitabine for advanced pancreatic cancer

Person or population: advanced pancreatic cancer
Setting: first-line therapy
Intervention: various types of chemotherapy
Comparison: gemcitabine

Outcomes	Anticipated risk of death* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments	Toxicity and QoL
	Risk with gemcitabine	Risk with various types of chemotherapy					
Overall survival - 5FU	Study population		HR 1.69 (1.26 to 2.27)	126 (1 RCT)	⊕⊕⊕◯ Moderate[a]	Only 1 study	More toxicity was seen in the gemcitabine arm. Clinical benefit was improved in the gemcitabine arm
	825 per 1000	948 per 1000 (889 to 981)					
Overall survival - FOLFIRINOX	Study population		HR 0.51 (0.43 to 0.60)	652 (2 RCTs)	⊕⊕⊕◯ Moderate[b]	-	More toxicity was seen in the FOLFIRINOX arm. Longer time to degradation of QoL in FOLFIRINOX arm
	794 per 1000	554 per 1000 (494 to 613)					
Overall survival - Fixed dose rate gemcitabine	Study population		HR 0.79 (0.66 to 0.94)	644 (2 RCTs)	⊕⊕⊕⊕ High	-	More toxicity in the fixed-dose rate arm. QoL was not tested
	880 per 1000	812 per 1000 (753 to 863)					
Overall survival - CO-101	Study population		HR 1.07 (0.86 to 1.34)	367 (1 RCT)	⊕⊕⊕◯ Moderate[c]	Only 1 study	Toxicity was similar in both arms, QoL was not tested
	854 per 1000	872 per 1000 (809 to 924)					

Overall survival - ZD9331	Study population		HR 0.86 (0.42 to 1.76)	55 (1 RCT)	⊕⊕⊕◯ Moderate[a,c]	Only 1 study	Toxicity was similar in both arms, QoL was not tested
	560 per 1000	506 per 1000 (292 to 764)					
Overall survival - Exatecan	Study population		HR 1.27 (0.96 to 1.68)	339 (1 RCT)	⊕⊕⊕◯ Moderate[c]	Only 1 study	Toxicity was similar in both arms, QoL was superior in the gemcitabine arm
	776 per 1000	851 per 1000 (763 to 919)					

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **HR**: hazard ratio; **RCT**: randomised controlled trial.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a] Small sample size; optimal information size not met.
[b] Moderate statistical heterogeneity.
[c] Confidence interval includes both benefit and harm.

Gemcitabine combinations versus gemcitabine alone for advanced pancreatic cancer

Person or population: advanced pancreatic cancer
Setting: first-line therapy
Intervention: gemcitabine combinations
Comparison: gemcitabine alone

Outcomes	Anticipated risk of death* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments	Toxicity and QoL
	Risk with gemcitabine alone	Risk with gemcitabine combinations					
Overall survival - Gemcitabine plus platinum agent	Study population 705 per 1000	683 per 1000 (628 to 733)	HR 0.94 (0.81 to 1.08)	1140 (6 RCTs)	⊕⊕◯◯ Low[a,b]	-	More toxicity in the combination arm with no differences shown in QoL
Overall survival - Gemcitabine plus fluoropyrimidine	Study population 690 per 1000	648 per 1000 (613 to 679)	HR 0.89 (0.81 to 0.97)	2718 (10 RCTs)	⊕⊕⊕⊕ High	-	More toxicity in the combination arm. 2 studies showed no difference in QoL, 2 studies showed an improved QoL in the combination arm
Overall survival - Gemcitabine plus topoisomerase inhibitor	Study population 800 per 1000	803 per 1000 (753 to 845)	HR 1.01 (0.87 to 1.16)	839 (3 RCTs)	⊕⊕⊕⊕ High	-	More toxicity in the combination arm. In 1 study, QoL was not different between the 2 arms
Overall survival - Gemcitabine plus taxane	Study population 779 per 1000	663 per 1000 (608 to 719)	HR 0.72 (0.62 to 0.84)	861 (1 RCT)	⊕⊕⊕⊕ High	1 study only	More toxicity in the combination arm. QoL not measured

Overall survival - Gemcitabine plus other combinations of chemotherapy	Study population		HR 0.55 (0.39 to 0.79)	166 (2 RCTs)	⊕⊕◯◯ Low[c,d,e]	-	Toxicity measured in 1 study and was not different. QoL was shown to be improved in the combination arms in both studies
	850 per 1000	648 per 1000 (523 to 777)					
Overall survival - Gemcitabine plus other agent(s)	Study population		HR 0.79 (0.56 to 1.10)	767 (4 RCTs)	⊕⊕◯◯ Low[b,f]		There was an increase in anaemia in the combination arm. 2 studies measured QoL and it was similar in both treatment arms
	825 per 1000	748 per 1000 (624 to 853)					

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **HR**: hazard ratio; **RCT**: randomised controlled trial.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a] Two studies were in abstract form and could not have full assessment completed.
[b] Confidence interval includes both benefit and harm.
[c] One study did not publish sufficient details to make a full assessment.
[d] There was moderate statistical heterogeneity.
[e] Optimal information size not met.
[f] High statistical heterogeneity which is likely due to the difference in agents used in the treatment arms.

Fluoropyrimidine combinations versus fluoropyrimidine alone for advanced pancreatic cancer

Person or population: advanced pancreatic cancer
Setting: first line therapy
Intervention: fluoropyrimidine combinations
Comparison: fluoropyrimidine alone

Outcomes	Anticipated risk of death* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Toxicity and QoL
	Risk with fluoropyrimidine alone	Risk with fluoropyrimidine combinations				
Overall survival	Study population		HR 0.84 (0.61 to 1.15)	491 (4 RCTs)	⊕⊕◯◯ Low[a,b]	Toxicity was not different between the 2 treatment arms. QoL was measured in 1 study and showed an improvement in the combination arm
	838 per 1000	783 per 1000 (671 to 877)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **HR**: hazard ratio; **RCT**: randomised controlled trial.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a] High statistical heterogeneity.
[b] Confidence interval includes both benefit and harm.

DISCUSSION

Summary of main results

1 Anti-cancer therapy versus best supportive care

We could neither prove nor rule out a survival benefit for anti-cancer therapy versus BSC alone (moderate-quality evidence due to imprecision; Summary of findings for the main comparison). This is in contrast to the previous version of this review, which found a benefit in the odds for death at both 6 months (OR 0.37, 95% CI 0.25 to 0.57, P < 0.001) and 12 months (OR 0.46, 95% CI 0.25 to 0.84, P = 0.01). Due to the new protocol used in this study, we excluded two studies that had featured in the previous review because they included people without histological confirmation (Mallinson 1980; Palmer 1994); this is the likely cause of these discrepant results. The differences in median survival were modest and ranged from 0.9 months in favour of BSC to 3.5 months in favour of anti-cancer therapy (Table 1).

There is evidence for improved QoL with the use of anti-cancer therapy in one study (Glimelius 1996), with Xinopoulos 2008 showing an early benefit that was not sustained after month 5.

Readers should interpret these results with caution, as the included studies span over 30 years, and Xinopoulos 2008 was the only study to use contemporary chemotherapy regimens. As it is unlikely that further studies will be conducted using BSC as the control arm, additional randomised data showing the effects of contemporary chemotherapy over BSC in the first-line setting may never be generated.

2 Various types of chemotherapy versus gemcitabine

The one study addressing gemcitabine versus 5FU chemotherapy, Burris 1997, showed inferior outcomes for OS (HR 1.69; P = 0.004), PFS (HR 1.47; P = 0.005) and QoL with the 5FU arm. Summary of findings 2 shows a rating of moderate-quality evidence due to only one small study being available for analysis. These results demonstrate that using gemcitabine reduces the risk of death by 41% and progression by 32% compared with 5FU therapy. The absolute improvement in OS is modest at just over one month. Gemcitabine may result in more grade 3/4 AEs. There is an improvement in QoL (clinical benefit response).

The analysis of two studies comparing FOLFIRINOX versus gemcitabine demonstrated an improvement in OS (HR 0.51; P < 0.001), PFS (HR 0.46; P < 0.001) and response rate (RR 3.38; P < 0.001) but also significantly more neutropenia and thrombocytopenia (Conroy 2011; Singhal 2014). There was improved QoL. Summary of findings 2 demonstrates the moderate quality of evidence rating based on inconsistency. These results suggest that FOLFIRINOX reduces the risk of death by 49%, reduces the risk of progression by 54% and triples the rate of response compared with gemcitabine. The absolute survival gains are still modest, with OS in the gemcitabine alone arm ranging from 6.8 months to 7.4 months and in the FOLFIRINOX arms between 10.8 months to 11.1 months.

The two studies that assessed the effects of giving gemcitabine at a fixed dose rate showed an improvement in OS (HR 0.79; P = 0.009) but also more haematological toxicity (Poplin 2009; Tempero 2003). Granted, the 'standard' gemcitabine arms differed between the two studies, but the study using a more intense control arm (gemcitabine 2200 mg/m² weekly) still found superiority in the FDR-gem arm. Summary of findings 2 details a high quality of evidence rating. This analysis suggests that using FDR-gem reduces the risk of death by 21%; however, the absolute survival gains are again small, with OS in the standard infusional gemcitabine arm ranging from 4.9 months to 5.0 months and in the FDR-gem arm from 6.2 months to 8.0 months.

The studies comparing exatecan, CO-101 and ZD9331 to gemcitabine did not show a survival benefit (Cheverton 2004; Poplin 2013; Smith 2003). None of these studies showed a difference in toxicity and in exatecan, analyses showed QoL to be superior in the gemcitabine arm. We rated each comparison as having moderate-quality evidence due to imprecision (Summary of findings 2).

3 Gemcitabine combination studies

3.1 Gemcitabine plus a platinum agent versus gemcitabine alone

The analysis of seven studies has shown that the combination of gemcitabine with a platinum agent did not significantly improve OS (HR 0.94; P = 0.38) but may improve PFS (HR 0.80; P = 0.01) (Colucci 2002; Colucci 2010; Heinemann 2006; Louvet 2005; Viret 2004; Wang 2002). This equates to a reduction in the risk of progression of 20%. Summary of findings 3 shows that the quality of evidence in this analysis was low, due to two studies being in abstract form and not publishing sufficient data to make a full assessment, along with imprecision. These results are in keeping with the findings of the previous review, which found a benefit in 6-month mortality (OR 0.59, P = 0.001) but not 12-month mortality. We were not able to include all the studies from the previous review (Li 2004 did not publish sufficient data); however, we included two additional studies (Colucci 2010; Viret 2004). The addition of platinum improved response rates but increased thrombocytopenia and nausea. There were no significant differences found in QoL between the control and treatment arms in the people tested. This suggests that while adding platinum increases side effects, this does not translate into a worse QoL. The median survival times were similar in the two groups (Table 3).

3.2 Gemcitabine plus fluoropyrimidine versus gemcitabine alone

The analysis of 10 studies shows that adding a fluoropyrimidine agent can improve OS (HR 0.88; P = 0.001), PFS (0.79; P < 0.001) and response rate (RR 1.78; P < 0.001), but at the cost of increased rates of neutropenia and diarrhoea (Berlin 2002; Cunningham 2009; Di Costanzo 2005; Herrmann 2007; Lee 2017; Ohkawa 2004; Ozaka 2012; Riess 2005; Scheithauer 2003; Ueno 2013). Summary of findings 3 show that the quality of evidence is high. This shows that the addition of 5FU reduces the risk of death by 12%, reduces the risk of progression by 21% and nearly doubles the rate of response, but it also increases toxicity. Two studies did not report any differences in QoL with the addition of a fluoropyrimidine agent; however, two studies did report an improvement, with Scheithauer 2003 showing less pain and Ueno 2013 showing an improvement in QALYs. The previous version of this review did not find significant benefits for adding fluoropyrimidine to gemcitabine; however, that version analysed only 5 studies, compared to the 10 studied here. Because this analysis included both intravenous and oral fluoropyrimidine agents, these results must be interpreted with caution. Moreover, two studies used S1 (Ozaka 2012; Ueno 2013), and one study used UFT (Ohkawa 2004), agents that have not been well studied in non-Asian populations. The absolute improvement in OS is small, ranging from 5.4 months to 8.8 months in the gemcitabine alone arm and 6.7 months to 13.7 months in the combination arm (Table 3).

3.3 Gemcitabine plus topoisomerase inhibitor versus gemcitabine alone

The analysis of three studies shows that the addition of a topoisomerase inhibitor to gemcitabine does not significantly improve OS (HR 1.01; P = 0.92) or PFS (HR 0.91; P = 0.26) (Abou-Alfa 2006; Rocha Lima 2004; Stathopoulos 2006). Response rates were also not significantly improved (RR 1.50; P = 0.11); however, neutropenia did. Only one study measured QoL and failed to find any differences between the two groups. The median survival times were similar in the two groups (Table 3).

We assessed the quality of evidence as high (Summary of findings 3).

3.4 Gemcitabine plus taxane versus gemcitabine alone

Our search yielded only one study that we could analyse in this category (Von Hoff 2013), and it found that adding nab-paclitaxel to gemcitabine significantly improved OS (HR 0.72; P < 0.001), PFS (HR 0.69; P < 0.001) and response rates (RR 3.29; P < 0.001). Summary of findings 3 show that the quality of evidence is high; however, there is only one study. This demonstrates that the addition of nab-paclitaxel to gemcitabine reduces the risk of death by 28%, reduces the risk of progression by 31% and more than triples the rate of response. There is an increased risk of neutropenia, neuropathy and fatigue, and QoL was not measured. Although there is only one study in this analysis, there was also another study, Corrie 2017, which we could not include; it used gemcitabine plus nab-paclitaxel as the control group and published similar OS, PFS and response data.

3.5 Gemcitabine plus other combinations of chemotherapy versus gemcitabine alone

The two studies analysed showed that combining gemcitabine with multiple other agents improves OS (HR 0.55; P = 0.001) and PFS (HR 0.43; P < 0.001) (Petrioli 2015; Reni 2005). Only one study reported response rates, which were not different between groups. Likewise, one study reported similar incidence of AEs. QoL was improved in both studies. Summary of findings 3 shows the low rating for quality of evidence due to one study not publishing enough data to make a full assessment and because of inconsistency. Given that only one study reported response rates and grade 3/4 AEs, the numbers of events in these analyses are small, and the conclusions that we can draw here are limited. This analysis suggests that the use of combination therapies containing gemcitabine may reduce the risk of death by 45% and reduce the risk of progression by 57%; however, we cannot make any assessment regarding the rates of side effects. There may be an improvement in QoL. Just one study reported median survival times, showing OS in the gemcitabine arm to be 7.1 months compared with 11.9 months in the combination arm (Table 3).

Multi-drug combinations including gemcitabine may be effective in improving survival outcomes, and given the positive results of the Conroy 2011 study, which uses FOLFIRINOX, the findings add weight to the argument that intensive chemotherapy has a place in the treatment of PC.

3.6 Gemcitabine plus other agent(s) versus gemcitabine alone

This group contains studies that did not fall into any of the other pooled analyses. The four studies analysed here are heterogenous in terms of the agents used (Gansauge 2002; Meng 2012; Oettle 2005; Ueno 2013 - EPA study). The analysis shows that OS is not significantly different in the combination arm. Three studies show improved response rates but also increased anaemia. There was high statistical heterogeneity seen in both survival analyses, which is likely to be accounted for by the varied agents used. QoL was not significantly different in the two studies that reported this outcome. Median survival times were longer in the Gansauge 2002 study but otherwise very similar (Table 3).

These data need to be interpreted with caution, as the studies used a wide range of agents. The results for Ukrain in Gansauge 2002 are highly provocative and may warrant further study in larger numbers, supported by a meta-analysis across different cancer types (Ernst 2005). We assessed the quality of evidence as low due to imprecision and inconsistency (Summary of findings 3).

4 Fluoropyrimidine combinations versus fluoropyrimidine alone

This analysis showed that pooling data from studies that added an agent to 5FU did not result in a significant benefit in OS (HR 0.84; P = 0.27) or PFS (0.52; P = 0.19) compared to 5FU alone (Ducreux 2004; Kovach 1974; Maisey 2002; Moertel 1979). However, in these two analyses, there was high statistical heterogeneity (I^2 = 66% and 89%, respectively), likely due to the range of agents tested. Three studies used fairly outdated chemotherapies (BCNU, MMC and streptozocin), whereas one study used oxaliplatin (Ducreux 2004). This study accounts for most of the heterogeneity seen, as it found a statistically significant benefit in both OS and PFS in contrast to the other studies. Response rates were not significantly improved (RR 1.18; P = 0.69), again with high statistical heterogeneity that was mainly due to the Kovach 1974 study, testing BCNU and reporting higher responses in the 5FU alone group. Grade 3/4 AEs were not significantly different between the two groups. Only Maisey 2002 assessed QoL, demonstrating an improvement in dyspnoea.

The conclusions that we can draw from this analysis are limited. It seems that from the results of the Ducreux 2004 study, oxaliplatin plus 5FU is an active combination compared with 5FU alone and does not measurably increase side effects.

The quality of evidence was assessed as low due to imprecision and statistical heterogeneity (Summary of findings 4).

Overall completeness and applicability of evidence

To our knowledge, this review contains a complete review of all the available evidence up until the censor date. We have made every attempt to conduct the analysis in a clinically relevant way in order to fulfil the objective of assisting patients and clinicians in decision-making.

Quality of the evidence

Two review authors independently assessed the risk of bias of the individual studies using the GRADE criteria, and we tabulate this information in Figure 2, Figure 3 and the 'Summary of findings' tables. Only four subgroup comparisons were of high quality, whereas the remainder of the comparisons provided moderate- or low-quality evidence. This was mainly due to inconsistency and small sample sizes. Given PC is a rare condition which is commonly seen in the elderly, recruiting to clinical studies is incredibly difficult. In addition, recent large scale sequencing studies have revealed the marked genetic heterogeneity in PC, which is likely to contribute to the inconsistent effects seen between studies (Bailey 2016). This should guide future studies and encourage stratified study design.

Potential biases in the review process

In order to reduce the potential biases in the review process, two separate review authors independently evaluated studies and extracted data, resolving disputes with adjudication by a third review author. We did not identify any other potential biases.

Agreements and disagreements with other studies or reviews

Unlike the previous version of this review (Yip 2009), we were unable to replicate the benefit seen for anti-cancer therapy versus best supportive care alone. As discussed in the main text, this was mainly due to the fact we were unable to include all the previously analysed studies due to lack of available time-to-event data.

We have added to the scope and results of the previous review by widening the inclusion criteria and have been able to provide wider recommendations.

AUTHORS' CONCLUSIONS

Implications for practice

Currently there is no way of rationally selecting the 'best' chemotherapy regimen for people with pancreatic cancer. For decades, gemcitabine has been the gold standard; however, there are now several more efficacious options that treating clinicians can consider. The treatment choice must be tailored to the person, taking into account the their performance status and the side effect profiles of the chemotherapy agents. The results of this analysis shows that in advanced pancreas cancer:

1. based on one study, gemcitabine is superior to 5FU alone, reducing the risk of death and progression and improving QoL;

2. compared to gemcitabine alone, multi-drug combinations improve survival outcomes and response rates in PC. FOLFIRINOX, GEMOXEL and gemcitabine/cisplatin/epirubicin and 5FU are active regimens. These data suggest that in people who are fit, multi-drug regimens may be appropriate, but the potential for increased toxicity must be taken into account;

3. gemcitabine given using a fixed dose rate schedule improves overall survival but increases toxicity compared with standard dosing;

4. gemcitabine plus platinum-based chemotherapy does not improve OS but does improve PFS and response rates;

5. gemcitabine plus fluoropyrimidine-based chemotherapy improves survival and response rates, albeit by a small amount;

6. based on one study, gemcitabine plus taxane improves survival outcomes and response rates but increases toxicity.

Implications for research

The results of this analysis suggest that using multi-drug regimens for advanced PC has the potential to improve outcomes. This must be weighed against the increase in toxicity. Currently, there are no effective biomarkers to predict in whom an aggressive approach is warranted, and this should be an area of further research. In addition, this analysis shows that there are many different chemotherapies which are beneficial in this disease, but currently there is no way of rationally selecting the 'best' chemotherapy regimen. Biomarker development has the potential to stratify people early in their disease course, inform clinical study design and avoid exposing people to ineffective chemotherapy.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Abou-Alfa 2006

Methods	Randomised phase III trial
Participants	Study was conducted in North America in 349 participants with locally advanced/metastatic pancreatic adenocarcinoma. The mean age in the gemcitabine + exatecan group was 63 years, and the mean age in gemcitabine group 62.3 years. Previous radiotherapy for locally advanced disease was allowed. 174 received gemcitabine. 175 received gemcitabine + exatecan
Interventions	Gemcitabine: 1000 mg/m² 7/8 weeks, then 3/4 weeks Gemcitabine + exatecan: gemcitabine 1000 mg/m² and exatecan 2 mg/m² days 1 and 8 every 3 weeks
Outcomes	Overall survival Time to progression Safety Quality of life Response rate Progression-free survival
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details given
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Overall survival primary endpoint
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in the survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods are reported in the results

Abou-Alfa 2006 (*Continued*)

Other bias	Low risk	No indication of other bias

Afchain 2009

Methods	Randomised phase II study
Participants	Study was conducted in France. 57 participants with metastatic adenocarcinoma without prior chemotherapy or radiotherapy. 20 participants received gemcitabine/oxaliplatin and 37 participants received simplified gemcitabine/oxaliplatin. Mean age was 66.6 years in the gemcitabine/oxaliplatin group and 64.9 years in the simplified gemcitabine/oxaliplatin group
Interventions	Gemcitabine/oxaliplatin: gemcitabine 1000 mg/m² on day 1, oxaliplatin 100 mg/m² day 2, every 2 weeks Simplified regimen: gemcitabine 1000 mg/m² day 1, oxaliplatin 100 mg/m² day 1, every 2 weeks
Outcomes	Progression-free survival Overall survival Response rate
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient details published
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods are reported in the results
Other bias	Low risk	No indication of other bias

Andren-Sandberg 1983

Methods	Randomised study
Participants	Study was conducted in Sweden. 47 participants with inoperable pancreatic cancer less than 71 years old. 22 received best supportive care and 25 received 5FU + CCNU + vincristine. The mean age was 58 years in the treatment group and 60 years in the best supportive care group
Interventions	5FU: 500 mg orally days 2-5 CCNU: 40 mg/m² orally days 2 + 3 Vincristine: 1 mg/m² day 1 Given every 6 weeks
Outcomes	Survival Quality of life
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient details published
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in the survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods are reported in the results
Other bias	Low risk	No indication of other bias

Berlin 2002

Methods	Randomised phase III trial
Participants	Study was conducted in North America. 322 participants with unresectable pancreatic ductal adenocarcinoma. Were allowed to have received adjuvant gemcitabine if completed > 6 months prior. Were allowed to have received radiotherapy if completed more than 4 weeks prior. 162 received gemcitabine. 160 received gemcitabine + 5-fluorouracil

Berlin 2002 (*Continued*)

	(5FU). The median age in the gemcitabine + 5FU group was 65.8 years and 64.3 years in the gemcitabine group
Interventions	Gemcitabine 1000 mg/m² 3/4 weeks Gemcitabine + 5FU: gemcitabine as above + 5FU 600 mg/m²/week bolus given 3/4 weeks
Outcomes	Overall survival Time to progression Response rate
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details given
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in survival analysis
Selective reporting (reporting bias)	Unclear risk	Insufficient details published
Other bias	Unclear risk	No indication of other bias

Boeck 2008

Methods	Randomised phase II trial
Participants	Study was conducted in Germany. 190 participants with advanced pancreatic cancer. 61 received capecitabine + oxaliplatin (CapOx), 64 received capecitabine + gemcitabine (CapGem) and 63 received gemcitabine + oxaliplatin (mGemOx). The median age was 62 years (CapOx), 63 years (CapGem) and 63 years (mGemOx) in the treatment groups
Interventions	CapOx: capecitabine 1000 mg/m² orally twice daily, days 1-14 every 3 weeks + oxaliplatin 130 mg/m² day 1 CapGem: capecitabine 825 mg/m² orally twice daily, days 1-14 every 3 weeks + gemc-

Boeck 2008 (*Continued*)

	itabine 1000 mg/m² days 1 + 8 mGemOx: gemcitabine 1000 mg/m² days 1 + 8 + oxaliplatin 130 mg/m² day 8
Outcomes	Progression-free survival after 3 months Overall survival Overall response rate Clinical benefit response Ca19.9 response
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	High risk for primary endpoint (PFS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat population reported for survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods are reported in the results
Other bias	Low risk	No indication of other bias

Bukowski 1983

Methods	Randomised study
Participants	Study was conducted in North America. 145 participants with inoperable pancreatic adenocarcinoma with no previous chemotherapy or radiotherapy. 73 were given mitomycin C + 5FU (MF), 72 were given streptozocin, mitomycin C and 5FU (SMF). The median age for participants in the SMF arm were 59 years and 59.5 years for those with measurable and non-measurable disease respectively. In the MF arm the median age was 60 years and 62 years for those with measurable and non-measurable disease respectively

Bukowski 1983 (*Continued*)

Interventions	MF 'good risk' - mitomycin C 20 mg/m² on day 1 + 5FU 1000 mg/m² days 1-4 and 29-32 every 56 days MF 'poor risk' - mitomycin C 15 mg/m² on day 1 with the same 5FU regimen above SMF 'good risk' - streptozocin 400 mg/m² days 1-4 and 29-32, mitomycin C 15 mg/m² on day 1 and 5FU 1000 mg/m² days 1-4 and 29-32, every 56 days SMF 'poor risk' - mitomycin given at 10 mg/m² day 1, with streptozocin and 5FU given as above
Outcomes	Overall survival Performance-free survival Response rate
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Primary outcome measure not stated, no intention-to-treat analysis
Incomplete outcome data (attrition bias) All outcomes	High risk	Only participants with measurable disease were included in survival analysis
Selective reporting (reporting bias)	High risk	Participants with non-measurable disease not comprehensively reported
Other bias	Low risk	No indication of other bias

Burris 1997

Methods	Randomised trial
Participants	Study was conducted in the United States and Canada. 126 participants with advanced, symptomatic pancreas cancer with stabilised pain. 63 received 5-fluorouracil (5FU). 63 received gemcitabine. Median age in the 5FU arm was 61 years and 62 years in the gemcitabine arm

Burris 1997 (*Continued*)

Interventions	5FU 600 mg/m² weekly Gemcitabine 1000 mg/m² 7/8 weeks then 3/4 weeks
Outcomes	Clinical benefit Response rate Overall survival Progression-free survival Safety
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization of patients with stabilized pain to treatment with either gemcitabine or 5-FU occurred immediately before starting study drug treatment and was performed at a central location"
Allocation concealment (selection bias)	Low risk	"Randomization of patients with stabilized pain to treatment with either gemcitabine or 5-FU occurred immediately before starting study drug treatment and was performed at a central location"
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Treatment was single blind. The study drug was not blinded to the investigator, because a rash was a potential side effect of treatment with both 5-FU and gemcitabine"
Blinding of outcome assessment (detection bias) All outcomes	High risk	High risk for the primary endpoint (clinical benefit)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled participants included in survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods are reported in the results
Other bias	Low risk	No indications of other bias

Cheverton 2004

Methods	Randomised phase III study
Participants	Study was conducted in Europe. 339 participants with locally advanced or metastatic pancreatic cancer and no prior chemotherapy. 170 received gemcitabine. 169 received exatecan. Of these 330 (165 vs 165) received treatment. Median age was not published

Cheverton 2004 (*Continued*)

Interventions	Gemcitabine 1000 mg/m² given 3/4 then 7/8 weeks Exatecan 0.5 mg/m² daily for 5 days every 3 weeks
Outcomes	Overall survival Response rates Time to tumour progression Quality of life
Notes	Abstract only

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient details published to make an assessment
Allocation concealment (selection bias)	Unclear risk	Insufficient details published to make an assessment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled participants included in survival analysis (intention-to-treat population reported)
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods are reported in the results
Other bias	Low risk	No indications of other bias

Colucci 2002

Methods	Randomised phase II trial
Participants	Study was conducted in Italy. 107 participants with locally advanced, metastatic pancreatic ductal adenocarcinoma with measurable disease and no prior therapy. 54 received gemcitabine. 53 received gemcitabine + cisplatin. The median age in the gemcitabine + cisplatin arm was 60 years, and it was 63 years in the gemcitabine alone arm
Interventions	Gemcitabine 1000 mg/m² weekly × 7, then 2 weeks rest. Then 3/4 weeks Gemcitabine + cisplatin: gemcitabine as above. Cisplatin 25 mg/m² days 1, 8, 15, 29, 36, 42 then 2 weeks rest. Then gemcitabine and cisplatin days 1, 8, 15 every 4 weeks

Colucci 2002 (*Continued*)

Outcomes	Overall response rate Time to progression (assessed at week 7 and then every 2 cycles of treatment) Overall survival
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details given
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Time to progression was the primary endpoint
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis was reported for the primary endpoint
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods are reported in the results
Other bias	Low risk	No indication of other bias

Colucci 2010

Methods	Randomised phase III trial
Participants	Study conducted in Italy. 400 participants with unresectable or metastatic pancreatic ductal adenocarcinoma with no prior chemotherapy. 199 received gemcitabine. 201 received gemcitabine + cisplatin. The median age of participants was 63 years
Interventions	Gemcitabine: 1000 mg/m² 7/8 weeks then 3/4 weeks Gemcitabine + cisplatin: gemcitabine as above. Cisplatin 25 mg/m² days 1, 8, 15, 29, 36, 42 then 1 week rest. Then cisplatin 25 mg/m² days 1, 8, 15 every 4 weeks
Outcomes	Overall survival Progression-free survival Overall response rate Toxicity Clinical benefit

Colucci 2010 (*Continued*)

	Quality of life
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomly assigned to standard arm or experimental arm in a 1:1 ratio. Telephone random assignment was performed centrally (Clinical Trials Unit, National Cancer Institute, Napoli, Italy), by a computer-driven minimization procedure"
Allocation concealment (selection bias)	Low risk	"Patients were randomly assigned to standard arm or experimental arm in a 1:1 ratio. Telephone random assignment was performed centrally (Clinical Trials Unit, National Cancer Institute, Napoli, Italy), by a computer-driven minimization procedure"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods are reported in the results
Other bias	Low risk	No indication of other bias

Conroy 2011

Methods	Randomised phase II/III study
Participants	Study was conducted in France. 342 participants with measurable, metastatic pancreatic ductal adenocarcinoma and no previous chemotherapy. 171 received gemcitabine. 171 received 5-fluorouracil (5FU) + oxaliplatin + irinotecan (FOLFIRINOX). The median age was 61 in both treatment groups
Interventions	Gemcitabine 1000 mg/m² 7/8 weeks then 3/4 weeks FOLFIRINOX: 5FU bolus 400 mg/m², 5FU CI 2400 mg/m² over 46 hours + leucovorin 400 mg/m² + oxaliplatin 85 mg/m² + irinotecan 180 mg/m² every 2 weeks

Conroy 2011 (*Continued*)

Outcomes	Overall survival Progression-free survival Response rate Safety Quality of life	
Notes	-	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization was performed centrally in a 1:1 ratio with stratification according to center, performance status (0 vs. 1), and primary tumor localization"
Allocation concealment (selection bias)	Low risk	"Randomization was performed centrally in a 1:1 ratio with stratification according to center, performance status (0 vs. 1), and primary tumor localization"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint and other endpoints. "Independent review of CT scans was performed"
Incomplete outcome data (attrition bias) All outcomes	Low risk	"All analyses were performed on an intention-to-treat-basis"
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods are reported in the results
Other bias	Low risk	No indications of other bias

Corrie 2017

Methods	Randomised phase II study
Participants	Study was conducted in the UK. 146 participants with metastatic pancreatic adenocarcinoma with no prior treatment. 75 received standard concomitant nab-paclitaxel and gemcitabine and 71 received sequential administration of nab-paclitaxel and gemcitabine. Median age was 66 years
Interventions	Standard regimen: nab-paclitaxel 125 mg/m² and gemcitabine 1000 mg/m² given immediately after each other on days 1, 8, 15 of a 4 week cycle Sequential regimen: nab-paclitaxel 125 mg/m² on days 1, 8, 15 and gemcitabine 1000

Corrie 2017 (*Continued*)

	mg/m² on days 2, 9, 16 of a 4-week cycle
Outcomes	Progression-free survival Safety Response rate Overall survival Quality of life
Notes	Abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Web based randomisation system with stratified block randomisation
Allocation concealment (selection bias)	Low risk	No evidence of selection bias
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	High for the primary endpoint (PFS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in the survival analyses
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods are reported in the results
Other bias	Low risk	None found

Cullinan 1985

Methods	Randomised trial
Participants	Study was conducted in North America. 305 participants with unresectable or metastatic pancreatic or gastric adenocarcinoma. Of the participants with pancreatic cancer, 50 received 5-fluorouracil (5FU), 44 received 5FU + doxorubicin (FA). 50 received 5FU + doxorubicin + mitomycin C (FAM). The majority of participants in the study were between 50 to 69 years old
Interventions	5FU: 500 mg/m² days 1-5 week 1, 4 and 8, then every 5 weeks FA: 5FU 400 mg/m² days 1-4 + doxorubicin 40 mg/m² day 1 week 1, 4 and 8, then every 5 weeks FAM: 5FU 600 mg/m² days 1, 8, 29, 36 + doxorubicin 30 mg/m² days 1 and 29 +

Cullinan 1985 (*Continued*)

	mitomycin C 10 mg/m² day 1, every 8 weeks
Outcomes	Overall survival Progression-free survival Response rate Toxicity Symptom control
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	High risk	10 participants excluded from survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods are reported in the results
Other bias	Low risk	No indication of other bias

Cullinan 1990

Methods	Randomised phase III trial
Participants	Study was conducted in North America. 187 participants with measurable, metastatic ductal or undifferentiated pancreatic cancer with no prior chemotherapy. 64 received 5-fluorouracil (5FU). 61 received 5FU + cyclophosphamide + methotrexate + vincristine (Mallison regimen). 59 received 5FU + doxorubicin + cisplatin (FAP). Median age for the 5FU, Mallinson and FAP arm was 60, 62 and 62 years respectively
Interventions	5FU: 500 mg/m²/day for 5 days every 5 weeks Mallinson: 5FU 270 mg/m²/day days 1-5 + cyclophosphamide 160 mg/m² days 1 + 5 + methotrexate 11 mg/m² days 1 + 4 + vincristine 0.7 mg/m² days 2 + 5 then maintenance with 5FU 350 mg/m² days 1-5 + mitomycin C 3.5 mg/m² days 1-5 every 5 weeks

Cullinan 1990 (*Continued*)

	FAP: 5FU 300 mg/m²/day days 1-5 + doxorubicin 40 mg/m² day 1 + cisplatin 60 mg/m² day 1, every 5 weeks
Outcomes	Overall survival
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for the primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Survival analysis conducted on all enrolled patients
Selective reporting (reporting bias)	Low risk	Only OS listed specifically as an endpoint in the methods, this is reported on all patients
Other bias	Unclear risk	No indication of other bias

Cunningham 2009

Methods	Randomised phase III trial
Participants	Study was conducted in the UK. 533 participants with locally advanced/metastatic pancreatic ductal adenocarcinoma. 266 received gemcitabine. 267 received gemcitabine + capecitabine. Median age of participants was 62 years
Interventions	Gemcitabine: 1000 mg/m² 7/8 weeks then 3/4 weeks Gemcitabine + capecitabine: gemcitabine 1000 mg/m² 3/4 weeks + capecitabine 830 mg/m² twice daily orally for 3 weeks then 1 week rest
Outcomes	Overall survival Progression-free survival Overall response rate Toxicity

Cunningham 2009 (*Continued*)

	Quality of life Pain
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomly assigned to each treatment arm on a 1:1 basis according to a computer-generated variable-size blocked randomization method. Randomization was stratified by performance status (0, 1 versus 2) and extent of disease"
Allocation concealment (selection bias)	Low risk	"Patients were randomly assigned to each treatment arm on a 1:1 basis according to a computer-generated variable-size blocked randomization method. Randomization was stratified by performance status (0, 1 versus 2) and extent of disease"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat population reported
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Di Costanzo 2005

Methods	Randomised phase II trial
Participants	Study was conducted in Italy. 94 participants with locally advanced/metastatic pancreatic ductal adenocarcinoma with measurable disease. 48 received gemcitabine. 43 received gemcitabine + 5-fluorouracil (5FU). Median age of participants was 63 years
Interventions	Gemcitabine: 1000 mg/m² weekly for 7 weeks then 2 weeks rest, then 3/4 weeks Gemcitabine + 5FU: Gemcitabine as above. 5FU 200 mg/m²/day for 6 weeks then 2 weeks rest, then 3/4 weeks

Di Costanzo 2005 (*Continued*)

Outcomes	Response rate Overall survival Safety Quality of life
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were centrally randomised by the central office of the Italian Oncology Group for Clinical Research (GOIRC) to receive: GEM alone (arm A) or in combination with CI 5-FU (arm B)"
Allocation concealment (selection bias)	Low risk	"Patients were centrally randomised by the central office of the Italian Oncology Group for Clinical Research (GOIRC) to receive: GEM alone (arm A) or in combination with CI 5-FU (arm B)"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	High risk for the primary outcome (response rate)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Only patients "evaluable for response" were assessed for the primary endpoint
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Ducreux 2004

Methods	Randomised phase II study
Participants	Study was conducted in France. 63 participants with locally advanced/metastatic pancreatic adenocarcinoma and measurable disease. Were allowed to have had previous 5FU and radiotherapy if more than 3 months prior to randomisation. 17 received oxaliplatin, 31 received 5FU + oxaliplatin and 15 received 5FU alone. The mean age was 57 years

Ducreux 2004 (*Continued*)

Interventions	Oxaliplatin: 130 mg/m² every 3 weeks 5FU/ oxaliplatin: 5FU 1000 mg/m²/day, days 1-4 and oxaliplatin as above 5FU alone given as above
Outcomes	Response rate
Notes	The oxaliplatin alone arm was not included in the meta-analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Eligible patients in this open-label study were stratified by center and disease stage (locally advanced versus metastatic) and centralized block randomization was used to assign patients to one of three arms"
Allocation concealment (selection bias)	Low risk	"Eligible patients in this open-label study were stratified by center and disease stage (locally advanced versus metastatic) and centralized block randomization was used to assign patients to one of three arms"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	External radiologist used to assess tumour response
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 56 participants were evaluable for response, 4 withdrew prior to first assessment and 2 participants had baseline assessments which were old or missing
Selective reporting (reporting bias)	Unclear risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Frey 1981

Methods	Randomised study
Participants	Study was conducted in North America. 152 male participants with unresectable cancer of the pancreas. 65 received 5-fluorouracil (5FU) and CCNU; 87 received best supportive care. The majority of participants were between the age of 50 and 59 years

Frey 1981 (*Continued*)

Interventions	5FU 9 mg/kg days 1-5 + CCNU 70 mg/m² day 1, every 6 weeks
Outcomes	Overall survival Toxicity
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details regarding the method of randomisation provided
Allocation concealment (selection bias)	Low risk	"Assignment of patients to treated or control groups in this multi-institutional trial was made by means of sealed, sequentially numbered envelopes distributed by a statistician from the Follow-up Agency, National Academy of Sciences-National Research Council."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled participants included in survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indications of other bias

Gansauge 2002

Methods	Randomised phase II trial
Participants	Study was conducted in Germany. 90 participants with unresectable pancreatic adenocarcinoma. 30 received gemcitabine. 30 received Ukrain (NSC-31570). 30 received Ukrain + gemcitabine. The mean age for the gemcitabine, Ukrain and Gemcitabine + Ukrain groups were 63.8, 60.6 and 58.2 respectively
Interventions	Gemcitabine: 1000 mg/m² 7/8 weeks then 34 weeks Ukrain: 20 mg weekly for 7 weeks, 1 week rest then 3/4 weeks up to 12 cycles Gemcitabine + Ukrain: as above

Gansauge 2002 (*Continued*)

Outcomes	Overall survival
Notes	This was a multi-armed study. Event rates were not available for the 3 arms. Only the gemcitabine and gemcitabine + Ukrain arms analysed

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient details published
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in the survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Glimelius 1996

Methods	Randomised study
Participants	Study was conducted in Sweden. 90 participants with non-curable pancreatic or biliary tract cancer. 53 had pancreatic cancer. 29 received 5FU/LV +/- etoposide. 24 received best supportive care. Median age for the chemotherapy and best supportive care arms were 65 and 64 respectively
Interventions	If participant was > 60 years, then 5FU/LV: 5FU 500 mg/m² + LV 60 mg/m² on days 1 + 2 every 14 days If participant was < 60 years old, then 5FU/LV: 5FU 500 mg/m² + LV 60 mg/m² + etoposide 120 mg/m²
Outcomes	Overall survival Quality of life Objective responses Toxicity

Glimelius 1996 (*Continued*)

Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention to treat analysis reported
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Heinemann 2006

Methods	Randomised phase III trial
Participants	Study was conducted in Germany. 195 participants with locally advanced/metastatic pancreatic adenocarcinoma with measurable disease. Previous radiotherapy was allowed if not on the target lesion. 97 received gemcitabine. 98 received gemcitabine + cisplatin. The median age of the gemcitabine + cisplatin and gemcitabine alone groups was 64 and 66 years respectively
Interventions	Gemcitabine: 1000 mg/m² day 1, 8, 15 every 4 weeks Gemcitabine + cisplatin: gemcitabine as above. Cisplatin 50 mg/m² days 1, 8, 15 every 4 weeks
Outcomes	Overall survival Progression-free survival Response rate Safety Quality of life
Notes	-

Heinemann 2006 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Central random assignment was performed before the start of treatment, and patients were assigned to one of the treatment arms."
Allocation concealment (selection bias)	Low risk	"Central random assignment was performed before the start of treatment, and patients were assigned to one of the treatment arms."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	"The primary outcome measure was OS, which was determined for all randomly assigned patients from the date of random assignment to the date of death or last contact."
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Herrmann 2007

Methods	Randomised phase III trial
Participants	Study conducted in eight European countries. 319 participants with inoperable/metastatic pancreatic ductal adenocarcinoma. 159 received gemcitabine. 160 received gemcitabine + capecitabine. The median age was not stated
Interventions	Gemcitabine: 1000 mg/m² 7/8 weeks then 3/4 weeks Capecitabine: 650 mg/m² twice daily orally, days 1-14 every 3 weeks
Outcomes	Overall survival Progression-free survival Overall response rate Safety Quality of life
Notes	-

Herrmann 2007 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Likely to be low risk but actual method of randomisation/ allocation not stated in publication
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for the primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Intent-to-treat analysis was applied to the analysis of all end points"
Selective reporting (reporting bias)	Low risk	No indication of reporting bias
Other bias	Low risk	No indication of other bias

Hirao 2011

Methods	Randomised phase II trial
Participants	Study was conducted in Japan. 90 participants with unresectable, metastatic pancreatic ductal adenocarcinoma with no prior therapy. 45 received gemcitabine on a 3 week schedule. 45 received gemcitabine on a 4-week schedule. The median age in the 4 week and 3 week schedule was 67 years and 66 years, respectively
Interventions	3 weeks: gemcitabine 1000 mg/m² days 1 and 8 4 weeks: gemcitabine 1000 mg/m² days 1, 8 and 15
Outcomes	Compliance rate Overall survival Progression-free survival Toxicity Response rate
Notes	-

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Hirao 2011 (*Continued*)

Random sequence generation (selection bias)	Low risk	"Randomization was performed centrally, and the random-allocation sequence had been generated previously by a statistician using a computer-generated random code"
Allocation concealment (selection bias)	Low risk	"Randomization was performed centrally, and the random-allocation sequence had been generated previously by a statistician using a computer-generated random code"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	High risk for primary endpoint (compliance rate)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat population included in analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of reporting bias

Huguier 2001

Methods	Randomised study	
Participants	Study was conducted in France. 45 participants with unresectable pancreatic ductal adenocarcinoma. 22 received 5-fluorouracil (5FU) + leucovorin (LV) + cisplatin; 23 received best supportive care. The median age of participants was 63.4 years	
Interventions	5FU: 375 mg/m²/day days 1-5 LV 200 mg/m²/day days 1-5 Cisplatin 15 mg/m²/day days 1-5	
Outcomes	Overall survival Side effects	
Notes	-	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Huguier 2001 (*Continued*)

Random sequence generation (selection bias)	Low risk	"Assignment of patients to chemotherapy or control group used a centralised random permuted block technique"
Allocation concealment (selection bias)	Low risk	"Assignment of patients to chemotherapy or control group used a centralised random permuted block technique"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled participants included in the survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indications of other bias

Kelsen 1991

Methods	Phase III randomised study
Participants	Study was conducted in North America. 82 participants with advanced pancreatic adenocarcinoma and no prior therapy. 42 received streptozocin, mitomycin C and 5FU (SMF). 50 received cisplatin, cytosine arabinoside and caffeine (CAC). The median age of participants was 59 years
Interventions	SMF: streptozocin 1 g/m² days 1, 8, 29 and 36 + mitomycin C 10 mg/m² day 1 + 5FU 600 mg/m² days 1, 8 and 36 every 8 weeks CAC: cisplatin 100 mg/m² day 1 + cytosine arabinoside 2 g/m² two doses day 1 + caffeine 400 mg/m² subcutaneous 2 doses day 1
Outcomes	Response
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published

Kelsen 1991 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	High risk for primary outcome (response rate)
Incomplete outcome data (attrition bias) All outcomes	High risk	Not all participants were assessed for the primary outcome measure
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Kovach 1974

Methods	Randomised study
Participants	Study was conducted in North America. 82 with unresectable pancreatic adenocarcinoma and measurable disease. 31 received 5FU, 21 received 1,3-bis-(2-chloroethyl)-1-nitrosurea (BCNU)and 30 received 5FU + BCNU
Interventions	5FU: 13.5 mg/kg/day for 5 days every 5 weeks BCNU: 50 mg/m²/day for 5 days every 8 weeks 5FU + carmustine: 5FU 10 mg/kg/day for 5 days and BCNU 40 mg/m²/day for 5 days every 8 weeks
Outcomes	Not stated
Notes	This is a multi-armed study. Event rates for each arm were not available. Only the 5FU and 5FU + carmustine arms were analysed

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study

Kovach 1974 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Primary outcome measure unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if all participants were included in survival analysis
Selective reporting (reporting bias)	Low risk	No indication of reporting bias
Other bias	Low risk	No indication of other bias

Kulke 2009

Methods	Randomised phase II trial
Participants	Study was conducted in North America. 245 participants with metastatic pancreatic adenocarcinoma. Adjuvant 5-fluorouracil was permitted with completed > 2 weeks prior. 62 received gemcitabine + cisplatin. 58 received gemcitabine. 65 received gemcitabine + docetaxel. 60 received gemcitabine + irinotecan. Median age of participants was 60.5 years
Interventions	Gemcitabine + cisplatin: gemcitabine 1000 mg/m² weekly × 3, cisplatin 50 mg/m² days 1 and 15 every 4 weeks Gemcitabine: 1500 mg/m² at 10 mg/m²/min, weekly × 3, every 4 weeks Gemcitabine + docetaxel: gemcitabine 1000 mg/m² weekly × 3, docetaxel 40 mg/m² days 1 + 8, every 4 weeks Gemcitbine + irinotecan: gemcitabine 1000 mg/m² days 1 and 8, irinotecan 100 mg/m² days 1 and 8 every 3 weeks
Outcomes	Overall survival Response rate Time to progression Toxicity
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient details published. "Patients were randomly assigned to receive one of the following four regimens: gemcitabine/cisplatin (arm A), fixed dose rate gemcitabine (arm B), gemcitabine/docetaxel (arm C), or gemcitabine/irinotecan (arm D)"

Kulke 2009 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Insufficient details published. "Patients were randomly assigned to receive one of the following four regimens: gemcitabine/cisplatin (arm A), fixed dose rate gemcitabine (arm B), gemcitabine/docetaxel (arm C), or gemcitabine/irinotecan (arm D)"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in the outcome analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Lee 2017

Methods	Phase III trial
Participants	Study was conducted in Korea. 214 treatment naive participants with locally advanced or metastatic pancreatic adenocarcinoma with ECOG 0-2. 108 participants received gemcitabine + capecitabine and 106 participants received gemcitabine alone. Median age was 54 years years
Interventions	Gemcitabine 1000 mg/m² 3/4 weeks Capecitabine 1600 mg/m² daily for 3/4 weeks
Outcomes	Overall survival Progression-free survival Overall response rate Disease control rate Toxicity
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"We randomly assigned eligible patients to each treatment arm on a 1:1 basis according to a computer-generated variable-size

Lee 2017 (*Continued*)

		blocked randomization method."
Allocation concealment (selection bias)	Low risk	"We randomly assigned eligible patients to each treatment arm on a 1:1 basis according to a computer-generated variable-size blocked randomization method."s
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients included in the survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	None found

Levi 2004

Methods	Randomised study
Participants	Study was conducted in Europe. 107 participants with advanced pancreatic cancer. Factorial design randomised participants to either 5FU given at a constant rate infusion or chronomodulated infusion, with or without cisplatin. Median age of participants was 63 years
Interventions	5FU: 5 g/m² (cycle 1) or 6 g/m² (cycle 2) or 6.5 g/m² (cycle 3) either at a constant rate infusion or chronomodulated (given between 10 pm and 10 am) Cisplatin: 100 mg/m² once per cycle
Outcomes	OS
Notes	Abstract only

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published

Levi 2004 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient details published
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient details published
Selective reporting (reporting bias)	Unclear risk	Insufficient details published
Other bias	Unclear risk	Insufficient details published

Li 2004

Methods	Randomised study
Participants	Study was conducted in China. 46 participants with metastatic pancreatic adenocarcinoma. 25 received gemcitabine. 21 received gemcitabine + cisplatin
Interventions	Gemcitabine: 1000 mg/m² IV 3/4 weeks Cisplatin: 25 mg/m²/week, 3/4 weeks
Outcomes	Overall survival
Notes	Abstract only

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient details published
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient details published

Li 2004 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Insufficient details published
Other bias	Unclear risk	Insufficient details published

Lohr 2012

Methods	Randomised phase II trial
Participants	Study was conducted in Europe. 200 participants with locally advanced/unresectable or metastatic pancreatic adenocarcinoma. 50 received gemcitabine. 50 received liposomal-paclitaxel (ET) 11 mg/m². 50 received ET 22 mg/m². 50 received ET 44 mg/m². The median age for the gemcitabine alone, ET 11mg/m^2, ET 22mg/m^2 and ET 44mg/m^2 group was 59.5, 63, 61 and 62.5 years, respectively.
Interventions	Gemcitabine: 1000 mg/m² weekly × 7 ET: Dose given twice weekly × 14
Outcomes	Overall survival Progression-free survival Response rate Quality of life Adverse events
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Patients were centrally randomized"
Allocation concealment (selection bias)	Low risk	"Patients were centrally randomized"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	PFS for intention-to-treat population not reported - only the "modified intention to treat" population
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results

Lohr 2012 (*Continued*)

Other bias	Low risk	No indication of other bias

Louvet 2005

Methods	Randomised phase III trial
Participants	Study was conducted in France. 326 participants with unresectable/metastatic pancreatic ductal adenocarcinoma with measurable disease. 156 received gemcitabine. 157 received gemcitabine + oxaliplatin. The median age was 60.1 years and 61.3 years in the gemcitabine and gemcitabine + oxaliplatin groups respectively
Interventions	Gemcitabine 1000 mg/m² 7/8 weeks then 3/4 weeks Gemcitabine + oxaliplatin: gemcitabine 1000 mg/m² day 1 + oxaliplatin 100 mg/m² day 2, every 2 weeks
Outcomes	Overall survival Clinical benefit Progression-free survival Safety
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization was performed centrally, and the minimization method was used to balance treatment allocation according to center, stage of disease (locally advanced v metastatic), and PS (0 or 1 v 2)."
Allocation concealment (selection bias)	Low risk	"Randomization was performed centrally, and the minimization method was used to balance treatment allocation according to center, stage of disease (locally advanced v metastatic), and PS (0 or 1 v 2)."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 'per protocol' participants analysed

Louvet 2005 (*Continued*)

Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Lutz 2005

Methods	Randomised phase II trial
Participants	Study was conducted in Europe. 96 participants with metastatic or locally advanced pancreatic ductal adenocarcinoma with no previous treatment. 49 received gemcitabine + docetaxel. 47 received cisplatin + docetaxel. The median age of participants was 58 years and 59 years in the gemcitabine + docetaxel and cisplatin and docetaxel groups respectively
Interventions	Gemcitabine + docetaxel: gemcitabine 800 mg/m² days 1 and 8 + docetaxel 85 mg/m² day 8 every 3 weeks Cisplatin + docetaxel: cisplatin 75 mg/m² day 1 every 3 weeks
Outcomes	Tumour response Rates of febrile neutropenia Duration of response Progression-free survival Overall survival
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Patients were centrally randomly assigned at the EORTC Data Center, Brussels, Belgium, and stratified using the minimization technique according to institution, performance status (0 v 1), and extent of disease (metastatic v locoregionally advanced)"
Allocation concealment (selection bias)	Low risk	"Patients were centrally randomly assigned at the EORTC Data Center, Brussels, Belgium, and stratified using the minimization technique according to institution, performance status (0 v 1), and extent of disease (metastatic v locoregionally advanced)"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study

Lutz 2005 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	High risk for primary endpoint (tumour response)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat population included in analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Maisey 2002

Methods	Randomised phase III trial
Participants	Study was conducted in the UK. 209 participants with locally advanced/metastatic pancreatic ductal adenocarcinoma. 107 received 5-fluorouracil (5FU). 102 received 5FU + mitomycin C (MMC). The median age of participants was 62 years and 61 years in the 5FU and 5FU + MMC groups respectively
Interventions	5FU 300 mg/m²/day via protracted venous infusion (PVI) for 12 weeks. If no progression, another 12 weeks 5FU + MMC: 5FU 300 mg/m²/day + MMC 10 mg/m² every 6 weeks × 4 cycles
Outcomes	Response rate Survival Toxicity QoL
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"...patients were randomly assigned to treatment with PVI 5-FU or PVI 5-FU/MMC on a 1:1 basis according to a computer generated randomization code. The patients were randomized centrally in blocks of six and stratified by center"
Allocation concealment (selection bias)	Low risk	"...patients were randomly assigned to treatment with PVI 5-FU or PVI 5-FU/MMC on a 1:1 basis according to a computer generated randomization code. The patients were randomized centrally in blocks of six and stratified by center"

Maisey 2002 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	High risk for primary endpoint (response rate)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in the survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Meng 2012

Methods	Randomised, placebo controlled, phase II trial
Participants	Study was conducted in China. 76 participants with unresectable pancreatic adenocarcinoma with measurable disease. 37 received gemcitabine + placebo. 39 received gemcitabine + huachansu. The median age of participants was 60.9 years
Interventions	Gemcitabine + placebo: 1000 mg/m² 3/4 weeks + saline Gemcitabine + huachansu: gemcitabine as above, huachansu 20 mL/m² 5 days per week, 3 weeks on, 1 week off
Outcomes	4 month progression-free survival Overall survival Overall response rate Time to progression Toxicity
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient details published - "Patients were randomised using a Bayesian algorithm"
Allocation concealment (selection bias)	Unclear risk	Insufficient details published - "Patients were randomised using a Bayesian algorithm"

Meng 2012 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled study
Blinding of outcome assessment (detection bias) All outcomes	High risk	High risk for primary endpoint (PFS at 4 months)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in the survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Moertel 1977

Methods	Randomised trial
Participants	Study was conducted in North America. 88 participants with unresectable pancreatic ductal adenocarcinoma with measurable disease. 40 received streptozocin + 5-fluorouracil (5FU). 48 received streptozocin and cyclophosphamide. Most participants were aged between 50 to 59 years old
Interventions	Streptozocin 500 mg/m² days 1-5 5FU 400 mg/m² days 1-5 every 6 weeks Cyclophosphamide 1000 mg/m² days 1 and 21 every 6 weeks
Outcomes	Not stated
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study

Moertel 1977 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Participants who died early or who were unable to continue their assigned treatment were declared to have progressive disease
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 74 participants included in survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Moertel 1979

Methods	Randomised trial
Participants	Study conducted in North American. 176 participants with metastatic pancreatic ductal adenocarcinoma. 89 received 5-fluorouracil (5FU). 87 received 5FU + streptozocin. Details on the age of participants not stated
Interventions	5FU 450 mg/m² days 1-5 every 5 weeks 5FU + streptozocin: 5FU 400 mg/m² days 1-5 + streptozocin 400 mg/m² days 1-5 every 5 weeks Participants were also randomised +/- spironolactone 50 mg 3 times per day
Outcomes	Survival
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient details published
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in the survival analysis

Moertel 1979 (*Continued*)

Selective reporting (reporting bias)	High risk	Toxicity data scarcely reported
Other bias	Low risk	No indication of other bias

Oettle 2005

Methods	Randomised phase III trial
Participants	Study was conducted in Germany. 565 participants with locally advanced/metastatic pancreatic adenocarcinoma with measurable disease. Radiotherapy permitted if completed > 4 weeks prior. 282 received gemcitabine. 283 received gemcitabine + pemetrexed. The median age of participants was 63 years
Interventions	Gemcitabine (G): 1000 mg/m² 3/4 weeks Gemcitabine + pemetrexed (PG): gemcitabine 1250 mg/m² days 1 and 8, pemetrexed 500 mg/m² day 8, every 21 days
Outcomes	Overall survival Progression-free survival Time to treatment failure Response rate Quality of life
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Eligible patients were randomly assigned using a centralized, automated randomization procedure to either the PG arm or the G arm"
Allocation concealment (selection bias)	Low risk	"Eligible patients were randomly assigned using a centralized, automated randomization procedure to either the PG arm or the G arm"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in the survival analysis

Oettle 2005 (*Continued*)

Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Ohkawa 2004

Methods	Randomised trial
Participants	Study was conducted in Japan. 19 participants with advanced pancreatic ductal adenocarcinoma with no previous treatment. 9 received gemcitabine. 10 received gemcitabine + tegafur-uracil (UFT). The median age of participants for the gemcitabine alone and gemcitabine + UFT groups was 58.4 years and 60.5 years respectively
Interventions	Gemcitabine: 1000 mg/m² 3/4 weeks. UFT 300 mg/day continuous
Outcomes	Response rate Survival time Time to progression
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	High risk for primary endpoint (response rate)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient details published
Selective reporting (reporting bias)	Unclear risk	Insufficient details published
Other bias	Low risk	No indication of other bias

Ozaka 2012

Methods	Randomised phase II trial
Participants	Study was conducted in Japan. 112 participants with locally advanced/metastatic pancreatic ductal adenocarcinoma with measurable disease. 59 received gemcitabine. 53 received gemcitabine + S1. The median age of participants was 64 years
Interventions	Gemcitabine: 1000 mg/m² 3/4 weeks Gemcitabine + S1: gemcitabine 1000 mg/m² day 1 and 8, S1 80 mg/m² twice daily orally, days 1-14 every 3 weeks
Outcomes	Response rate Toxicity Clinical benefit rate Progression-free survival Overall survival
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Random assignment was performed centrally by a web-based assistant system (Xexible license assisted data server, JACCRO, Tokyo), using a computer-driven minimization procedure"
Allocation concealment (selection bias)	Low risk	"Random assignment was performed centrally by a web-based assistant system (Xexible license assisted data server, JACCRO, Tokyo), using a computer-driven minimization procedure"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	High risk for primary endpoint (response rate)
Incomplete outcome data (attrition bias) All outcomes	High risk	Intention-to-treat population not reported for PFS
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Petrioli 2015

Methods	Randomised phase II study
Participants	Study was conducted in Italy. 67 participants with metastatic, histologically proven pancreatic cancer and ECOG ≤ 2 and no prior chemotherapy. 33 given gemcitabine alone and 34 given gemcitabine + oxaliplatin + capecitabine (GEMOXEL). The median age of participants in the GEMOXEL and gemcitabine groups was 69 years and 67 years, respectively
Interventions	Gemcitabine: 1000 mg/m² for 7/8 weeks then days 1, 8 and 15 every 28 days GEMOXEL: gemcitabine 1000 mg/m² days 1, 8, 15 and 22. Oxaliplatin 100 mg/m² day 2, capectiabine 1500 mg/m²/day in 2 divided doses, days 1-14 every 21 days
Outcomes	Disease control rate in per protocol population Safety Progression-free survival Quality of life Overall survival
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	High risk for primary endpoint (disease control rate)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in the survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Poplin 2009

Methods	Randomised phase III trial
Participants	Study was conducted in North America. 824 participants with locally advanced/ metastatic pancreatic ductal adenocarcinoma with measurable disease. Were allowed to have had adjuvant radiotherapy if completed more than 4 weeks prior. 275 received standard gemcitabine. 277 received fixed dose rate gemcitabine (FDR). 272 received gemcitabine + oxaliplatin. The median age was 64 years, 61 years and 63 years for the gemcitabine, FDR and gemcitabine + oxaliplatin groups, respectively
Interventions	Gemcitabine: 1000 mg/m² over 30 min 7/8 weeks then 3/4 weeks FDR: gemcitabine 1500 mg/m² given over 150 min infusion day 1, 8, 15 every 4 weeks Gemcitabine + oxaliplatin: gemcitabine 1000 mg/m² over 100 min day 1 + oxaliplatin 100 mg/m² day 2, every 2 weeks
Outcomes	Overall survival Response rate Progression-free survival Symptoms
Notes	Gemcitabine + oxaliplatin arm has not been analysed as the gemcitabine dose schedule is not standard

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomly assigned to treatment using a dynamic balancing algorithm that stratified for performance status, 0 to 1 and versus 2, and for locally advanced versus metastatic disease"
Allocation concealment (selection bias)	Unclear risk	"Patients were randomly assigned to treatment using a dynamic balancing algorithm that stratified for performance status, 0 to 1 and versus 2, and for locally advanced versus metastatic disease"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat population included in survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results

Poplin 2009 (*Continued*)

Other bias	Low risk	No indication of other bias

Poplin 2013

Methods	Randomised, multicentre, phase II trial
Participants	This was an international study. 367 participants with metastatic pancreatic ductal adenocarcinoma. 185 received gemcitabine. 182 received lipid-drug conjugate of gemcitabine (CO-101). The median age of participants in the low hENT1 group was 62 years, and was 61 years in the high hENT group
Interventions	Gemcitabine 100 mg/m² 7/8 weeks then 3/4 weeks CO-101 120 mg/m² 3/4 weeks
Outcomes	Overall survival in low hENT1 participants Overall survival Progression-free survival Response rate
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Treatment on the Low hENT1 in Adenocarcinoma of the Pancreas (LEAP) study was randomly assigned (1:1 to gemcitabine or CO-101; Fig 1), and treatment allocation was stratified for Eastern Cooperative Oncology Group (ECOG) performances status (PS; 0 v 1) and geographic location (North America v South America v Australia v Eastern Europe v Western Europe)."
Allocation concealment (selection bias)	Low risk	"Treatment on the Low hENT1 in Adenocarcinoma of the Pancreas (LEAP) study was randomly assigned (1:1 to gemcitabine or CO-101; Fig 1), and treatment allocation was stratified for Eastern Cooperative Oncology Group (ECOG) performances status (PS; 0 v 1) and geographic location (North America v South America v Australia v Eastern Europe v Western Europe)."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study

Poplin 2013 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in the analyses
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indications of other bias

Reni 2005

Methods	Randomised phase III trial
Participants	Study was conducted in Italy. 99 participants with locally advanced/metastatic pancreatic adenocarcinoma with measurable disease. 47 received gemcitabine. 52 received cisplatin, epirubicin, gemcitabine and 5-fluorouracil (5FU) (PEGF). The median age of participants was 62 years and 59 years in the PEGF and gemcitabine groups respectively
Interventions	Gemcitabine: 1000 mg/m² 7/8 weeks then 3/4 weeks PEGF: cisplatin 40 mg/m² day 1, epirubicin 40 mg/m² day 1, gemcitabine 600 mg/m² days 1 and 8, 5FU 200 mg/m²/day every 28 days
Outcomes	Progression-free survival Overall survival Response rate Safety Quality of life
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomisationwas done by a secretary at a central location by a phone call. The random-allocation sequence had been generated previously by a statistician (LG) by use of a computer-generated random code."
Allocation concealment (selection bias)	Low risk	"Randomisationwas done by a secretary at a central location by a phone call. The random-allocation sequence had been generated previously by a statistician (LG) by use of a computer-generated random code."

Reni 2005 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	PFS was primary outcome, but radiologist evaluating progression was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in the survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Reni 2012

Methods	Randomised phase II trial
Participants	Study was conducted in Italy. 105 participants with unresectable/metastatic pancreatic ductal adenocarcinoma. 53 participants had capecitabine, cisplatin, gemcitabine and docetaxel (PDXG). 52 participants had capecitabine, epirubicin, cisplatin, gemcitabine (PEXG). The median age of participants was 61 years and 59 years in the PDXG and PEXG arms, respectively
Interventions	PDXG: capecitabine 1250 mg/m² days 1-28, cisplatin 30 mg/m² days 1 and 15, gemcitabine 800 mg/m² days 1 and 15, docetaxel 25 mg/m² days 1 and 15 every 4 weeks PEXG: capecitabine as above, cisplatin as above, gemcitabine as above, epirubicin 30 mg/m² days 1 and 15 every 4 weeks
Outcomes	Progression-free survival at 6 months Overall survival Toxicity Response rate
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Patients fulfilling all inclusion criteria were registered by the attending physician at an independent Contract Research Organization (CRO) that performed randomization on a 1:1 basis to either arm A or B. Patients were stratified according to stage of disease (III vs. IV)"

Reni 2012 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	"Patients fulfilling all inclusion criteria were registered by the attending physician at an independent Contract Research Organization (CRO) that performed randomization on a 1:1 basis to either arm A or B. Patients were stratified according to stage of disease (III vs. IV)"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	PFS primary outcome but radiologists blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat population included in survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Riess 2005

Methods	Randomised phase III trial
Participants	473 participants with locally advanced/metastatic pancreatic ductal adenocarcinoma with no prior therapy. 238 received gemcitabine. 235 received gemcitabine + 5-fluorouracil (5FU) + folinic acid (FA)
Interventions	Gemcitabine: 1000 mg/m² 7/8 weeks, then 3/4 weeks Gemcitabine + 5FU + FA: gemcitabine 1000 mg/m² + 5FU 750 mg/m² as a 24 hour infusion + FA 200 mg/m² days 1, 8, 15 every 6 weeks
Outcomes	Overall survival Time to progression Toxicity
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details given
Allocation concealment (selection bias)	Unclear risk	No details given

Riess 2005 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient details published
Selective reporting (reporting bias)	Unclear risk	Insufficient details published
Other bias	Low risk	No indication of other bias

Rocha Lima 2004

Methods	Randomised phase III trial
Participants	Study was conducted in North America. 360 participants with locally advanced/ metastatic pancreatic adenocarcinoma with measurable disease. Adjuvant radiotherapy and 5-fluorouracil (5FU) were permitted. 180 received gemcitabine. 180 received gemcitabine + irinotecan. The median age of participants was 63.2 years and 60.2 years in the gemcitabine + irinotecan and the gemcitabine alone group, respectively
Interventions	Gemcitabine: 1000 mg/m² 7/8 weeks then 3/4 weeks Gemcitabine + irinotecan: gemcitabine 1000 mg/m² and irinotecan 100 mg/m² days 1 and 8, every 21 days
Outcomes	Overall survival Quality of life
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Patients were centrally randomly assigned and stratified by ECOG performance status (0, 1, or 2), extent of disease (locally advanced or metastatic), and previous radiotherapy for pancreatic cancer (yes or no)."
Allocation concealment (selection bias)	Low risk	"Patients were centrally randomly assigned and stratified by ECOG performance status (0, 1, or 2), extent of disease (locally advanced or metastatic), and previous radiotherapy for pancreatic cancer (yes or no)."

Rocha Lima 2004 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in the survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Scheithauer 2003

Methods	Randomised phase II trial
Participants	Study was conducted in Austria. 83 participants with metastatic pancreatic ductal adenocarcinoma. Adjuvant 5-fluorouracil (5FU) and radiotherapy (RT) was permitted if completed > 6 months prior to randomisation. 42 received gemcitabine. 41 received gemcitabine + capecitabine. The median age of participants was 66 years and 64 years in the gemcitabine alone and the gemcitabine + capecitabine groups respectively
Interventions	Gemcitabine: 2200 mg/m² day 1, every 2 weeks Gemcitabine + capecitabine: gemcitabine as above, capecitabine 2500 mg/m²/day orally days 1-7 every 2 weeks
Outcomes	Progression-free survival Overall survival Response rate
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient details published. "Patients were then assigned to one treatment regimen by the central office located at the University in Vienna"
Allocation concealment (selection bias)	Unclear risk	Insufficient details published. "Patients were then assigned to one treatment regimen by the central office located at the University in Vienna"

Scheithauer 2003 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	PFS primary endpoint but independently reviewed
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in the survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Singhal 2014

Methods	Phase III randomised trial
Participants	310 participants with metastatic PC. Half received FOLFIRINOX and half received gemcitabine. Details on age of participants not published
Interventions	FOLFIRINOX: Oxaliplatin 85 mg/m² + irinotecan 180 mg/m² + LV 400 mg/m² + 5FU 400 mg/m² bolus + 5FU 2400 mg/m² as 46 hours continuous infusion every 2 weeks Gemcitabine: 1000 mg/m² days 1, 8, 15 every 28 days
Outcomes	Overall survival Progression-free survival Response rate Quality of life Adverse events
Notes	Abstract only

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study

Singhal 2014 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient details published
Selective reporting (reporting bias)	Unclear risk	Insufficient details published
Other bias	Unclear risk	Insufficient details published

Smith 2003

Methods	Randomised phase II/III study
Participants	Study was conducted in the UK. 55 participants with locally advanced or metastatic pancreatic adenocarcinoma with no prior treatment. 30 received ZD9331, 25 received gemcitabine alone. The median age of participants was 59.8 years and 60.8 years in the ZD9331 and gemcitabine arms respectively
Interventions	ZD9331: 130 mg/m² days 1, 8 every 21 days Gemcitabine: 1000 mg/m² weekly, 7/8 weeks, then 3/4 weeks
Outcomes	Tumour response Clinical benefit response PFS OS
Notes	Study supported by Astra Zeneca Ltd

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient details published - "Patients were then randomised to receive either ZD9331 or gemcitabine and were stratified by centre..."
Allocation concealment (selection bias)	Unclear risk	Insufficient details published - "Patients were then randomised to receive either ZD9331 or gemcitabine and were stratified by centre..."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study

Smith 2003 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat population included in survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Stathopoulos 2006

Methods	Randomised phase III trial
Participants	Study was conducted in Greece. 130 participants with locally advanced/metastatic pancreatic adenocarcinoma and no prior therapy. 70 received gemcitabine. 60 received gemcitabine + irinotecan. The median age of participants was 64 years
Interventions	Gemcitabine: 900 mg/m², 3/4 weeks Gemcitabine + irinotecan: gemcitabine 900 mg/m² days 1 and 8, irinotecan 300 mg/m² day 8, every 3 weeks
Outcomes	Overall survival Response rate Progression-free survival Toxicity
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Patients were centrally randomised by computer at a one-to-one ratio to receive either monotherapy (arm G) with gemcitabine"
Allocation concealment (selection bias)	Low risk	"Patients were centrally randomised by computer at a one-to-one ratio to receive either monotherapy (arm G) with gemcitabine"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study

Stathopoulos 2006 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants analysed for primary outcome
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Takada 1998

Methods	Randomised study
Participants	Study was conducted in Japan. 83 participants with unresectable pancreatic adenocarcinoma or biliary tract carcinoma, aged < 75 years. Of the participants with pancreatic cancer, 28 received 5-fluorouracil (5FU), doxorubicin and mitomycin C (MMC), and 24 received palliative surgery. The median age in the chemotherapy arm was 62.8 years and was 61.5 years in the palliative surgery arm
Interventions	5FU 200 mg/m² Doxorubicin 15 mg/m² MMC 5 mg/m² given weekly × 4, then 1 week break. 2 cycles given
Outcomes	Overall survival Response rates Performance status Adverse events
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"Patients were assigned at random to the therapy group or the control group using the envelope method in each facility..."
Allocation concealment (selection bias)	Low risk	"Registration procedures were conducted by telephoning the Study Group Office when the envelope was opened"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study

Takada 1998 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled participants included in survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indications of other bias

Tempero 2003

Methods	Randomised phase II trial
Participants	Study was conducted in North America. 92 participants with locally advanced/metastatic pancreatic ductal adenocarcinoma. 49 received dose-intense gemcitabine. 43 received fixed dose rate infusion gemcitabine (FDR). The median age of participants was 62 years
Interventions	Dose-intense gemcitabine: 2200 mg/m² IV over 30 min given days 1, 8, 15 every 28 days FDR: 1500 mg/m² given at 10 mg/m²/min given days 1, 8, 15 every 28 days
Outcomes	Time to treatment failure Time to progression Median survival Response rate Toxicity
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient details published - "Patients were randomly assigned to the following two treatment arms"
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)

Tempero 2003 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants analysed for the primary endpoint
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indications of other bias

Topham 1991

Methods	Randomised trial
Participants	Study was conducted in the UK. 62 participants with locally advanced or metastatic pancreatic adenocarcinoma. 32 were given epirubicin alone, 30 were given 5FU + epirubicin + mitomycin C (FEM). No details on the median ages of participants was published
Interventions	Epirubicin: 100 mg IV every 4 weeks FEM: 5FU 1g IV days 1 and 28, epirubicin 600 mg IV days 1 + 8, mitomycin C 10 mg day 1 every 8 weeks
Outcomes	Not stated
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Insufficient details published. Unclear what the primary endpoint was
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat population included in survival analysis
Selective reporting (reporting bias)	Unclear risk	Endpoints not clearly stated in the methods.
Other bias	Low risk	No indication of other bias

Ueno 2013

Methods	Randomised phase III trial
Participants	Study was conducted in Japan. 832 participants with locally advanced/metastatic pancreatic ductal adenocarcinoma, ECOG 0-1. 277 received gemcitabine. 280 received S1. 275 received gemcitabine + S1. Half the patients were under 65 years old and half were 65 years old or more
Interventions	Gemcitabine: 1000 mg/m² 3/4 weeks S1: orally, twice daily. Body surface area (BSA) < 1.25 m², 80 mg/day; BSA 1.25 m² to 1.5 m², 100 mg/day; BSA > 1.5 m², 120 mg/day. Days 1-28, every 42 days Gemcitabine + S1: gemcitabine 1000 mg/m² days 1 and 8, S1 (dosing as above), days 1-14 every 21 days
Outcomes	Overall survival Progression-free survival Overall response rate Safety Quality of life
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Random assignment was performed centrally with stratification by extent of disease (locally advanced disease v metastatic disease) and institution using the minimization method"
Allocation concealment (selection bias)	Low risk	"Random assignment was performed centrally with stratification by extent of disease (locally advanced disease v metastatic disease) and institution using the minimization method"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in the survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results

Ueno 2013 (*Continued*)

Other bias	Low risk	No indication of other bias

Ueno 2013 - EPA study

Methods	Randomised phase II trial
Participants	Study was conducted in Japan. 66 participants with advanced pancreatic adenocarcinoma. 23 received gemcitabine. 43 received gemcitabine + EPA enriched oral supplement. Median ages of participants were not published
Interventions	Gemcitabine: 1000 mg/m² 3/4 weeks Gemcitabine + EPA: gemcitabine as above. EPA 1 tablet orally, daily continuous
Outcomes	1-year survival
Notes	Abstract only

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient details published
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient details published
Selective reporting (reporting bias)	Unclear risk	Insufficient details published
Other bias	Low risk	No indication of other bias

Viret 2004

Methods	Randomised phase II trial
Participants	Study was conducted in France. 83 participants with stage III/IV pancreatic ductal adenocarcinoma. 41 received gemcitabine. 42 received gemcitabine + cisplatin. Median age was 63 years and 61.5 years in the gemcitabine alone and the gemcitabine + cisplatin arms respectively
Interventions	Gemcitabine 1000 mg/m² 7/8 weeks then 3/4 weeks Gemcitabine + cisplatin: gemcitabine 1000 mg/m² weekly × 3, cisplatin 75 mg/m² day 15 every 4 weeks
Outcomes	Time to treatment failure Toxicity Overall survival Reponse rate Quality of life
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non blinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	High risk for primary endpoint (time to treatment failure)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient details published
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Unclear risk	Insufficient details published

Von Hoff 2013

Methods	Randomised phase III trial
Participants	This was an international study. 861 participants with metastatic pancreatic ductal adenocarcinoma with measurable disease and no prior therapy. 43 received gemcitabine. 431 received gemcitabine + nab-paclitaxel. The median age of participants was 63 years
Interventions	Gemcitabine: 1000 mg/m² 7/8 weeks then 3/4 weeks Gemcitabine + nab-paclitaxel: nab-paclitaxel 125 mg/m² followed by gemcitabine 1000 mg/m² days 1, 8, 15 every 4 weeks
Outcomes	Overall survival Progression-free survival Response rate
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Likely to be low, but insufficient details published- "In this international, multicenter, open-label, randomized, phase 3 study, we randomly assigned eligible patients, in a 1:1 ratio"
Allocation concealment (selection bias)	Unclear risk	Likely to be low, but insufficient details published - "In this international, multicenter, open-label, randomized, phase 3 study, we randomly assigned eligible patients, in a 1:1 ratio"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in the survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indication of other bias

Wang 2002

Methods	Randomised phase III trial
Participants	42 participants with measurable or evaluable stage III/IV pancreatic cancer. 20 received gemcitabine. 22 participants with gemcitabine + cisplatin
Interventions	Gemcitabine 1000 mg/m² 7/8 weeks then 3/4 weeks Gemcitabine + cisplatin: gemcitabine 1000 mg/m² 3/4 weeks + cisplatin 60 mg/m² day 15 every 3 every 4 weeks
Outcomes	Clinical benefit Duration of clinical benefit Duration of response Time to progression Survival Toxicity
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient details published
Allocation concealment (selection bias)	Unclear risk	Insufficient details published
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient details published
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient details published
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient details published
Selective reporting (reporting bias)	Unclear risk	Insufficient details published
Other bias	Unclear risk	Insufficient details published

Xinopoulos 2008

Methods	Randomised study
Participants	Study was conducted in Greece. 49 participants with locally advanced PC with normal liver function tests after biliary stent insertion. 33 received no further treatment after stent insertion, 16 received gemcitabine. Median age of participants not published
Interventions	Gemcitabine 1000 mg/m² weekly × 3, then 1 week off
Outcomes	Overall survival Quality of life Requirement for 2nd stent insertion
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Patients' allocation into the 2 arms was based on a sequence of random binary numbers (i.e.111100111010...) that was developed in a computer based program"
Allocation concealment (selection bias)	Low risk	"Patients' allocation into the 2 arms was based on a sequence of random binary numbers (i.e.111100111010...) that was developed in a computer based program"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for primary endpoint (OS)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in the survival analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported in the results
Other bias	Low risk	No indications of other bias

5FU: 5-fluorouracil; **IV**: intravenous; **OS**: overall survival; **PFS**: progression-free survival: **QoL**: quality of life.

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

Study	Reason for exclusion
Abdel Wahab 1999	May include participants who did not have histological confirmation of their tumour. An attempt to contact authors was made
Aigner 1998	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)
Alberts 2005	Biological agent (addressed in another Cochrane Review)
Andersen 1981	Not all participants had advanced pancreatic cancer.
Ardalan 1988	Survival was not an endpoint.
Astsaturov 2011	Second.line treatment (addressed in another Cochrane Review)
Baker 1976	The survival data of the subgroup of participants with pancreatic cancer are not published separately
Benavides 2014	Biological agent (addressed in another Cochrane Review)
Benson 2014	Biological agent (addressed in another Cochrane Review)
Benson 2017	Biological agent - addressed in another review
Berglund 2010	Cross-over study.
Bramhall 2001	Biological agent (addressed in another Cochrane Review)
Bramhall 2002	Biological agent (addressed in another Cochrane Review)
Buanes 2009	Immunotherapy (addressed in another Cochrane Review)
Bukowski 1993	Non-randomised study
Burtness 2016	Biological agent (addressed in another Cochrane Review)
Cantore 2004	Second-line treatment (addressed in another Cochrane Review)
Cascinu 2008	Biological agent (addressed in another Cochrane Review)
Cascinu 2013	Biological agent (addressed in another Cochrane Review)
Catenacci 2013	Biological agent (addressed in another Cochrane Review)
Chai 2013	Immunotherapy (addressed in another Cochrane Review)
Chauffert 2008	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)

(*Continued*)

Chen 2006	Biological agent (addressed in another Cochrane Review)
Chung 2004	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)
Chung 2015	Second-line treatment (addressed in another Cochrane Review)
Ciuleanu 2009	Second-line treatment (addressed in another Cochrane Review)
Cohen 2005	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)
Cohen 2010	Insufficient data published
Dahan 2010	Cross-over study
Dalgleish 2015	Immunotherapy (addressed in another Cochrane Review)
Deplanque 2015	Biological agent (addressed in another Cochrane Review)
Ducreux 2002	Contains ampullary cancers
Duffy 2015	Second-line study - addressed in another review (ongoing study)
El-Khoueiry 2012	Biological agent (addressed in another Cochrane Review)
Evans 2014	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)
Friess 2006	Biological agent (addressed in another Cochrane Review)
Fuchs 2015	Biological agent (addressed in another Cochrane Review)
Fukutomi 2015	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)
Gill 2014	Second-line treatment (addressed in another Cochrane Review)
Gilliam 2012	Immunotherapy (addressed in another Cochrane Review)
GISTG 1985 (radiotherapy)	Locally advanced study (addressed in another Cochrane Review)
GITSG 1979	Preliminary results only. Included acinar and undifferentiated pathologies
GITSG 1985	Insufficient data published
GITSG 1988	Participants with acinar pathology included
Gong 2007	Non-randomised study

(*Continued*)

Gonçalves 2012	Biological agent (addressed in another Cochrane Review)
Haas 2015	Biological agent - addressed in another review (ongoing study)
Hammel 2013	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)
Han 2006	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)
Hazel 1981	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)
Heinemann 2013	Biological agent (addressed in another Cochrane Review)
Heinemann 2013 (GUT)	Cross-over study
Herman 2013	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)
Hingorani 2015	Biological agent - addressed in another review (ongoing study)
Horton 1981	Cross-over study
Hurwitz 2015	Second-line treatment (addressed in another Cochrane Review)
Hurwitz 2015 (JANUS 1)	Biological agent - addressed in another review (ongoing study)
Infante 2013	Biological agent (addressed in another Cochrane Review)
Ioka 2009	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)
Ioka 2013	Second-line treatment (addressed in another Cochrane Review)
Jacobs 2004	Second-line treatment (addressed in another Cochrane Review)
Javle 2011	Cross-over study
Johnson 2001	Not all participants had a histological diagnosis
Kim 2011	Insufficient data published
Kindler 2008	Biological agent (addressed in another Cochrane Review)
Kindler 2010	Biological agent (addressed in another Cochrane Review)
Kindler 2011	Biological agent (addressed in another Cochrane Review)
Kindler 2012	Biological agent (addressed in another Cochrane Review)
Kindler 2015	Biological agent - addressed in another review

(*Continued*)

Klaassen 1985	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)
Ko 2012	Biological agent (addressed in another Cochrane Review)
Ko 2016	Biological agent - addressed in another review
Lasalvia-Prisco 2012	Immunotherapy (addressed in another Cochrane Review)
Le (Ipilimumab) 2013	Second-line treatment (addressed in another Cochrane Review)
Le 2013	Immunotherapy (addressed in another Cochrane Review)
Le 2015	Immunotherapy agent - addressed in another review
Li 2003	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)
Li 2016	Locally advanced study (address in another Cochrane Review)
Linstadt 1988	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)
Loehrer 2011	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)
Lokich 1979	Included participants with acinar pathology
Lygidakis 1995	Not all participants had advanced pancreatic cancer
Mallinson 1980	Not all participants had histologically confirmed pancreatic ductal adenocarcinoma (PDAC)
Meyer 2008	Survival was not an endpoint
Middleton 2014	Immunotherapy (addressed in another Cochrane Review)
Mitry 2006	Non-randomised study
Mizuno 2013	May include adenosquamous participants. An attempt to contact authors was made
Modiano 2012	Biological agent (addressed in another Cochrane Review)
Moertel 1981	Participants with acinar and undifferentiated pathology were included
Moore 2003	Biological agent (addressed in another Cochrane Review)
Moore 2007	Biological agent (addressed in another Cochrane Review)
Mukherjee 2013	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)

(*Continued*)

Nakai 2012	Not all participants had histologically confirmed PDAC
Nio 2010	Retrospective study
O'Neil 2015	Biological agent (addressed in another Cochrane Review)
O'Reilly 2013	Biological agent - addressed in another review (ongoing study)
O'Reilly 2015	Second-line study - addressed in another review (ongoing study)
Oberic 2011	Insufficient data published
Oster 1986	Participants with acinar pathology were included
Palmer 1994	Not all participants had a histologically confirmed PDAC
Pandya 2013	Biological agent (addressed in another Cochrane Review)
Pelzer 2011	Second-line treatment (addressed in another Cochrane Review)
Philip 2010	Biological agent (addressed in another Cochrane Review)
Philip 2014	Biological agent (addressed in another Cochrane Review)
Propper 2014	Second-line treatment (addressed in another Cochrane Review)
Queisser 1979	Insufficient information published
Ramanathan 2011	Insufficient data published
Reni 2009	Retrospective analysis
Reni 2013	Second-line treatment (addressed in another Cochrane Review)
Richards 2011	Biological agent (addressed in another Cochrane Review)
Richly 2013	Biological agent (addressed in another Cochrane Review)
Riess 2010	Biological agent (addressed in another Cochrane Review)
Rougier 2013	Biological agent (addressed in another Cochrane Review)
Ryan 2013	Biological agent (addressed in another Cochrane Review)
Saif 2009	Biological agent (addressed in another Cochrane Review)

(*Continued*)

Sakata 1992	Insufficient information published - pancreas cancer subgroup not reported separately
Schein 1978	Participants with acinar and undifferentiated pathology were included
Schmitz-Winnenthal 2013	Overall survival not an endpoint
Senzer 2006	Insufficient data published
Shapiro 2005	Insufficient data published
Shinchi 2002	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)
Shinchi 2014	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)
Spano 2008	Biological agent (addressed in another Cochrane Review)
Strumberg 2013	Biological agent (addressed in another Cochrane Review)
Sudo 2014	Included adenosquamous pathology
Sultana 2009	Insufficient data published
Sun 2011	Insufficient data published
Sunamura 2004	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)
Tagliaferri 2013	Insufficient data published
Takada 1994	Includes participants with biliary tract cancer. Subgroup analysis of pancreatic cancer participants not available
Topham 1993	Preliminary results only
Trouilloud 2012	Insufficient data published
Tuinmann 2008	Interim analysis only. Full results not published
Ulrich-Pur 2003	Second-line treatment (addressed in another Cochrane Review)
Van Cutsem 2004	Biological agent (addressed in another Cochrane Review)
Van Cutsem 2009	Biological agent (addressed in another Cochrane Review)
Van Cutsem 2013	Insufficient data published
Van Cutsem 2014	Biological agent (addressed in another Cochrane Review)

(*Continued*)

Van Cutsem 2015	Biological agent (addressed in another Cochrane Review)
Von Hoff 1990	Immunotherapy (addressed in another Cochrane Review)
Von Hoff 2014	Second-line treatment (addressed in another Cochrane Review)
Voorthuizen 2006	Biological agent (addressed in another Cochrane Review)
Wagener 2002	Immunotherapy (addressed in another Cochrane Review)
Wang 2000	All participants had locally advanced PC (addressed in another Cochrane Review)
Wang 2004	All participants had locally advanced PC (addressed in another Cochrane Review)
Wang 2015	Biological agent (addressed in another Cochrane Review)
Wiedenmann 2008	Biological agent (addressed in another Cochrane Review)
Wilkowski 2009	Participants with locally advanced pancreatic cancer (addressed in another Cochrane Review)
Wolpin 2013	Biological agent (addressed in another Cochrane Review)
Wright 2006	Immunotherapy (addressed in another Cochrane Review)
Yamaue 2015	Biological agent (addressed in another Cochrane Review)
Yongxiang 2001	Non-randomised study
Yoo 2009	Second-line treatment (addressed in another Cochrane Review)
Zemskov 2000	Non-randomised study
Zhang 2007	All participants had locally advanced PC (addressed in another Cochrane Review)

PC: pancreatic cancer; **PDAC**: pancreatic ductal adenocarcinoma.

DATA AND ANALYSES

Comparison 1. Anti-cancer therapy versus best supportive care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	4	298	Hazard Ratio (Random, 95% CI)	1.08 [0.88, 1.33]

Comparison 2. Various types of chemotherapy versus gemcitabine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	8		Hazard Ratio (Random, 95% CI)	Subtotals only
1.1 5-FU	1	126	Hazard Ratio (Random, 95% CI)	1.69 [1.26, 2.27]
1.2 FOLFIRINOX	2	652	Hazard Ratio (Random, 95% CI)	0.51 [0.43, 0.60]
1.3 CO-101	1	367	Hazard Ratio (Random, 95% CI)	1.07 [0.86, 1.34]
1.4 ZD9331	1	55	Hazard Ratio (Random, 95% CI)	0.86 [0.42, 1.76]
1.5 Fixed dose rate gemcitabine	2	644	Hazard Ratio (Random, 95% CI)	0.79 [0.66, 0.94]
1.6 Exatecan	1	339	Hazard Ratio (Random, 95% CI)	1.27 [0.96, 1.68]
2 Progression-free survival	5		Hazard Ratio (Random, 95% CI)	Subtotals only
2.1 5-FU	1	126	Hazard Ratio (Random, 95% CI)	1.47 [1.12, 1.92]
2.2 FOLFIRINOX	2	652	Hazard Ratio (Random, 95% CI)	0.46 [0.38, 0.57]
2.3 ZD9331	1	55	Hazard Ratio (Random, 95% CI)	0.78 [0.46, 1.32]
2.4 Fixed dose rate gemcitabine	1	552	Hazard Ratio (Random, 95% CI)	0.88 [0.77, 1.01]
3 Degradation of QoL at 6 months	2		Hazard Ratio (Random, 95% CI)	0.46 [0.35, 0.61]
4 Response rates	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 5-FU	1	126	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.01, 2.71]
4.2 FOLFIRINOX	1	342	Risk Ratio (M-H, Random, 95% CI)	3.38 [2.01, 5.65]
4.3 CO-101	1	358	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.43, 1.04]
4.4 ZD9331	1	55	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.04, 4.33]
4.5 Fixed dose rate gemcitabine	2	644	Risk Ratio (M-H, Random, 95% CI)	1.59 [0.91, 2.79]
4.6 Exatecan (DX-8951f)	1	276	Risk Ratio (M-H, Random, 95% CI)	0.10 [0.01, 0.78]
5 Grade 3/4 anaemia	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 5-FU	1	126	Risk Ratio (M-H, Random, 95% CI)	0.08 [0.00, 1.34]
5.2 FOLFIRINOX	1	342	Risk Ratio (M-H, Random, 95% CI)	1.3 [0.59, 2.88]
5.3 CO-101	1	360	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.59, 1.73]
5.4 ZD9331	1	55	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.01, 6.58]
5.5 Fixed dose rate gemcitabine	2	644	Risk Ratio (M-H, Random, 95% CI)	1.79 [1.22, 2.63]
5.6 Exatecan	1	330	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.43, 2.34]
6 Grade 3/4 neutropenia	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 5-FU	1	126	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.06, 0.61]

6.2 FOLFIRINOX	1	342	Risk Ratio (M-H, Random, 95% CI)	2.14 [1.52, 3.01]
6.3 CO-101	1	360	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.83, 2.07]
6.4 ZD9331	1	55	Risk Ratio (M-H, Random, 95% CI)	4.17 [0.52, 33.37]
6.5 Fixed dose rate gemcitabine	2	644	Risk Ratio (M-H, Random, 95% CI)	1.85 [1.53, 2.23]
6.6 Exatecan	1	330	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.64, 1.55]
7 Grade 3/4 thrombocytopenia	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 5-FU	1	126	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.02, 1.34]
7.2 FOLFIRINOX	1	342	Risk Ratio (M-H, Random, 95% CI)	2.5 [0.99, 6.29]
7.3 CO-101	1	360	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.51, 2.34]
7.4 ZD9331	1	55	Risk Ratio (M-H, Random, 95% CI)	3.33 [0.40, 27.94]
7.5 Fixed dose rate gemcitabine	2	644	Risk Ratio (M-H, Random, 95% CI)	2.77 [1.99, 3.86]
7.6 Exatecan	1	330	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.37, 1.54]
8 Grade 3/4 nausea	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 5-FU	1	126	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.10, 1.35]
8.2 ZD9331	1	55	Risk Ratio (M-H, Random, 95% CI)	2.52 [0.11, 59.18]
8.3 Fixed dose rate gemcitabine	2	644	Risk Ratio (M-H, Random, 95% CI)	1.52 [0.94, 2.46]
8.4 Exatecan	1	330	Risk Ratio (M-H, Random, 95% CI)	1.75 [0.52, 5.86]
9 Grade 3/4 diarrhoea	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 5-FU	1	126	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.32, 28.07]
9.2 ZD9331	1	55	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.01, 6.58]
9.3 Fixed dose rate gemcitabine	2	644	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.16, 1.23]

Comparison 3. Gemcitabine combinations versus gemcitabine alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	26		Hazard Ratio (Random, 95% CI)	Subtotals only
1.1 Gemcitabine plus platinum agent	6	1140	Hazard Ratio (Random, 95% CI)	0.94 [0.81, 1.08]
1.2 Gemcitabine plus fluoropyrimidine	10	2718	Hazard Ratio (Random, 95% CI)	0.88 [0.81, 0.95]
1.3 Gemcitabine plus topoisomerase inhibitor	3	839	Hazard Ratio (Random, 95% CI)	1.01 [0.87, 1.16]
1.4 Gemcitabine plus taxane	1	861	Hazard Ratio (Random, 95% CI)	0.72 [0.62, 0.84]
1.5 Gemcitabine plus other combinations of chemotherapy	2	166	Hazard Ratio (Random, 95% CI)	0.55 [0.39, 0.79]
1.6 Gemcitabine plus other agent(s)	4	767	Hazard Ratio (Random, 95% CI)	0.79 [0.56, 1.10]
2 Progression-free survival	18		Hazard Ratio (Random, 95% CI)	Subtotals only
2.1 Gemcitabine plus platinum agent	4	1015	Hazard Ratio (Random, 95% CI)	0.80 [0.68, 0.95]
2.2 Gemcitabine plus fluoropyrimidine	8	2608	Hazard Ratio (Random, 95% CI)	0.79 [0.72, 0.87]

2.3 Gemcitabine plus topoisomerase inhibitor	2	709	Hazard Ratio (Random, 95% CI)	0.91 [0.78, 1.07]
2.4 Gemcitabine plus taxane	1	861	Hazard Ratio (Random, 95% CI)	0.69 [0.58, 0.82]
2.5 Gemcitabine plus other combinations of chemotherapy	2	166	Hazard Ratio (Random, 95% CI)	0.43 [0.30, 0.62]
2.6 Gemcitabine plus other agent(s)	1	76	Hazard Ratio (Random, 95% CI)	1.05 [0.68, 1.62]
3 Response rates	24		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Gemcitabine plus platinum agent	7	1186	Risk Ratio (M-H, Random, 95% CI)	1.48 [1.11, 1.98]
3.2 Gemcitabine plus fluoropyrimidine	9	2176	Risk Ratio (M-H, Random, 95% CI)	1.78 [1.29, 2.47]
3.3 Gemcitabine plus topoisomerase inhibitor	3	729	Risk Ratio (M-H, Random, 95% CI)	1.50 [0.92, 2.46]
3.4 Gemcitabine plus taxane	1	861	Risk Ratio (M-H, Random, 95% CI)	3.29 [2.24, 4.84]
3.5 Gemcitabane plus other combinations of chemotherapy	1	67	Risk Ratio (M-H, Random, 95% CI)	1.94 [0.83, 4.56]
3.6 Gemcitabine plus other agent(s)	3	691	Risk Ratio (M-H, Random, 95% CI)	3.66 [1.04, 12.82]
4 Grade 3/4 anaemia	23		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Gemcitabine plus platinum agent	7	1156	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.87, 2.31]
4.2 Gemcitabine plus fluoropyrimidine	8	2158	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.84, 1.45]
4.3 Gemcitabine plus topoisomerase inhibitor	3	797	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.72, 1.66]
4.4 Gemcitabine plus taxane	1	793	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.73, 1.52]
4.5 Gemcitabine plus other combinations of chemotherapy	1	67	Risk Ratio (M-H, Random, 95% CI)	1.94 [0.53, 7.13]
4.6 Gemcitabine plus other agent(s)	3	688	Risk Ratio (M-H, Random, 95% CI)	3.58 [1.93, 6.62]
5 Grade 3/4 neutropenia	23		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Gemcitabine plus platinum agent	6	961	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.90, 1.97]
5.2 Gemcitabine plus fluoropyrimidine	9	2177	Risk Ratio (M-H, Random, 95% CI)	1.53 [1.34, 1.74]
5.3 Gemcitabine plus topoisomerase inhibitor	3	797	Risk Ratio (M-H, Random, 95% CI)	1.54 [1.04, 2.30]
5.4 Gemcitabine plus taxane	1	793	Risk Ratio (M-H, Random, 95% CI)	1.42 [1.16, 1.75]
5.5 Gemcitabine plus other combinations of chemotherapy	1	67	Risk Ratio (M-H, Random, 95% CI)	1.94 [0.65, 5.83]
5.6 Gemcitabine plus other agent(s)	3	688	Risk Ratio (M-H, Random, 95% CI)	2.02 [0.88, 4.66]
6 Grade 3/4 thrombocytopenia	23		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Gemcitabine plus platinum agent	6	1110	Risk Ratio (M-H, Random, 95% CI)	1.96 [1.00, 3.84]
6.2 Gemcitabine plus fluoropyrimidine	9	2177	Risk Ratio (M-H, Random, 95% CI)	1.48 [1.00, 2.18]
6.3 Gemcitabine plus topoisomerase inhibitor	3	797	Risk Ratio (M-H, Random, 95% CI)	2.28 [0.97, 5.36]
6.4 Gemcitabine plus taxane	1	793	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.93, 2.07]

6.5 Gemcitabine plus other combinations of chemotherapy	1	67	Risk Ratio (M-H, Random, 95% CI)	1.94 [0.74, 5.07]
6.6 Gemcitabine plus other agent(s)	3	688	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.45, 4.39]
7 Grade 3/4 nausea	21		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Gemcitabine plus platinum agent	6	1110	Risk Ratio (M-H, Random, 95% CI)	2.28 [1.40, 3.71]
7.2 Gemcitabine plus fluoropyrimidine	7	2075	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.87, 1.84]
7.3 Gemcitabine plus topoisomerase inhibitor	3	797	Risk Ratio (M-H, Random, 95% CI)	1.55 [0.94, 2.55]
7.4 Gemcitabine plus other combinations of chemotherapy	1	67	Risk Ratio (M-H, Random, 95% CI)	10.69 [0.61, 185.91]
7.5 Gemcitabine plus other agent(s)	4	748	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.48, 3.26]
8 Grade 3/4 diarrhoea	17		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Gemcitabine plus platinum agent	6	1110	Risk Ratio (M-H, Random, 95% CI)	1.48 [0.62, 3.53]
8.2 Gemcitabine plus fluoropyrimidine	8	2087	Risk Ratio (M-H, Random, 95% CI)	2.16 [1.34, 3.47]
8.3 Gemcitabine plus topoisomerase inhibitor	3	797	Risk Ratio (M-H, Random, 95% CI)	3.47 [0.74, 16.33]
9 Grade 3/4 neuropathy	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 Gemcitabine plus taxane	1	793	Risk Ratio (M-H, Random, 95% CI)	22.35 [7.10, 70.40]
10 Grade 3/4 fatigue	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 Gemcitabine plus taxane	1	793	Risk Ratio (M-H, Random, 95% CI)	2.48 [1.63, 3.79]

Comparison 4. Fluoropyrimidine combinations versus fluoropyrimidine alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	4	491	Hazard Ratio (Random, 95% CI)	0.84 [0.61, 1.15]
2 Progression-free survival	2	255	Hazard Ratio (Random, 95% CI)	0.52 [0.19, 1.38]
3 Response rates	4	410	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.52, 2.68]
4 Grade 3/4 anaemia	2	255	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.06, 3.62]
5 Grade 3/4 neutropenia	2	255	Risk Ratio (M-H, Random, 95% CI)	5.70 [0.73, 44.46]
6 Grade 3/4 thrombocytopenia	2	255	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.34, 5.80]
7 Grade 3/4 fatigue	1	209	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.58, 1.43]
8 Grade 3/4 nausea	2	255	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.32, 3.53]
9 Grade 3/4 diarrhoea	2	255	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.31, 2.78]

Analysis 1.1. Comparison 1 Anti-cancer therapy versus best supportive care, Outcome 1 Overall survival.

Review: Chemotherapy and radiotherapy for advanced pancreatic cancer

Comparison: 1 Anti-cancer therapy versus best supportive care

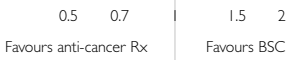
Outcome: 1 Overall survival

Study or subgroup	Anti-cancer therapy N	Best supportive care N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
Frey 1981	65	87	0.2311 (0.166)		39.3 %	1.26 [0.91, 1.74]
Huguier 2001	22	23	-0.0513 (0.2606)		15.9 %	0.95 [0.57, 1.58]
Takada 1998	28	24	-0.0834 (0.2443)		18.1 %	0.92 [0.57, 1.49]
Xinopoulos 2008	16	33	0.0488 (0.2018)		26.6 %	1.05 [0.71, 1.56]
Total (95% CI)	**131**	**167**			**100.0 %**	**1.08 [0.88, 1.33]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.55$, df = 3 (P = 0.67); $I^2 = 0.0\%$

Test for overall effect: Z = 0.77 (P = 0.44)

Test for subgroup differences: Not applicable

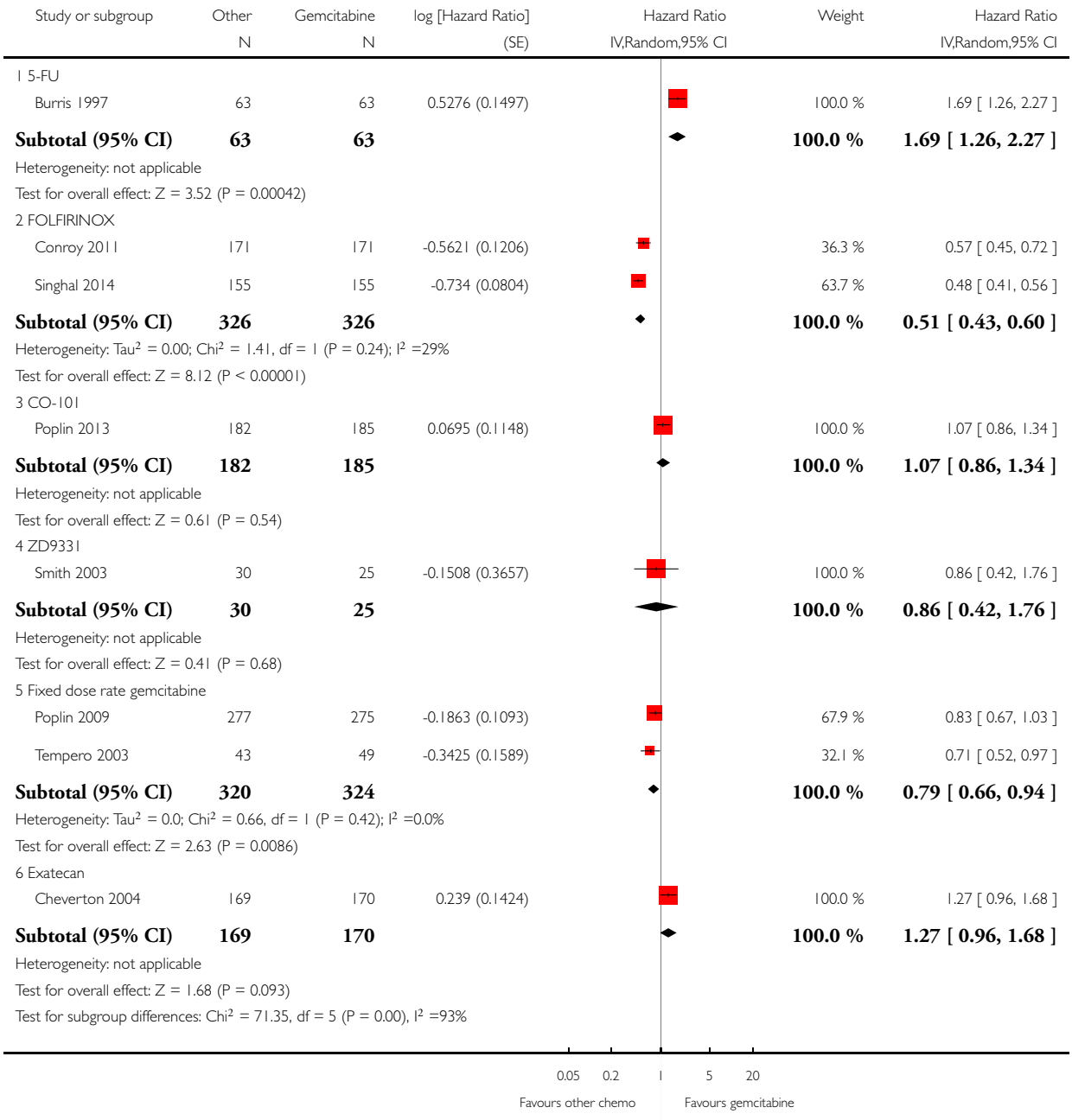


Analysis 2.1. Comparison 2 Various types of chemotherapy versus gemcitabine, Outcome 1 Overall survival.

Review: Chemotherapy and radiotherapy for advanced pancreatic cancer

Comparison: 2 Various types of chemotherapy versus gemcitabine

Outcome: 1 Overall survival

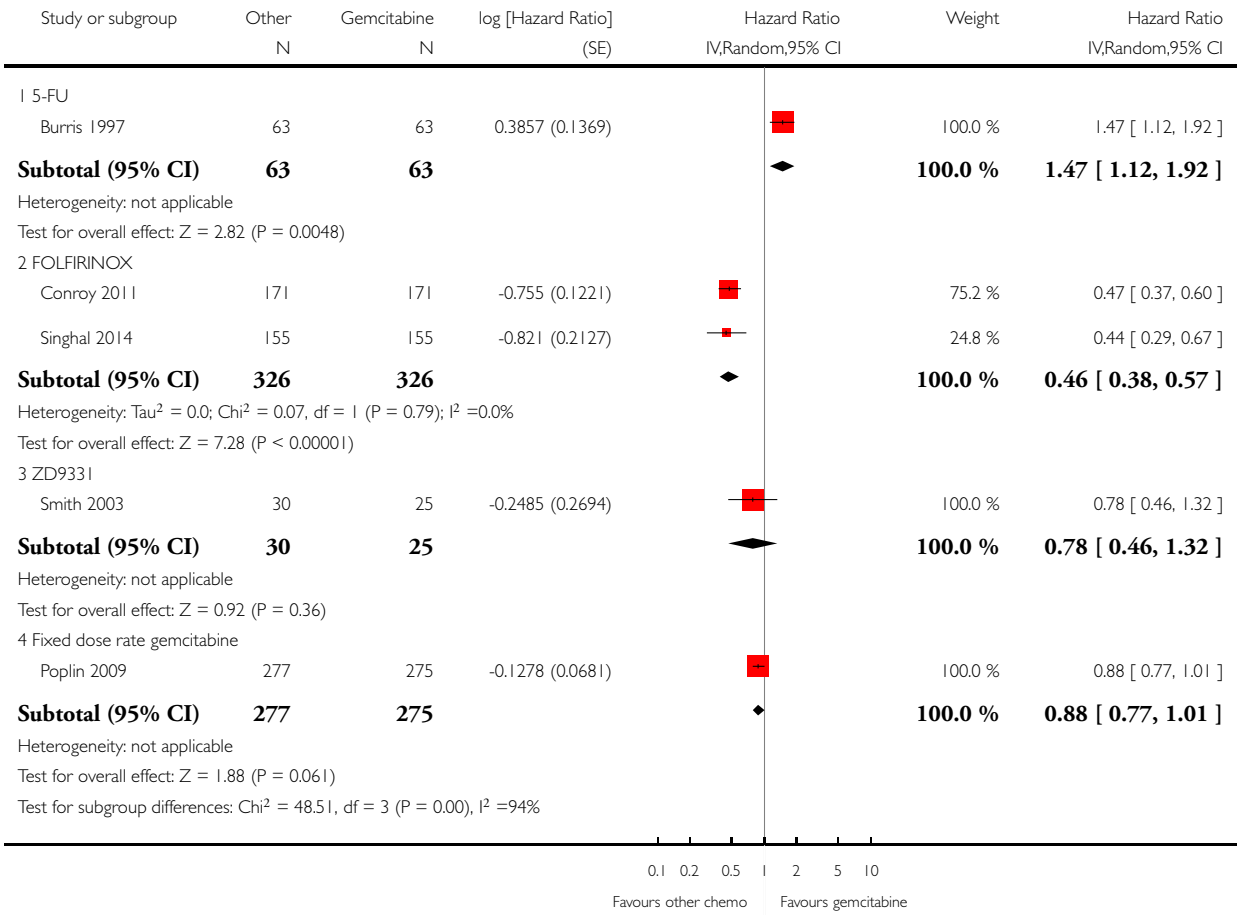


Analysis 2.2. Comparison 2 Various types of chemotherapy versus gemcitabine, Outcome 2 Progression-free survival.

Review: Chemotherapy and radiotherapy for advanced pancreatic cancer

Comparison: 2 Various types of chemotherapy versus gemcitabine

Outcome: 2 Progression-free survival



Analysis 2.3. Comparison 2 Various types of chemotherapy versus gemcitabine, Outcome 3 Degradation of QoL at 6 months.

Review: Chemotherapy and radiotherapy for advanced pancreatic cancer

Comparison: 2 Various types of chemotherapy versus gemcitabine

Outcome: 3 Degradation of QoL at 6 months

Study or subgroup	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
Conroy 2011	-0.755 (0.2032)		51.8 %	0.47 [0.32, 0.70]
Singhal 2014	-0.7985 (0.2106)		48.2 %	0.45 [0.30, 0.68]
Total (95% CI)			**100.0 %**	**0.46 [0.35, 0.61]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.02$, df = 1 (P = 0.88); $I^2 = 0.0\%$

Test for overall effect: Z = 5.31 (P < 0.00001)

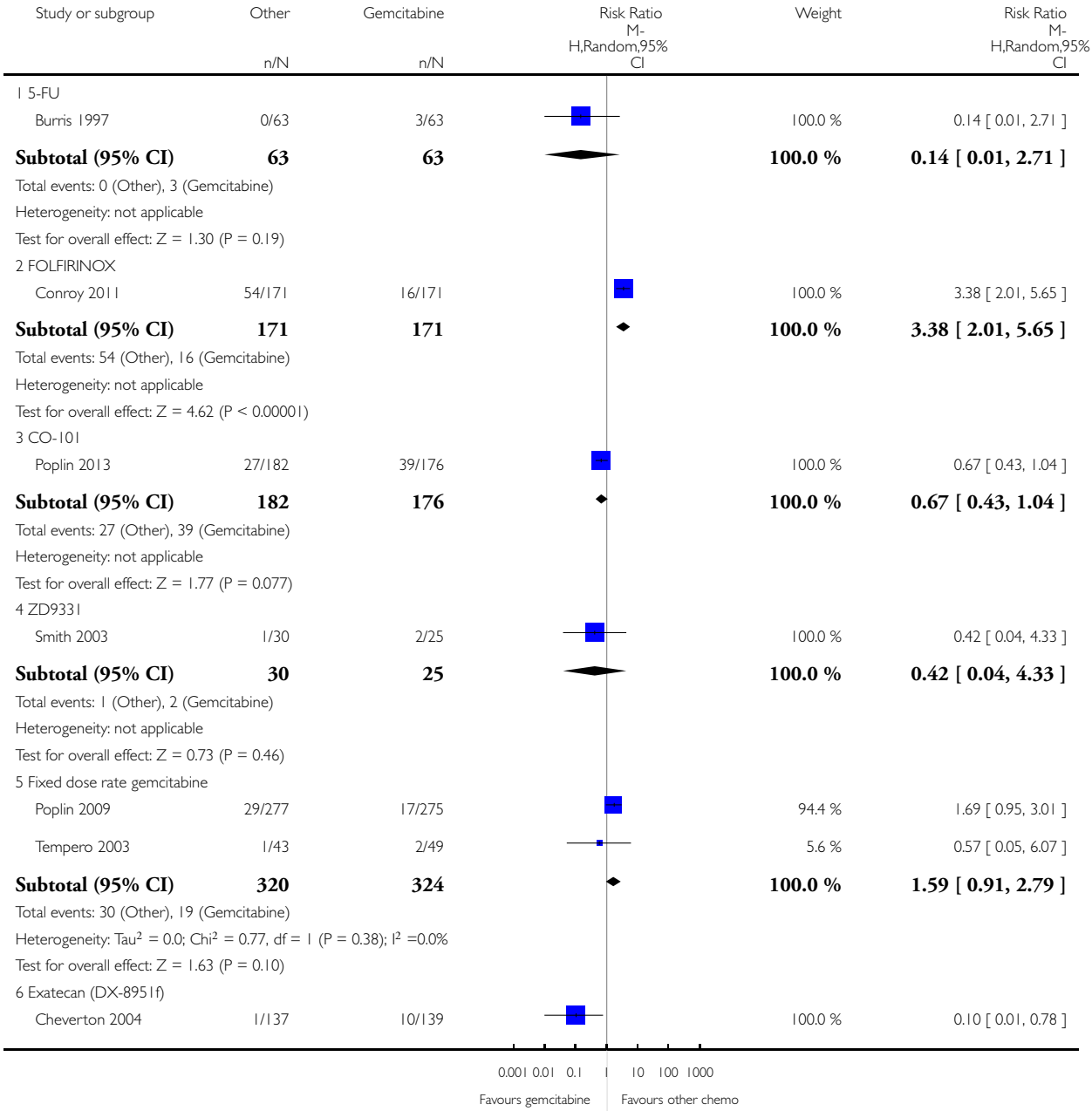
Test for subgroup differences: Not applicable

Analysis 2.4. Comparison 2 Various types of chemotherapy versus gemcitabine, Outcome 4 Response rates.

Review: Chemotherapy and radiotherapy for advanced pancreatic cancer

Comparison: 2 Various types of chemotherapy versus gemcitabine

Outcome: 4 Response rates



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Study or subgroup	Other n/N	Gemcitabine n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**137**	**139**		**100.0 %**	**0.10 [0.01, 0.78]**
Total events: 1 (Other), 10 (Gemcitabine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.20 (P = 0.028)					
Test for subgroup differences: Chi^2 = 31.24, df = 5 (P = 0.00), I^2 =84%					

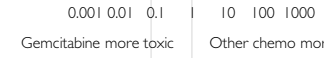
Analysis 2.5. Comparison 2 Various types of chemotherapy versus gemcitabine, Outcome 5 Grade 3/4 anaemia.

Review: Chemotherapy and radiotherapy for advanced pancreatic cancer

Comparison: 2 Various types of chemotherapy versus gemcitabine

Outcome: 5 Grade 3/4 anaemia

Study or subgroup	Other chemotherapy n/N	Gemcitabine n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 5-FU					
Burris 1997	0/63	6/63		100.0 %	0.08 [0.00, 1.34]
Subtotal (95% CI)	**63**	**63**		**100.0 %**	**0.08 [0.00, 1.34]**
Total events: 0 (Other chemotherapy), 6 (Gemcitabine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.76 (P = 0.078)					
2 FOLFIRINOX					
Conroy 2011	13/171	10/171		100.0 %	1.30 [0.59, 2.88]
Subtotal (95% CI)	**171**	**171**		**100.0 %**	**1.30 [0.59, 2.88]**
Total events: 13 (Other chemotherapy), 10 (Gemcitabine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.65 (P = 0.52)					
3 CO-101					
Poplin 2013	23/179	23/181		100.0 %	1.01 [0.59, 1.73]



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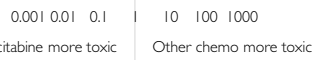
Study or subgroup	Other chemotherapy n/N	Gemcitabine n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**179**	**181**		**100.0 %**	**1.01 [0.59, 1.73]**
Total events: 23 (Other chemotherapy), 23 (Gemcitabine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.04 (P = 0.97)					
4 ZD9331					
Smith 2003	0/30	1/25		100.0 %	0.28 [0.01, 6.58]
Subtotal (95% CI)	**30**	**25**		**100.0 %**	**0.28 [0.01, 6.58]**
Total events: 0 (Other chemotherapy), 1 (Gemcitabine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.79 (P = 0.43)					
5 Fixed dose rate gemcitabine					
Poplin 2009	52/277	26/275		76.8 %	1.99 [1.28, 3.08]
Tempero 2003	10/43	9/49		23.2 %	1.27 [0.57, 2.82]
Subtotal (95% CI)	**320**	**324**		**100.0 %**	**1.79 [1.22, 2.63]**
Total events: 62 (Other chemotherapy), 35 (Gemcitabine)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.93, df = 1 (P = 0.33); I^2 =0.0%					
Test for overall effect: Z = 2.95 (P = 0.0031)					
6 Exatecan					
Cheverton 2004	10/165	10/165		100.0 %	1.00 [0.43, 2.34]
Subtotal (95% CI)	**165**	**165**		**100.0 %**	**1.00 [0.43, 2.34]**
Total events: 10 (Other chemotherapy), 10 (Gemcitabine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
Test for subgroup differences: Chi^2 = 8.46, df = 5 (P = 0.13), I^2 =41%					



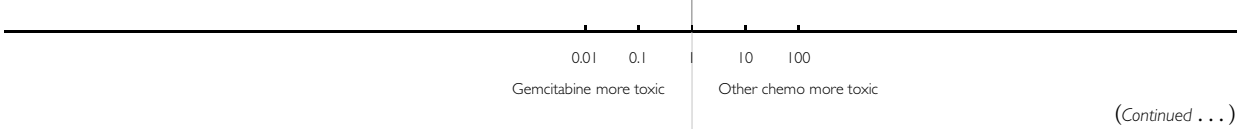
Analysis 2.6. Comparison 2 Various types of chemotherapy versus gemcitabine, Outcome 6 Grade 3/4 neutropenia.

Review: Chemotherapy and radiotherapy for advanced pancreatic cancer

Comparison: 2 Various types of chemotherapy versus gemcitabine

Outcome: 6 Grade 3/4 neutropenia

Study or subgroup	Other n/N	Gemcitabine n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 5-FU					
Burris 1997	3/63	16/63		100.0 %	0.19 [0.06, 0.61]
Subtotal (95% CI)	**63**	**63**		**100.0 %**	**0.19 [0.06, 0.61]**
Total events: 3 (Other), 16 (Gemcitabine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.77 (P = 0.0055)					
2 FOLFIRINOX					
Conroy 2011	75/171	35/171		100.0 %	2.14 [1.52, 3.01]
Subtotal (95% CI)	**171**	**171**		**100.0 %**	**2.14 [1.52, 3.01]**
Total events: 75 (Other), 35 (Gemcitabine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.38 (P = 0.000012)					
3 CO-101					
Poplin 2013	35/179	27/181		100.0 %	1.31 [0.83, 2.07]
Subtotal (95% CI)	**179**	**181**		**100.0 %**	**1.31 [0.83, 2.07]**
Total events: 35 (Other), 27 (Gemcitabine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.16 (P = 0.25)					
4 ZD9331					
Smith 2003	5/30	1/25		100.0 %	4.17 [0.52, 33.37]
Subtotal (95% CI)	**30**	**25**		**100.0 %**	**4.17 [0.52, 33.37]**
Total events: 5 (Other), 1 (Gemcitabine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.34 (P = 0.18)					
5 Fixed dose rate gemcitabine					
Poplin 2009	162/277	87/275		88.6 %	1.85 [1.51, 2.26]
Tempero 2003	21/43	13/49		11.4 %	1.84 [1.05, 3.21]
Subtotal (95% CI)	**320**	**324**		**100.0 %**	**1.85 [1.53, 2.23]**
Total events: 183 (Other), 100 (Gemcitabine)					
Heterogeneity: Tau² = 0.0; Chi² = 0.00, df = 1 (P = 0.99); I² =0.0%					
Test for overall effect: Z = 6.39 (P < 0.00001)					
6 Exatecan					



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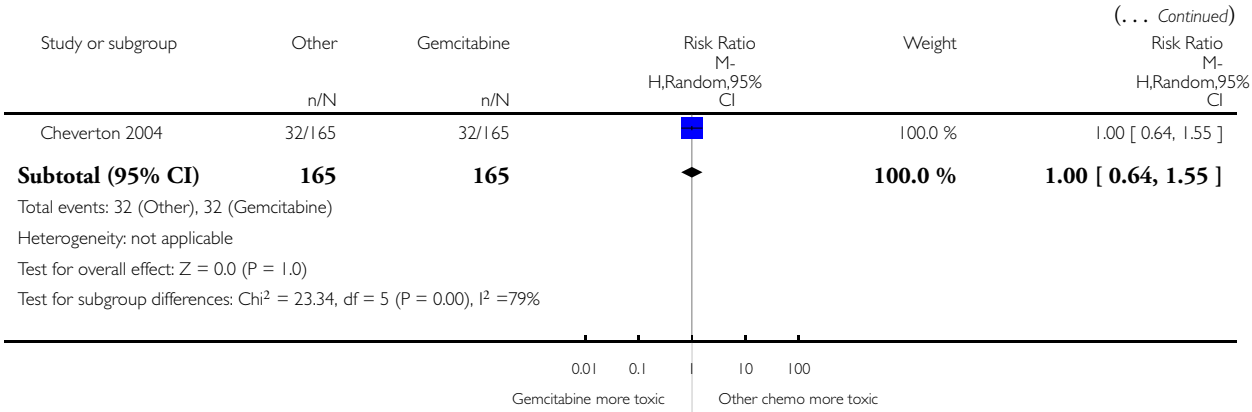
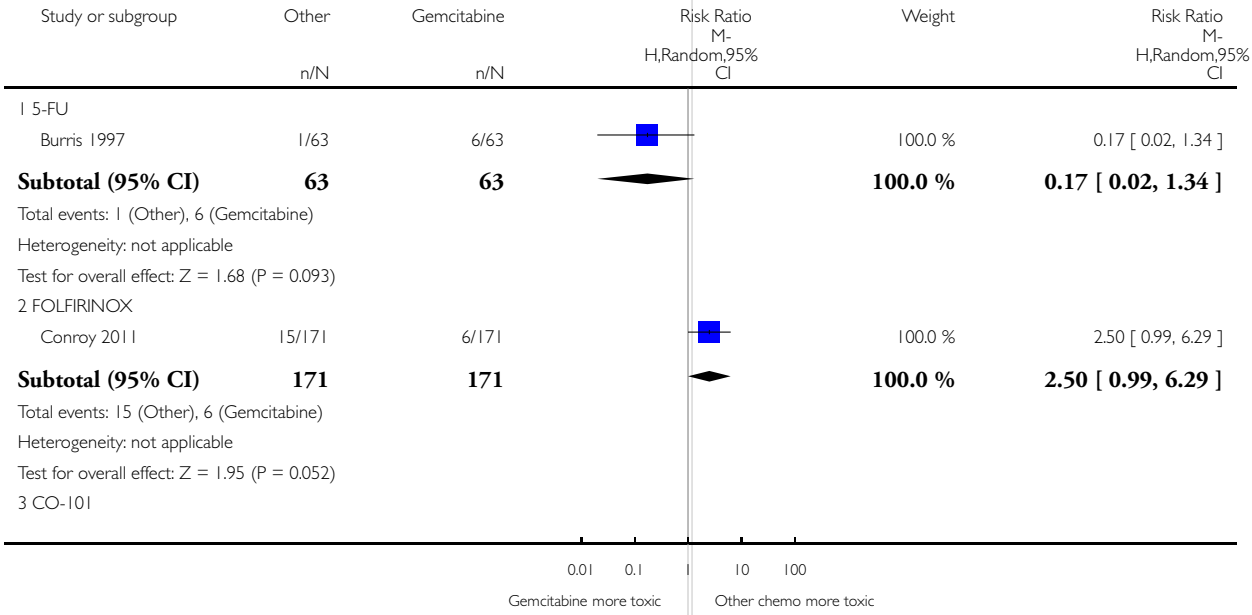


Analysis 2.7. Comparison 2 Various types of chemotherapy versus gemcitabine, Outcome 7 Grade 3/4 thrombocytopenia.

Review: Chemotherapy and radiotherapy for advanced pancreatic cancer

Comparison: 2 Various types of chemotherapy versus gemcitabine

Outcome: 7 Grade 3/4 thrombocytopenia



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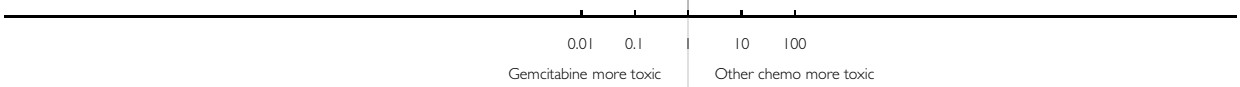
Study or subgroup	Other n/N	Gemcitabine n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Poplin 2013	13/179	12/181		100.0 %	1.10 [0.51, 2.34]
Subtotal (95% CI)	**179**	**181**		**100.0 %**	**1.10 [0.51, 2.34]**
Total events: 13 (Other), 12 (Gemcitabine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.24 (P = 0.81)					
4 ZD9331					
Smith 2003	4/30	1/25		100.0 %	3.33 [0.40, 27.94]
Subtotal (95% CI)	**30**	**25**		**100.0 %**	**3.33 [0.40, 27.94]**
Total events: 4 (Other), 1 (Gemcitabine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.11 (P = 0.27)					
5 Fixed dose rate gemcitabine					
Poplin 2009	91/277	34/275		86.8 %	2.66 [1.86, 3.80]
Tempero 2003	16/43	5/49		13.2 %	3.65 [1.46, 9.12]
Subtotal (95% CI)	**320**	**324**		**100.0 %**	**2.77 [1.99, 3.86]**
Total events: 107 (Other), 39 (Gemcitabine)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.40, df = 1 (P = 0.53); I^2 =0.0%					
Test for overall effect: Z = 6.00 (P < 0.00001)					
6 Exatecan					
Cheverton 2004	12/165	16/165		100.0 %	0.75 [0.37, 1.54]
Subtotal (95% CI)	**165**	**165**		**100.0 %**	**0.75 [0.37, 1.54]**
Total events: 12 (Other), 16 (Gemcitabine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.79 (P = 0.43)					
Test for subgroup differences: Chi^2 = 19.19, df = 5 (P = 0.00), I^2 =74%					

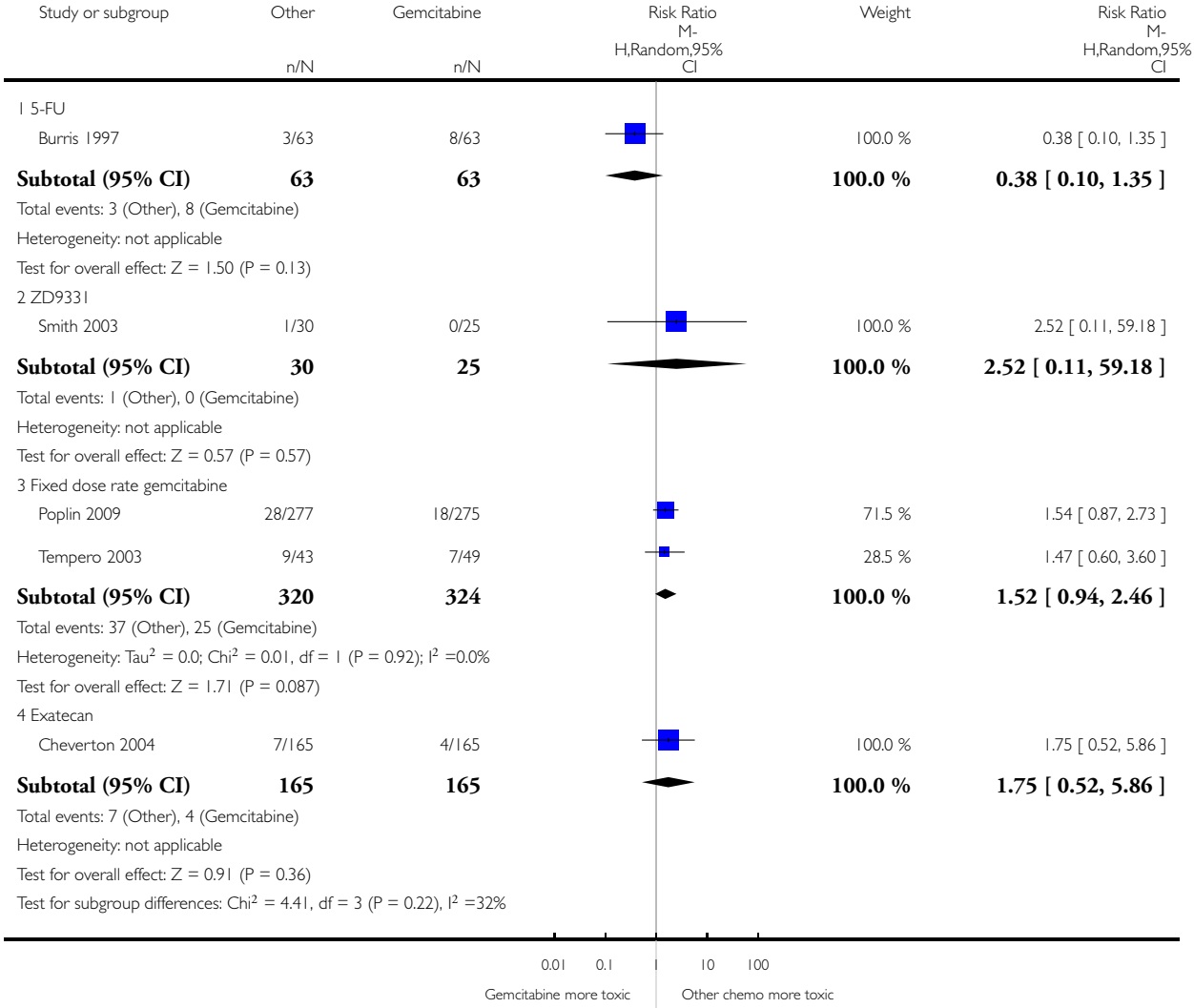


Analysis 2.8. Comparison 2 Various types of chemotherapy versus gemcitabine, Outcome 8 Grade 3/4 nausea.

Review: Chemotherapy and radiotherapy for advanced pancreatic cancer

Comparison: 2 Various types of chemotherapy versus gemcitabine

Outcome: 8 Grade 3/4 nausea

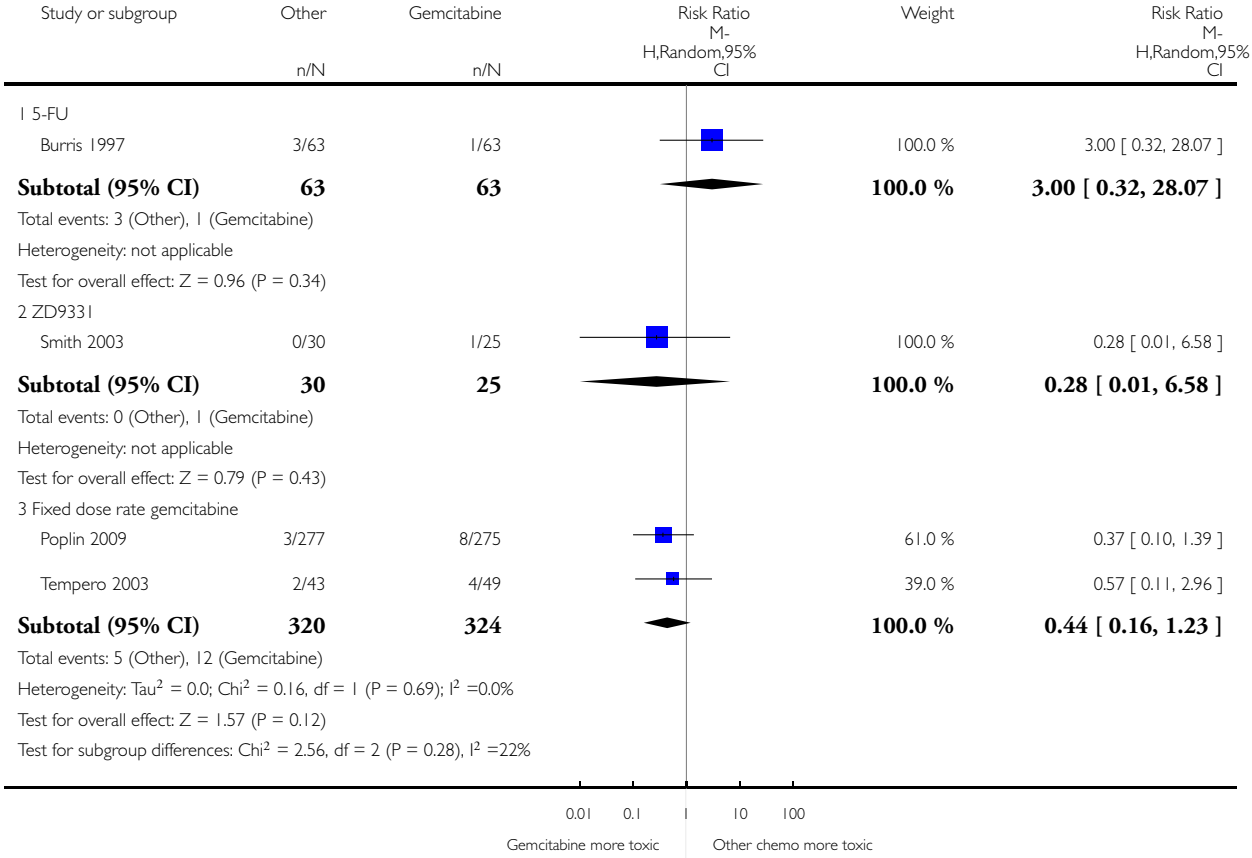


Analysis 2.9. Comparison 2 Various types of chemotherapy versus gemcitabine, Outcome 9 Grade 3/4 diarrhoea.

Review: Chemotherapy and radiotherapy for advanced pancreatic cancer

Comparison: 2 Various types of chemotherapy versus gemcitabine

Outcome: 9 Grade 3/4 diarrhoea



Analysis 3.1. Comparison 3 Gemcitabine combinations versus gemcitabine alone, Outcome 1 Overall survival.

Review: Chemotherapy and radiotherapy for advanced pancreatic cancer

Comparison: 3 Gemcitabine combinations versus gemcitabine alone

Outcome: 1 Overall survival

Study or subgroup	Gemcitabine combinations N	Gemcitabine alone N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
1 Gemcitabine plus platinum agent						
Colucci 2002	53	54	-0.1393 (0.2069)		11.2 %	0.87 [0.58, 1.31]
Colucci 2010	201	199	0.0953 (0.1081)		32.1 %	1.10 [0.89, 1.36]
Heinemann 2006	98	97	-0.2231 (0.1468)		20.1 %	0.80 [0.60, 1.07]
Louvet 2005	157	156	-0.1625 (0.1291)		24.7 %	0.85 [0.66, 1.09]
Viret 2004	42	41	-0.0834 (0.2267)		9.5 %	0.92 [0.59, 1.43]
Wang 2002	22	20	0.5596 (0.4603)		2.5 %	1.75 [0.71, 4.31]
Subtotal (95% CI)	**573**	**567**			**100.0 %**	**0.94 [0.81, 1.08]**
Heterogeneity: Tau^2 = 0.00; Chi^2 = 5.90, df = 5 (P = 0.32); I^2 =15%						
Test for overall effect: Z = 0.88 (P = 0.38)						
2 Gemcitabine plus fluoropyrimidine						
Berlin 2002	160	162	-0.1985 (0.1185)		11.9 %	0.82 [0.65, 1.03]
Cunningham 2009	267	266	-0.1508 (0.0907)		20.3 %	0.86 [0.72, 1.03]
Di Costanzo 2005	43	48	0.0198 (0.2069)		3.9 %	1.02 [0.68, 1.53]
Herrmann 2007	160	159	-0.1393 (0.1333)		9.4 %	0.87 [0.67, 1.13]
Lee 2017	108	106	-0.1985 (0.1031)		15.7 %	0.82 [0.67, 1.00]
Ohkawa 2004	10	9	0.47 (0.5177)		0.6 %	1.60 [0.58, 4.41]
Ozaka 2012	53	59	-0.462 (0.2192)		3.5 %	0.63 [0.41, 0.97]
Riess 2005	235	238	0.0392 (0.097)		17.8 %	1.04 [0.86, 1.26]
Scheithauer 2003	41	42	-0.3011 (0.2426)		2.8 %	0.74 [0.46, 1.19]
Ueno 2013 (1)	275	277	-0.1278 (0.1095)		14.0 %	0.88 [0.71, 1.09]
Subtotal (95% CI)	**1352**	**1366**			**100.0 %**	**0.88 [0.81, 0.95]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 8.53, df = 9 (P = 0.48); I^2 =0.0%						
Test for overall effect: Z = 3.19 (P = 0.0014)						
3 Gemcitabine plus topoisomerase inhibitor						
Abou-Alfa 2006	175	174	-0.0101 (0.1151)		41.2 %	0.99 [0.79, 1.24]
Rocha Lima 2004	180	180	0.0296 (0.1101)		45.0 %	1.03 [0.83, 1.28]

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Study or subgroup	Gemcitabine combinations N	Gemcitabine alone N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
Stathopoulos 2006	60	70	-0.0101 (0.1992)		13.8 %	0.99 [0.67, 1.46]
Subtotal (95% CI)	**415**	**424**			**100.0 %**	**1.01 [0.87, 1.16]**
Heterogeneity: Tau² = 0.0; Chi² = 0.07, df = 2 (P = 0.96); I² =0.0%						
Test for overall effect: Z = 0.11 (P = 0.92)						
4 Gemcitabine plus taxane						
Von Hoff 2013	431	430	-0.3285 (0.0763)		100.0 %	0.72 [0.62, 0.84]
Subtotal (95% CI)	**431**	**430**			**100.0 %**	**0.72 [0.62, 0.84]**
Heterogeneity: not applicable						
Test for overall effect: Z = 4.31 (P = 0.000017)						
5 Gemcitabine plus other combinations of chemotherapy						
Petrioli 2015	34	33	-0.7985 (0.2421)		44.8 %	0.45 [0.28, 0.72]
Reni 2005	52	47	-0.4308 (0.2108)		55.2 %	0.65 [0.43, 0.98]
Subtotal (95% CI)	**86**	**80**			**100.0 %**	**0.55 [0.39, 0.79]**
Heterogeneity: Tau² = 0.02; Chi² = 1.31, df = 1 (P = 0.25); I² =24%						
Test for overall effect: Z = 3.26 (P = 0.0011)						
6 Gemcitabine plus other agent(s)						
Gansauge 2002 (2)	30	30	-0.9416 (0.3158)		17.4 %	0.39 [0.21, 0.72]
Meng 2012	39	37	-0.0834 (0.2097)		25.9 %	0.92 [0.61, 1.39]
Oettle 2005	283	282	-0.0202 (0.1052)		36.6 %	0.98 [0.80, 1.20]
Ueno 2013 – EPA study	43	23	-0.2357 (0.2759)		20.2 %	0.79 [0.46, 1.36]
Subtotal (95% CI)	**395**	**372**			**100.0 %**	**0.79 [0.56, 1.10]**
Heterogeneity: Tau² = 0.07; Chi² = 7.87, df = 3 (P = 0.05); I² =62%						
Test for overall effect: Z = 1.40 (P = 0.16)						
Test for subgroup differences: Chi² = 17.77, df = 5 (P = 0.00), I² =72%						

(1) This is a multi-armed study. Only these two arms have been analysed.

(2) This is a multi-armed study. Only these two arms have been analysed

Analysis 3.2. Comparison 3 Gemcitabine combinations versus gemcitabine alone, Outcome 2 Progression-free survival.

Review: Chemotherapy and radiotherapy for advanced pancreatic cancer

Comparison: 3 Gemcitabine combinations versus gemcitabine alone

Outcome: 2 Progression-free survival

Study or subgroup	Gemcitabine combinations N	Gemcitabine alone N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
1 Gemcitabine plus platinum agent						
Colucci 2002	53	54	-0.4005 (0.1392)		22.8 %	0.67 [0.51, 0.88]
Colucci 2010	201	199	-0.0305 (0.0983)		32.2 %	0.97 [0.80, 1.18]
Heinemann 2006	98	97	-0.2877 (0.14)		22.7 %	0.75 [0.57, 0.99]
Louvet 2005	157	156	-0.2485 (0.1424)		22.2 %	0.78 [0.59, 1.03]
Subtotal (95% CI)	**509**	**506**			**100.0 %**	**0.80 [0.68, 0.95]**
Heterogeneity: Tau^2 = 0.01; Chi^2 = 5.56, df = 3 (P = 0.14); I^2 =46%						
Test for overall effect: Z = 2.54 (P = 0.011)						
2 Gemcitabine plus fluoropyrimidine						
Berlin 2002	160	162	-0.2614 (0.1105)		12.6 %	0.77 [0.62, 0.96]
Cunningham 2009	267	266	-0.2485 (0.0852)		17.2 %	0.78 [0.66, 0.92]
Herrmann 2007	160	159	-0.1508 (0.1198)		11.2 %	0.86 [0.68, 1.09]
Lee 2017	108	106	-0.1393 (0.0895)		16.3 %	0.87 [0.73, 1.04]
Ozaka 2012	53	59	-0.5276 (0.1734)		6.3 %	0.59 [0.42, 0.83]
Riess 2005	235	238	-0.0726 (0.0963)		15.0 %	0.93 [0.77, 1.12]
Scheithauer 2003	41	42	-0.1863 (0.1571)		7.5 %	0.83 [0.61, 1.13]
Ueno 2013 (1)	275	277	-0.4155 (0.1024)		13.9 %	0.66 [0.54, 0.81]
Subtotal (95% CI)	**1299**	**1309**			**100.0 %**	**0.79 [0.72, 0.87]**
Heterogeneity: Tau^2 = 0.01; Chi^2 = 10.56, df = 7 (P = 0.16); I^2 =34%						
Test for overall effect: Z = 4.83 (P < 0.00001)						
3 Gemcitabine plus topoisomerase inhibitor						
Abou-Alfa 2006	175	174	-0.0726 (0.1098)		55.5 %	0.93 [0.75, 1.15]
Rocha Lima 2004	180	180	-0.1165 (0.1225)		44.5 %	0.89 [0.70, 1.13]
Subtotal (95% CI)	**355**	**354**			**100.0 %**	**0.91 [0.78, 1.07]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.07, df = 1 (P = 0.79); I^2 =0.0%						
Test for overall effect: Z = 1.13 (P = 0.26)						
4 Gemcitabine plus taxane						
Von Hoff 2013	431	430	-0.3711 (0.0886)		100.0 %	0.69 [0.58, 0.82]

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Study or subgroup	Gemcitabine combinations N	Gemcitabine alone N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
Subtotal (95% CI)	**431**	**430**			**100.0 %**	**0.69 [0.58, 0.82]**
Heterogeneity: not applicable						
Test for overall effect: Z = 4.19 (P = 0.000028)						
5 Gemcitabine plus other combinations of chemotherapy						
Petrioli 2015	34	33	-1.0498 (0.2606)		43.4 %	0.35 [0.21, 0.58]
Reni 2005	52	47	-0.6733 (0.2221)		56.6 %	0.51 [0.33, 0.79]
Subtotal (95% CI)	**86**	**80**			**100.0 %**	**0.43 [0.30, 0.62]**
Heterogeneity: Tau^2 = 0.01; Chi^2 = 1.21, df = 1 (P = 0.27); I^2 =17%						
Test for overall effect: Z = 4.48 (P < 0.00001)						
6 Gemcitabine plus other agent(s)						
Meng 2012	39	37	0.0488 (0.2207)		100.0 %	1.05 [0.68, 1.62]
Subtotal (95% CI)	**39**	**37**			**100.0 %**	**1.05 [0.68, 1.62]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.22 (P = 0.83)						
Test for subgroup differences: Chi^2 = 17.48, df = 5 (P = 0.00), I^2 =71%						

(1) This is a multi-armed study. Only these two arms have been analysed

Analysis 3.3. Comparison 3 Gemcitabine combinations versus gemcitabine alone, Outcome 3 Response rates.

Review: Chemotherapy and radiotherapy for advanced pancreatic cancer

Comparison: 3 Gemcitabine combinations versus gemcitabine alone

Outcome: 3 Response rates

Study or subgroup	Gemcitabine combinations n/N	Gemcitabine alone n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Gemcitabine plus platinum agent					
Colucci 2002	14/53	5/54		9.2 %	2.85 [1.11, 7.36]
Colucci 2010	26/201	20/199		27.3 %	1.29 [0.74, 2.23]
Heinemann 2006	11/98	9/97		11.8 %	1.21 [0.52, 2.79]
Li 2004	2/21	3/25		2.9 %	0.79 [0.15, 4.31]
Louvet 2005	42/157	27/156		44.6 %	1.55 [1.01, 2.38]
Viret 2004	3/42	2/41		2.7 %	1.46 [0.26, 8.31]
Wang 2002	2/22	1/20		1.5 %	1.82 [0.18, 18.55]
Subtotal (95% CI)	**594**	**592**		**100.0 %**	**1.48 [1.11, 1.98]**
Total events: 100 (Gemcitabine combinations), 67 (Gemcitabine alone)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.90, df = 6 (P = 0.82); I^2 =0.0%					
Test for overall effect: Z = 2.69 (P = 0.0070)					
2 Gemcitabine plus fluoropyrimidine					
Berlin 2002	11/160	9/162		9.2 %	1.24 [0.53, 2.91]
Cunningham 2009	51/267	33/266		17.9 %	1.54 [1.03, 2.31]
Di Costanzo 2005	17/43	18/48		15.1 %	1.05 [0.63, 1.77]
Herrmann 2007	15/160	12/159		11.1 %	1.24 [0.60, 2.57]
Lee 2017	38/108	10/106		12.6 %	3.73 [1.96, 7.09]
Ohkawa 2004	3/10	0/9		1.3 %	6.36 [0.37, 108.56]
Ozaka 2012	15/53	4/59		7.0 %	4.17 [1.48, 11.80]
Scheithauer 2003	7/41	6/42		7.4 %	1.20 [0.44, 3.25]
Ueno 2013	71/242	32/241		18.5 %	2.21 [1.52, 3.22]
Subtotal (95% CI)	**1084**	**1092**		**100.0 %**	**1.78 [1.29, 2.47]**
Total events: 228 (Gemcitabine combinations), 124 (Gemcitabine alone)					
Heterogeneity: Tau^2 = 0.11; Chi^2 = 16.58, df = 8 (P = 0.03); I^2 =52%					
Test for overall effect: Z = 3.48 (P = 0.00051)					
3 Gemcitabine plus topoisomerase inhibitor					

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Study or subgroup	Gemcitabine combinations n/N	Gemcitabine alone n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Abou-Alfa 2006	11/175	8/174		31.1 %	1.37 [0.56, 3.32]
Rocha Lima 2004	29/180	7/70		40.4 %	1.61 [0.74, 3.51]
Stathopoulos 2006	9/60	7/70		28.5 %	1.50 [0.59, 3.79]
Subtotal (95% CI)	**415**	**314**		**100.0 %**	**1.50 [0.92, 2.46]**
Total events: 49 (Gemcitabine combinations), 22 (Gemcitabine alone)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.07, df = 2 (P = 0.96); I^2 =0.0%					
Test for overall effect: Z = 1.61 (P = 0.11)					
4 Gemcitabine plus taxane					
Von Hoff 2013	99/431	30/430		100.0 %	3.29 [2.24, 4.84]
Subtotal (95% CI)	**431**	**430**		**100.0 %**	**3.29 [2.24, 4.84]**
Total events: 99 (Gemcitabine combinations), 30 (Gemcitabine alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 6.05 (P < 0.00001)					
5 Gemcitabane plus other combinations of chemotherapy					
Petrioli 2015	12/34	6/33		100.0 %	1.94 [0.83, 4.56]
Subtotal (95% CI)	**34**	**33**		**100.0 %**	**1.94 [0.83, 4.56]**
Total events: 12 (Gemcitabine combinations), 6 (Gemcitabine alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.52 (P = 0.13)					
6 Gemcitabine plus other agent(s)					
Gansauge 2002	16/30	1/30		24.4 %	16.00 [2.26, 113.12]
Meng 2012	3/34	1/32		20.9 %	2.82 [0.31, 25.77]
Oettle 2005	42/283	20/282		54.7 %	2.09 [1.26, 3.47]
Subtotal (95% CI)	**347**	**344**		**100.0 %**	**3.66 [1.04, 12.82]**
Total events: 61 (Gemcitabine combinations), 22 (Gemcitabine alone)					
Heterogeneity: Tau^2 = 0.68; Chi^2 = 4.24, df = 2 (P = 0.12); I^2 =53%					
Test for overall effect: Z = 2.03 (P = 0.043)					
Test for subgroup differences: Chi^2 = 12.71, df = 5 (P = 0.03), I^2 =61%					

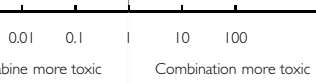
Analysis 3.4. Comparison 3 Gemcitabine combinations versus gemcitabine alone, Outcome 4 Grade 3/4 anaemia.

Review: Chemotherapy and radiotherapy for advanced pancreatic cancer

Comparison: 3 Gemcitabine combinations versus gemcitabine alone

Outcome: 4 Grade 3/4 anaemia

Study or subgroup	Gemcitabine combinations n/N	Gemcitabine alone n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Gemcitabine plus platinum agent					
Colucci 2002	3/51	2/53		6.7 %	1.56 [0.27, 8.95]
Colucci 2010	9/186	2/189		8.5 %	4.57 [1.00, 20.88]
Heinemann 2006	13/98	10/97		21.4 %	1.29 [0.59, 2.79]
Li 2004	2/21	2/25		6.0 %	1.19 [0.18, 7.74]
Louvet 2005	10/157	16/156		21.9 %	0.62 [0.29, 1.33]
Viret 2004	16/42	11/41		25.9 %	1.42 [0.75, 2.68]
Wang 2002	9/21	2/19		9.7 %	4.07 [1.00, 16.52]
Subtotal (95% CI)	**576**	**580**		**100.0 %**	**1.41 [0.87, 2.31]**
Total events: 62 (Gemcitabine combinations), 45 (Gemcitabine alone)					
Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 8.99$, df = 6 (P = 0.17); $I^2 = 33\%$					
Test for overall effect: Z = 1.38 (P = 0.17)					
2 Gemcitabine plus fluoropyrimidine					
Berlin 2002	16/158	16/158		17.2 %	1.00 [0.52, 1.93]
Cunningham 2009	9/251	14/247		11.1 %	0.63 [0.28, 1.43]
Di Costanzo 2005	3/41	3/49		3.1 %	1.20 [0.25, 5.61]
Herrmann 2007	12/159	10/156		11.3 %	1.18 [0.52, 2.65]
Lee 2017	5/103	4/101		4.5 %	1.23 [0.34, 4.43]
Ozaka 2012	4/53	3/59		3.5 %	1.48 [0.35, 6.33]
Scheithauer 2003	2/41	0/42		0.8 %	5.12 [0.25, 103.48]
Ueno 2013	46/267	39/273		48.4 %	1.21 [0.82, 1.78]
Subtotal (95% CI)	**1073**	**1085**		**100.0 %**	**1.11 [0.84, 1.45]**
Total events: 97 (Gemcitabine combinations), 89 (Gemcitabine alone)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.28$, df = 7 (P = 0.86); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.72 (P = 0.47)					
3 Gemcitabine plus topoisomerase inhibitor					
Abou-Alfa 2006	10/168	12/157		26.8 %	0.78 [0.35, 1.75]



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Study or subgroup	Gemcitabine combinations n/N	Gemcitabine alone n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Rocha Lima 2004	28/173	22/169		66.0 %	1.24 [0.74, 2.08]
Stathopoulos 2006	3/60	3/70		7.2 %	1.17 [0.24, 5.57]
Subtotal (95% CI)	**401**	**396**		**100.0 %**	**1.09 [0.72, 1.66]**
Total events: 41 (Gemcitabine combinations), 37 (Gemcitabine alone)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.92, df = 2 (P = 0.63); I^2 =0.0%					
Test for overall effect: Z = 0.41 (P = 0.68)					
4 Gemcitabine plus taxane					
Von Hoff 2013	53/405	48/388		100.0 %	1.06 [0.73, 1.52]
Subtotal (95% CI)	**405**	**388**		**100.0 %**	**1.06 [0.73, 1.52]**
Total events: 53 (Gemcitabine combinations), 48 (Gemcitabine alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.30 (P = 0.76)					
5 Gemcitabine plus other combinations of chemotherapy					
Petrioli 2015	6/34	3/33		100.0 %	1.94 [0.53, 7.13]
Subtotal (95% CI)	**34**	**33**		**100.0 %**	**1.94 [0.53, 7.13]**
Total events: 6 (Gemcitabine combinations), 3 (Gemcitabine alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.00 (P = 0.32)					
6 Gemcitabine plus other agent(s)					
Meng 2012	5/39	2/37		15.2 %	2.37 [0.49, 11.48]
Oettle 2005	38/273	8/273		68.4 %	4.75 [2.26, 9.99]
Ueno 2013 – EPA study	6/43	2/23		16.4 %	1.60 [0.35, 7.32]
Subtotal (95% CI)	**355**	**333**		**100.0 %**	**3.58 [1.93, 6.62]**
Total events: 49 (Gemcitabine combinations), 12 (Gemcitabine alone)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.91, df = 2 (P = 0.39); I^2 =0.0%					
Test for overall effect: Z = 4.06 (P = 0.000049)					
Test for subgroup differences: Chi^2 = 13.88, df = 5 (P = 0.02), I^2 =64%					

Analysis 3.5. Comparison 3 Gemcitabine combinations versus gemcitabine alone, Outcome 5 Grade 3/4 neutropenia.

Review: Chemotherapy and radiotherapy for advanced pancreatic cancer

Comparison: 3 Gemcitabine combinations versus gemcitabine alone

Outcome: 5 Grade 3/4 neutropenia

Study or subgroup	Gemcitabine combinations n/N	Gemcitabine alone n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Gemcitabine plus platinum agent					
Colucci 2002	9/51	5/53		10.3 %	1.87 [0.67, 5.21]
Colucci 2010	46/186	26/189		24.4 %	1.80 [1.16, 2.78]
Li 2004	4/21	2/25		5.1 %	2.38 [0.48, 11.74]
Louvet 2005	32/157	43/156		25.6 %	0.74 [0.50, 1.10]
Viret 2004	24/42	16/41		23.5 %	1.46 [0.92, 2.33]
Wang 2002	7/21	5/19		11.1 %	1.27 [0.48, 3.33]
Subtotal (95% CI)	**478**	**483**		**100.0 %**	**1.34 [0.90, 1.97]**
Total events: 122 (Gemcitabine combinations), 97 (Gemcitabine alone)					
Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 10.94$, df = 5 (P = 0.05); $I^2 = 54\%$					
Test for overall effect: Z = 1.46 (P = 0.14)					
2 Gemcitabine plus fluoropyrimidine					
Berlin 2002	11/158	8/158		2.2 %	1.38 [0.57, 3.33]
Cunningham 2009	87/251	54/247		19.9 %	1.59 [1.19, 2.12]
Di Costanzo 2005	1/41	1/49		0.2 %	1.20 [0.08, 18.52]
Herrmann 2007	36/159	30/156		9.1 %	1.18 [0.76, 1.81]
Lee 2017	18/103	12/101		3.7 %	1.47 [0.75, 2.89]
Ohkawa 2004	1/10	1/9		0.2 %	0.90 [0.07, 12.38]
Ozaka 2012	29/53	13/59		5.8 %	2.48 [1.45, 4.26]
Scheithauer 2003	4/41	3/42		0.8 %	1.37 [0.33, 5.73]
Ueno 2013	166/267	112/273		58.1 %	1.52 [1.28, 1.80]
Subtotal (95% CI)	**1083**	**1094**		**100.0 %**	**1.53 [1.34, 1.74]**
Total events: 353 (Gemcitabine combinations), 234 (Gemcitabine alone)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 4.87$, df = 8 (P = 0.77); $I^2 = 0.0\%$					
Test for overall effect: Z = 6.41 (P < 0.00001)					
3 Gemcitabine plus topoisomerase inhibitor					
Abou-Alfa 2006	51/168	23/157		34.1 %	2.07 [1.33, 3.22]

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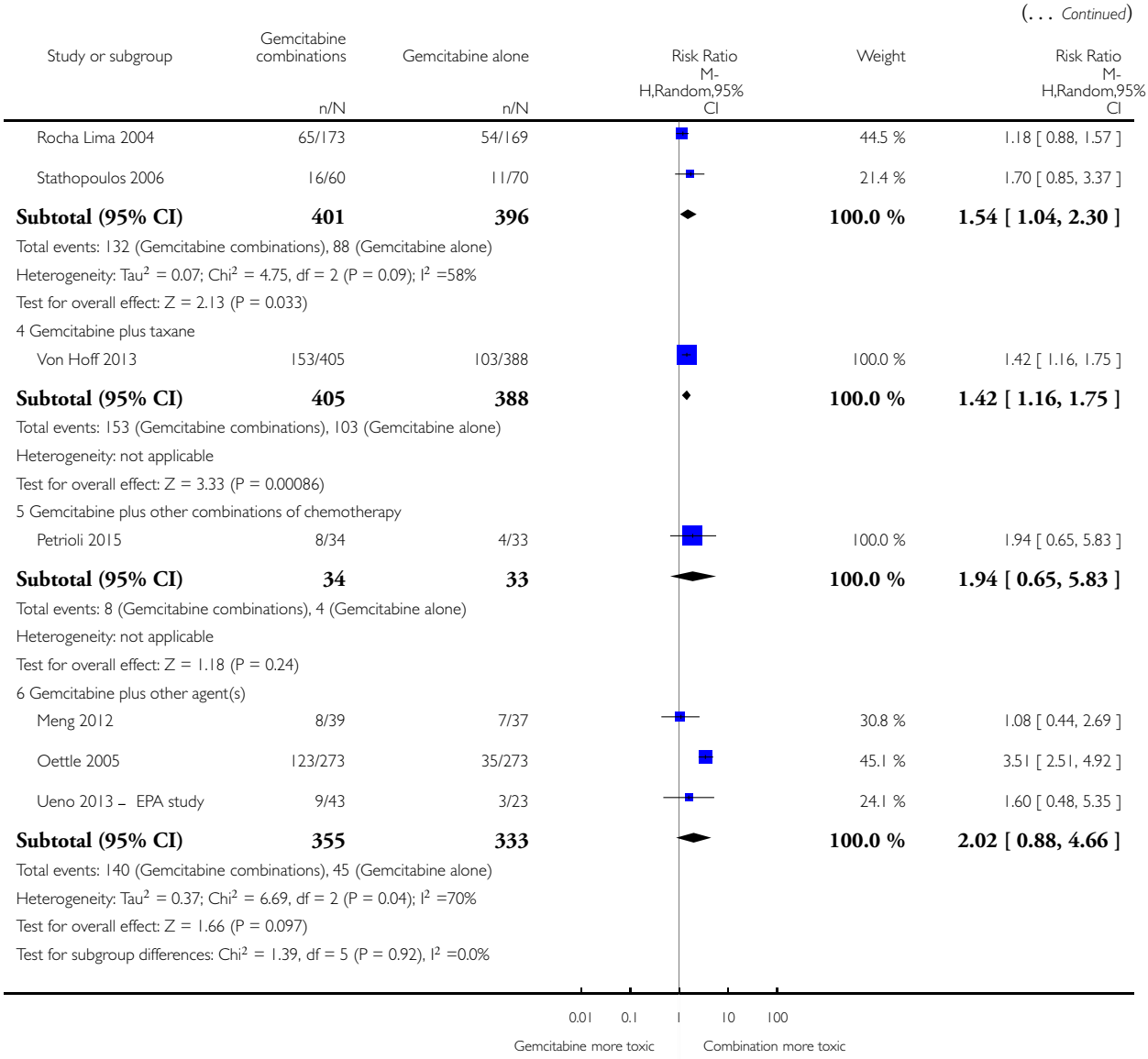
Study or subgroup	Gemcitabine combinations n/N	Gemcitabine alone n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Rocha Lima 2004	65/173	54/169		44.5 %	1.18 [0.88, 1.57]
Stathopoulos 2006	16/60	11/70		21.4 %	1.70 [0.85, 3.37]
Subtotal (95% CI)	**401**	**396**		**100.0 %**	**1.54 [1.04, 2.30]**
Total events: 132 (Gemcitabine combinations), 88 (Gemcitabine alone)					
Heterogeneity: Tau^2 = 0.07; Chi^2 = 4.75, df = 2 (P = 0.09); I^2 =58%					
Test for overall effect: Z = 2.13 (P = 0.033)					
4 Gemcitabine plus taxane					
Von Hoff 2013	153/405	103/388		100.0 %	1.42 [1.16, 1.75]
Subtotal (95% CI)	**405**	**388**		**100.0 %**	**1.42 [1.16, 1.75]**
Total events: 153 (Gemcitabine combinations), 103 (Gemcitabine alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.33 (P = 0.00086)					
5 Gemcitabine plus other combinations of chemotherapy					
Petrioli 2015	8/34	4/33		100.0 %	1.94 [0.65, 5.83]
Subtotal (95% CI)	**34**	**33**		**100.0 %**	**1.94 [0.65, 5.83]**
Total events: 8 (Gemcitabine combinations), 4 (Gemcitabine alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.18 (P = 0.24)					
6 Gemcitabine plus other agent(s)					
Meng 2012	8/39	7/37		30.8 %	1.08 [0.44, 2.69]
Oettle 2005	123/273	35/273		45.1 %	3.51 [2.51, 4.92]
Ueno 2013 – EPA study	9/43	3/23		24.1 %	1.60 [0.48, 5.35]
Subtotal (95% CI)	**355**	**333**		**100.0 %**	**2.02 [0.88, 4.66]**
Total events: 140 (Gemcitabine combinations), 45 (Gemcitabine alone)					
Heterogeneity: Tau^2 = 0.37; Chi^2 = 6.69, df = 2 (P = 0.04); I^2 =70%					
Test for overall effect: Z = 1.66 (P = 0.097)					
Test for subgroup differences: Chi^2 = 1.39, df = 5 (P = 0.92), I^2 =0.0%					



Analysis 3.6. Comparison 3 Gemcitabine combinations versus gemcitabine alone, Outcome 6 Grade 3/4 thrombocytopenia.

Review: Chemotherapy and radiotherapy for advanced pancreatic cancer

Comparison: 3 Gemcitabine combinations versus gemcitabine alone

Outcome: 6 Grade 3/4 thrombocytopenia

Study or subgroup	Gemcitabine combinations n/N	Gemcitabine alone n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Gemcitabine plus platinum agent					
Colucci 2002	1/51	1/53		5.0 %	1.04 [0.07, 16.18]
Colucci 2010	29/186	10/189		22.9 %	2.95 [1.48, 5.87]
Heinemann 2006	4/98	10/97		16.3 %	0.40 [0.13, 1.22]
Louvet 2005	22/157	5/156		18.9 %	4.37 [1.70, 11.25]
Viret 2004	14/42	5/41		19.2 %	2.73 [1.08, 6.90]
Wang 2002	8/21	4/19		17.7 %	1.81 [0.65, 5.06]
Subtotal (95% CI)	**555**	**555**		**100.0 %**	**1.96 [1.00, 3.84]**
Total events: 78 (Gemcitabine combinations), 35 (Gemcitabine alone)					
Heterogeneity: Tau^2 = 0.39; Chi^2 = 12.28, df = 5 (P = 0.03); I^2 =59%					
Test for overall effect: Z = 1.97 (P = 0.049)					
2 Gemcitabine plus fluoropyrimidine					
Berlin 2002	30/158	16/158		22.6 %	1.88 [1.07, 3.30]
Cunningham 2009	28/251	14/247		20.7 %	1.97 [1.06, 3.65]
Di Costanzo 2005	1/41	0/49		1.5 %	3.57 [0.15, 85.39]
Herrmann 2007	7/159	12/156		13.0 %	0.57 [0.23, 1.42]
Lee 2017	1/103	5/101		3.1 %	0.20 [0.02, 1.65]
Ohkawa 2004	1/10	0/9		1.6 %	2.73 [0.12, 59.57]
Ozaka 2012	8/53	3/59		7.7 %	2.97 [0.83, 10.61]
Scheithauer 2003	0/41	1/42		1.5 %	0.34 [0.01, 8.14]
Ueno 2013	46/267	30/273		28.3 %	1.57 [1.02, 2.41]
Subtotal (95% CI)	**1083**	**1094**		**100.0 %**	**1.48 [1.00, 2.18]**
Total events: 122 (Gemcitabine combinations), 81 (Gemcitabine alone)					
Heterogeneity: Tau^2 = 0.09; Chi^2 = 11.59, df = 8 (P = 0.17); I^2 =31%					
Test for overall effect: Z = 1.95 (P = 0.052)					
3 Gemcitabine plus topoisomerase inhibitor					
Abou-Alfa 2006	26/168	7/157		40.2 %	3.47 [1.55, 7.77]

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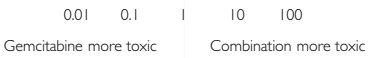
Study or subgroup	Gemcitabine combinations n/N	Gemcitabine alone n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Rocha Lima 2004	34/173	24/169		52.4 %	1.38 [0.86, 2.23]
Stathopoulos 2006	3/60	0/70		7.4 %	8.15 [0.43, 154.64]
Subtotal (95% CI)	**401**	**396**		**100.0 %**	**2.28 [0.97, 5.36]**
Total events: 63 (Gemcitabine combinations), 31 (Gemcitabine alone)					
Heterogeneity: Tau^2 = 0.30; Chi^2 = 4.86, df = 2 (P = 0.09); I^2 =59%					
Test for overall effect: Z = 1.90 (P = 0.058)					
4 Gemcitabine plus taxane					
Von Hoff 2013	52/405	36/388		100.0 %	1.38 [0.93, 2.07]
Subtotal (95% CI)	**405**	**388**		**100.0 %**	**1.38 [0.93, 2.07]**
Total events: 52 (Gemcitabine combinations), 36 (Gemcitabine alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.59 (P = 0.11)					
5 Gemcitabine plus other combinations of chemotherapy					
Petrioli 2015	10/34	5/33		100.0 %	1.94 [0.74, 5.07]
Subtotal (95% CI)	**34**	**33**		**100.0 %**	**1.94 [0.74, 5.07]**
Total events: 10 (Gemcitabine combinations), 5 (Gemcitabine alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.35 (P = 0.18)					
6 Gemcitabine plus other agent(s)					
Meng 2012	2/39	4/37		25.6 %	0.47 [0.09, 2.44]
Oettle 2005	49/273	17/273		48.6 %	2.88 [1.70, 4.88]
Ueno 2013 – EPA study	4/43	2/23		25.8 %	1.07 [0.21, 5.41]
Subtotal (95% CI)	**355**	**333**		**100.0 %**	**1.41 [0.45, 4.39]**
Total events: 55 (Gemcitabine combinations), 23 (Gemcitabine alone)					
Heterogeneity: Tau^2 = 0.62; Chi^2 = 5.14, df = 2 (P = 0.08); I^2 =61%					
Test for overall effect: Z = 0.59 (P = 0.56)					
Test for subgroup differences: Chi^2 = 1.87, df = 5 (P = 0.87), I^2 =0.0%					

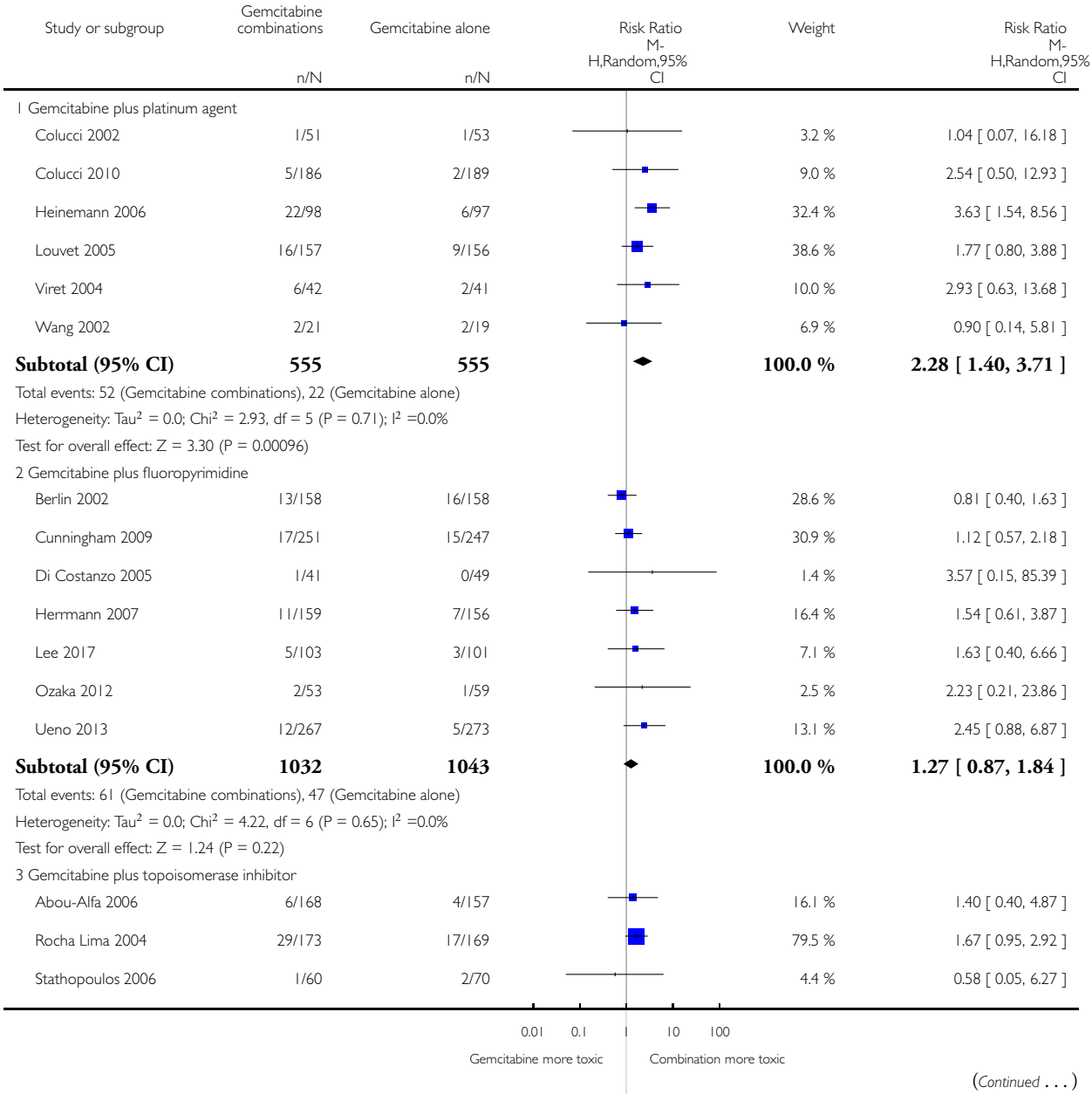


Analysis 3.7. Comparison 3 Gemcitabine combinations versus gemcitabine alone, Outcome 7 Grade 3/4 nausea.

Review: Chemotherapy and radiotherapy for advanced pancreatic cancer

Comparison: 3 Gemcitabine combinations versus gemcitabine alone

Outcome: 7 Grade 3/4 nausea



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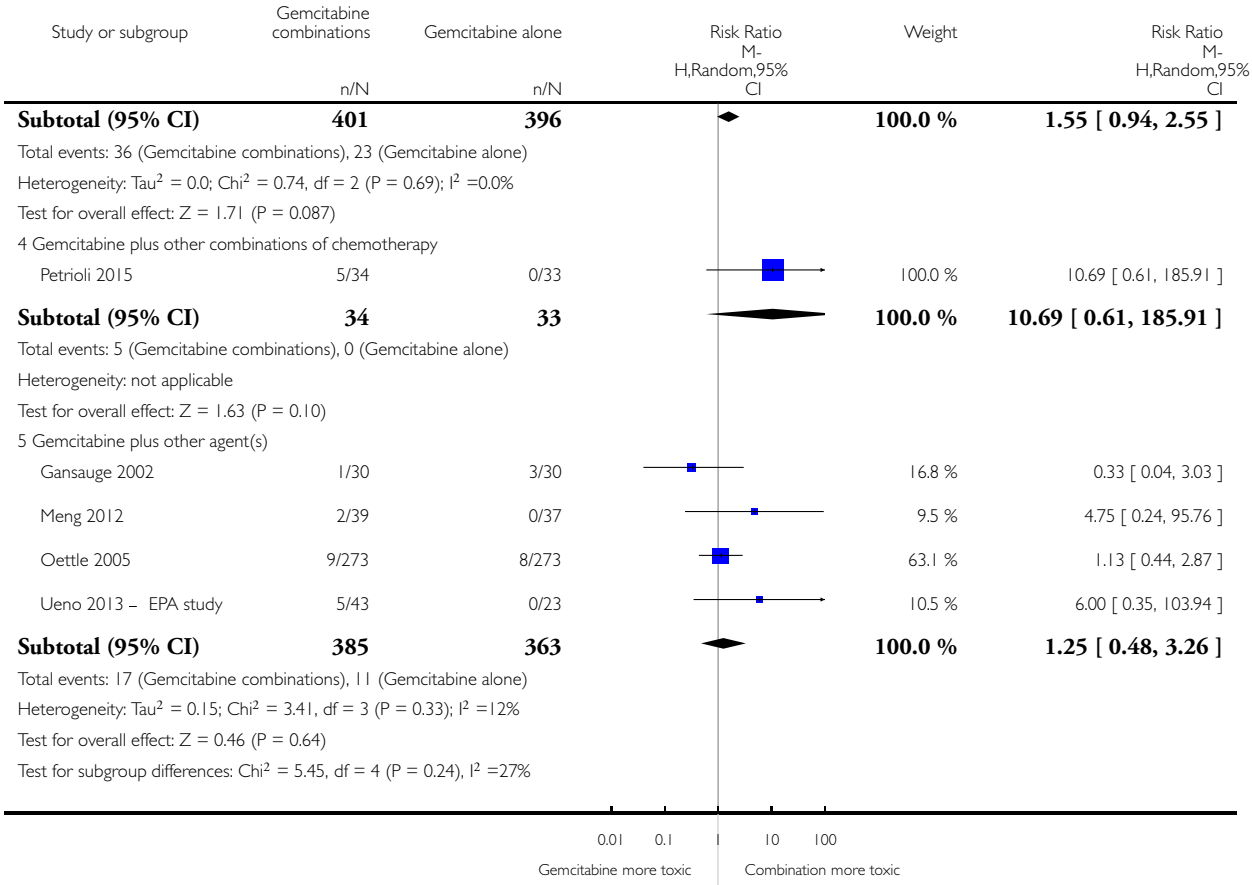
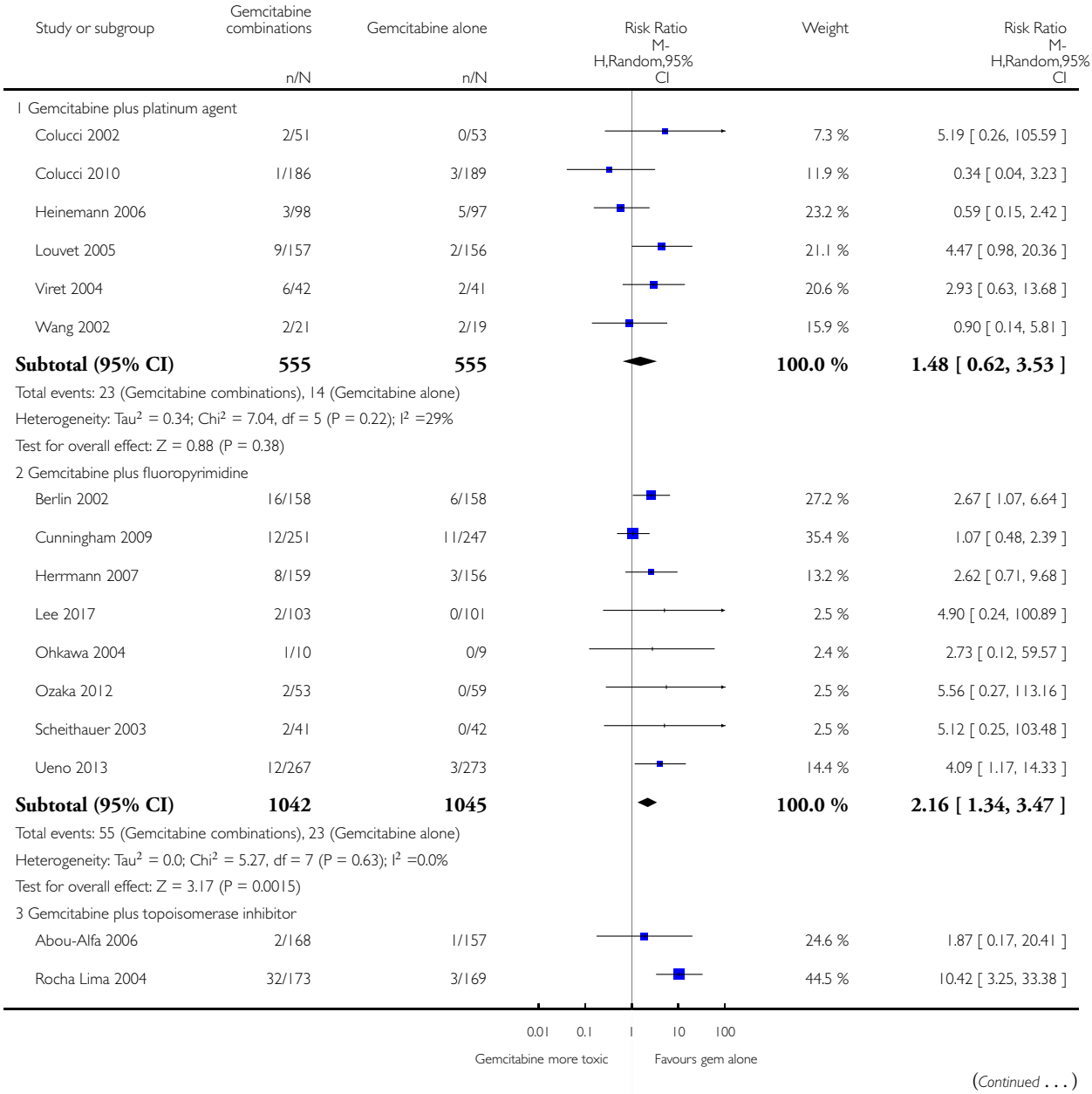


Analysis 3.8. Comparison 3 Gemcitabine combinations versus gemcitabine alone, Outcome 8 Grade 3/4 diarrhoea.

Review: Chemotherapy and radiotherapy for advanced pancreatic cancer

Comparison: 3 Gemcitabine combinations versus gemcitabine alone

Outcome: 8 Grade 3/4 diarrhoea



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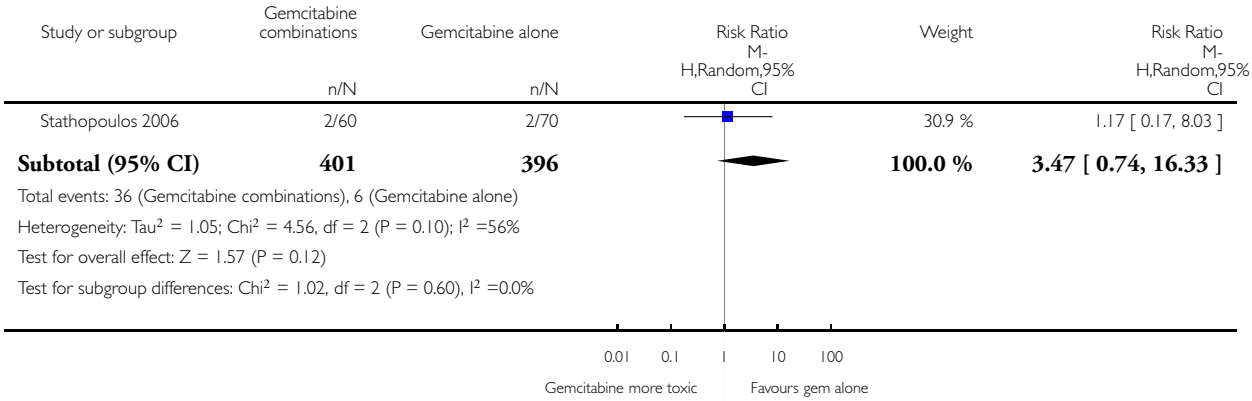
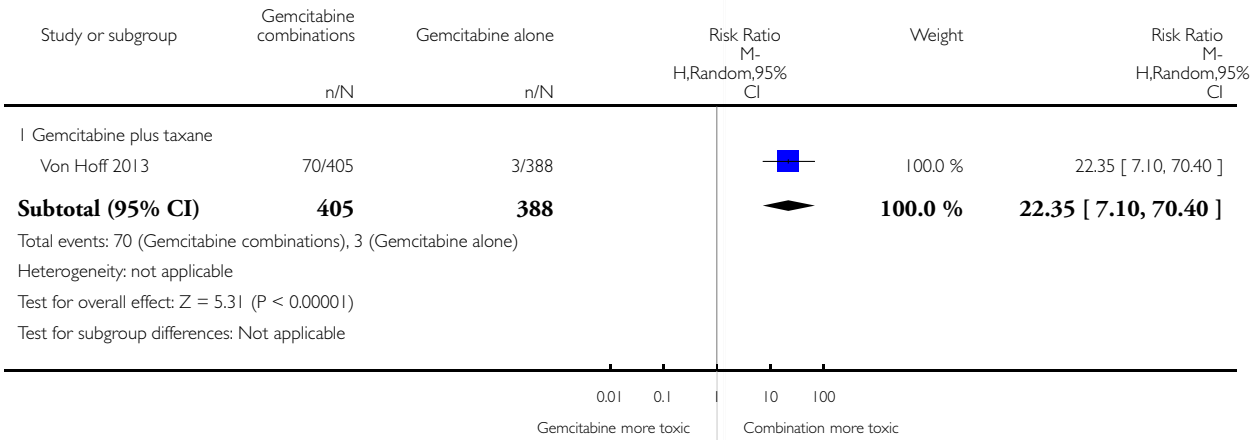


Analysis 3.9. Comparison 3 Gemcitabine combinations versus gemcitabine alone, Outcome 9 Grade 3/4 neuropathy.

Review: Chemotherapy and radiotherapy for advanced pancreatic cancer

Comparison: 3 Gemcitabine combinations versus gemcitabine alone

Outcome: 9 Grade 3/4 neuropathy



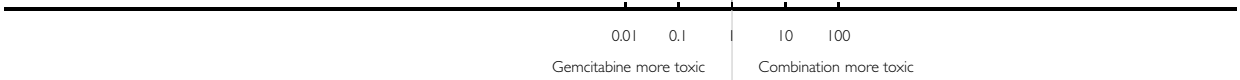
Analysis 3.10. Comparison 3 Gemcitabine combinations versus gemcitabine alone, Outcome 10 Grade 3/4 fatigue.

Review: Chemotherapy and radiotherapy for advanced pancreatic cancer

Comparison: 3 Gemcitabine combinations versus gemcitabine alone

Outcome: 10 Grade 3/4 fatigue

Study or subgroup	Gemcitabine combinations n/N	Gemcitabine alone n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Gemcitabine plus taxane					
Von Hoff 2013	70/405	27/388		100.0 %	2.48 [1.63, 3.79]
Subtotal (95% CI)	**405**	**388**		**100.0 %**	**2.48 [1.63, 3.79]**
Total events: 70 (Gemcitabine combinations), 27 (Gemcitabine alone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.23 (P = 0.000023)					
Test for subgroup differences: Not applicable					



Analysis 4.1. Comparison 4 Fluoropyrimidine combinations versus fluoropyrimidine alone, Outcome 1 Overall survival.

Review: Chemotherapy and radiotherapy for advanced pancreatic cancer

Comparison: 4 Fluoropyrimidine combinations versus fluoropyrimidine alone

Outcome: 1 Overall survival

Study or subgroup	5FU combination N	5FU alone N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
Ducreux 2004 (1)	31	15	-1.0498 (0.3393)		14.8 %	0.35 [0.18, 0.68]
Kovach 1974 (2)	30	30	0.0198 (0.254)		20.6 %	1.02 [0.62, 1.68]
Maisey 2002	102	107	-0.1054 (0.1282)		32.7 %	0.90 [0.70, 1.16]
Moertel 1979	87	89	0.0198 (0.1369)		31.8 %	1.02 [0.78, 1.33]
Total (95% CI)	**250**	**241**			**100.0 %**	**0.84 [0.61, 1.15]**

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 8.83$, df = 3 (P = 0.03); $I^2 = 66\%$

Test for overall effect: Z = 1.10 (P = 0.27)

Test for subgroup differences: Not applicable

(1) This is a multi-armed study, only the 5FU v 5FU + oxaliplatin arms have been analysed

(2) This is a multi-armed study, only these two arms have been analysed

Analysis 4.2. Comparison 4 Fluoropyrimidine combinations versus fluoropyrimidine alone, Outcome 2 Progression-free survival.

Review: Chemotherapy and radiotherapy for advanced pancreatic cancer

Comparison: 4 Fluoropyrimidine combinations versus fluoropyrimidine alone

Outcome: 2 Progression-free survival

Study or subgroup	5FU combination N	5FU alone N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
Ducreux 2004	31	15	-1.204 (0.3207)		45.5 %	0.30 [0.16, 0.56]
Maisey 2002	102	107	-0.1985 (0.1107)		54.5 %	0.82 [0.66, 1.02]
Total (95% CI)	**133**	**122**			**100.0 %**	**0.52 [0.19, 1.38]**

Heterogeneity: Tau² = 0.45; Chi² = 8.78, df = 1 (P = 0.003); I² =89%

Test for overall effect: Z = 1.31 (P = 0.19)

Test for subgroup differences: Not applicable

Analysis 4.3. Comparison 4 Fluoropyrimidine combinations versus fluoropyrimidine alone, Outcome 3 Response rates.

Review: Chemotherapy and radiotherapy for advanced pancreatic cancer

Comparison: 4 Fluoropyrimidine combinations versus fluoropyrimidine alone

Outcome: 3 Response rates

Study or subgroup	5FU combination n/N	5FU alone n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Ducreux 2004	3/31	0/15		6.9 %	3.50 [0.19, 63.72]
Kovach 1974	5/31	10/30		30.6 %	0.48 [0.19, 1.25]
Maisey 2002	18/102	9/107		36.1 %	2.10 [0.99, 4.45]
Moertel 1979	6/48	5/46		26.4 %	1.15 [0.38, 3.51]
Total (95% CI)	**212**	**198**		**100.0 %**	**1.18 [0.52, 2.68]**

Total events: 32 (5FU combination), 24 (5FU alone)

Heterogeneity: Tau² = 0.33; Chi² = 6.19, df = 3 (P = 0.10); I² =52%

Test for overall effect: Z = 0.40 (P = 0.69)

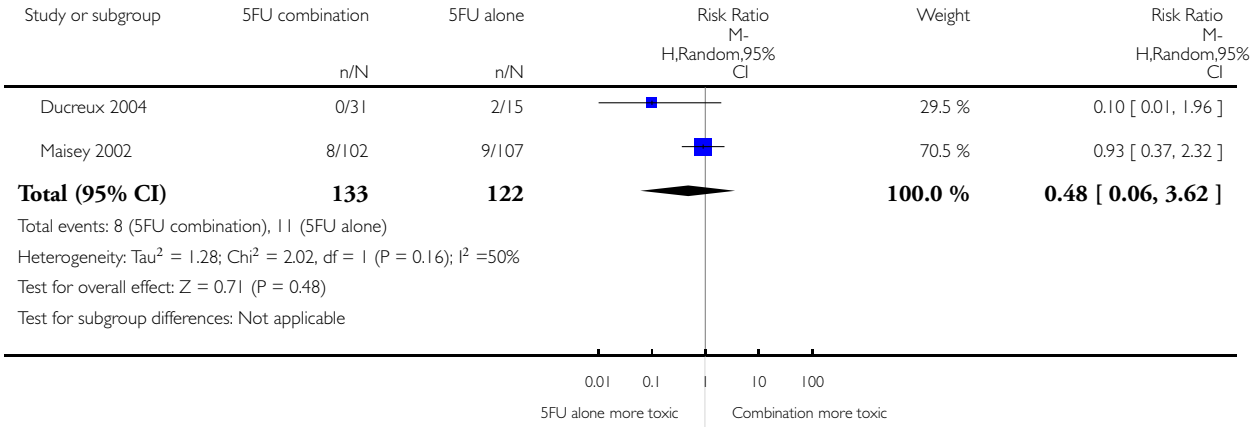
Test for subgroup differences: Not applicable

Analysis 4.4. Comparison 4 Fluoropyrimidine combinations versus fluoropyrimidine alone, Outcome 4 Grade 3/4 anaemia.

Review: Chemotherapy and radiotherapy for advanced pancreatic cancer

Comparison: 4 Fluoropyrimidine combinations versus fluoropyrimidine alone

Outcome: 4 Grade 3/4 anaemia



Analysis 4.5. Comparison 4 Fluoropyrimidine combinations versus fluoropyrimidine alone, Outcome 5 Grade 3/4 neutropenia.

Review: Chemotherapy and radiotherapy for advanced pancreatic cancer

Comparison: 4 Fluoropyrimidine combinations versus fluoropyrimidine alone

Outcome: 5 Grade 3/4 neutropenia

Study or subgroup	5FU combination n/N	5FU alone n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Ducreux 2004	4/31	0/15		51.6 %	4.50 [0.26, 78.53]
Maisey 2002	3/102	0/107		48.4 %	7.34 [0.38, 140.36]
Total (95% CI)	**133**	**122**		**100.0 %**	**5.70 [0.73, 44.46]**

Total events: 7 (5FU combination), 0 (5FU alone)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.05$, df = 1 (P = 0.82); $I^2 = 0.0\%$

Test for overall effect: Z = 1.66 (P = 0.097)

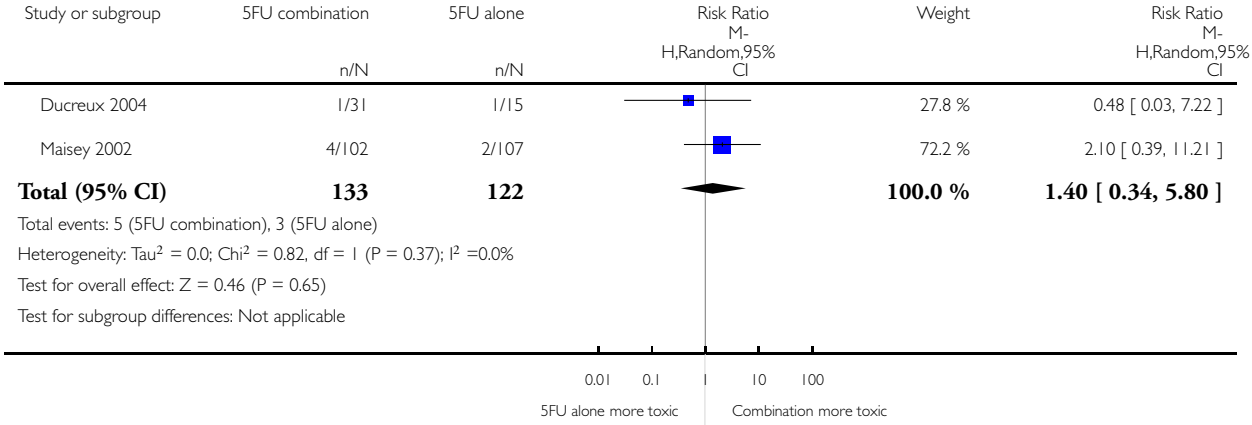
Test for subgroup differences: Not applicable

Analysis 4.6. Comparison 4 Fluoropyrimidine combinations versus fluoropyrimidine alone, Outcome 6 Grade 3/4 thrombocytopenia.

Review: Chemotherapy and radiotherapy for advanced pancreatic cancer

Comparison: 4 Fluoropyrimidine combinations versus fluoropyrimidine alone

Outcome: 6 Grade 3/4 thrombocytopenia

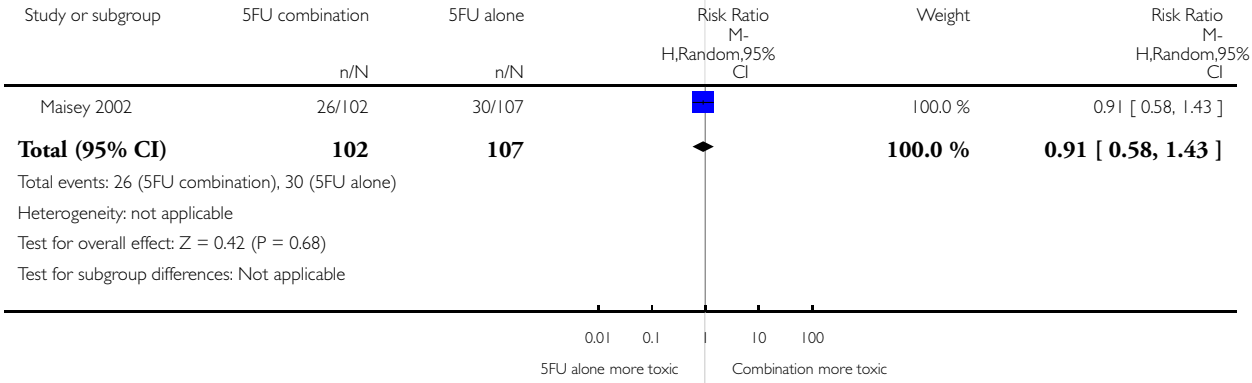


Analysis 4.7. Comparison 4 Fluoropyrimidine combinations versus fluoropyrimidine alone, Outcome 7 Grade 3/4 fatigue.

Review: Chemotherapy and radiotherapy for advanced pancreatic cancer

Comparison: 4 Fluoropyrimidine combinations versus fluoropyrimidine alone

Outcome: 7 Grade 3/4 fatigue

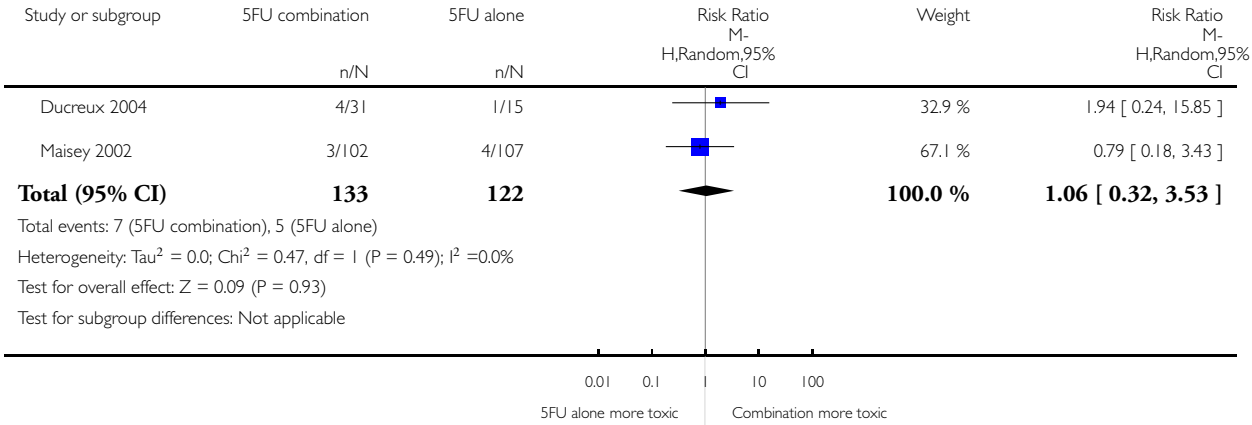


Analysis 4.8. Comparison 4 Fluoropyrimidine combinations versus fluoropyrimidine alone, Outcome 8 Grade 3/4 nausea.

Review: Chemotherapy and radiotherapy for advanced pancreatic cancer

Comparison: 4 Fluoropyrimidine combinations versus fluoropyrimidine alone

Outcome: 8 Grade 3/4 nausea

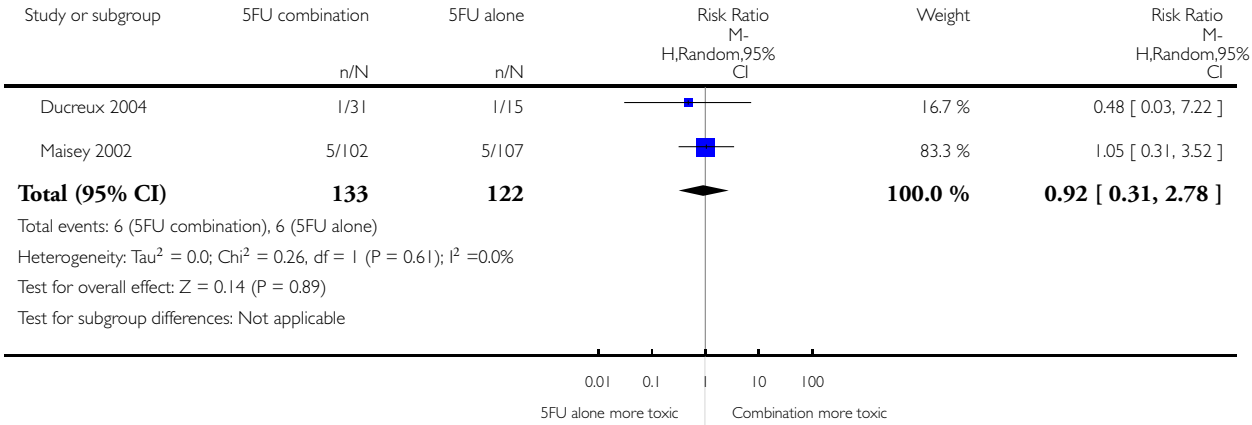


Analysis 4.9. Comparison 4 Fluoropyrimidine combinations versus fluoropyrimidine alone, Outcome 9 Grade 3/4 diarrhoea.

Review: Chemotherapy and radiotherapy for advanced pancreatic cancer

Comparison: 4 Fluoropyrimidine combinations versus fluoropyrimidine alone

Outcome: 9 Grade 3/4 diarrhoea



ADDITIONAL TABLES

Table 1. Median survival times and quality of life results of anti-cancer therapy versus best supportive care

Study	Anti-cancer therapy details	Median survival:anti-cancer therapy vs best supportive care (months)	Quality of life
Andren-Sandberg 1983	5FU + CCNU	5 vs 4	No difference in Karnofsky performance status (KPS) score
Frey 1981	5FU + CCNU	3.0 vs 3.9	Not addressed
Glimelius 1996	5FU + LV	6.0 vs 2.5	EORTC QLQ-C30 results favoured the anti-cancer therapy (NB: high rate of dropouts in the later time points)
Huguier 2001	5FU + LV + cisplatin	8.6 vs 7.0	Not addressed
Takada 1998	5FU + doxorubicin + MMC	4.9 vs 5.0	Not addressed

Table 1. Median survival times and quality of life results of anti-cancer therapy versus best supportive care (*Continued*)

Xinopoulos 2008	Gemcitabine	5.25 vs 5.5	Superior QoL (EORTC QLQ-C30) in the gemcitabine group during the 1st month (P = 0.028), no difference from the 2nd to the 4th month; in the 5th and 6th month superior QoL in the BSC group (P = 0.010 and < 0.001)

5FU: 5-Fluorouracil; **CCNU**: chloroethylcyclohexylnitrosurea; **EORTC QLQ-C30**: European Organisation for Research and Treatment of Cancer quality of life questionnaire for cancer patients; **LV**: leucovorin; **MMC**: 5FU+doxorubicin + mitomycin C

Table 2. Median survival times and quality of life results of various types of chemotherapy versus gemcitabine

Study	Type of other chemotherapy	Median survival:other chemotherapy vs gemcitabine (months)	Quality of life
Burris 1997	5FU	4.4 vs 5.7	Improved clinical benefit 4.8% vs 23.8%. Median time to benefit 7 vs 3 weeks. Duration of benefit 18 vs 13 weeks
Conroy 2011	FOLFIRINOX	11.1 vs 6.8	QLQ-C30: decrease in Global Health Status and QoL scale at 3 months 17% vs 31%; at 6 months 31% vs 66% Median time to definitive deterioration: not reached vs 5.7 months
Singhal 2014	FOLFIRINOX	10.8 vs 7.4	Definitive degradation of QoL at six months: 29% vs 59%
Poplin 2013	CO-101	5.2 vs 6.0	Not addressed
Smith 2003	ZD-9331	5.0 vs 3.6	Not addressed
Poplin 2009	Fixed dose rate gemcitabine 1500 mg/m² over 150 min	6.2 vs 4.9	Not addressed
Tempero 2003	Fixed dose rate gemcitabine 1500 mg/m² at 10 mg/m²/min	8.0 vs 5.0	Not addressed
Cheverton 2004	Exatecan (DX-8951f)	5.0 vs 6.6	Time to worsening of clinical benefit was longer in the gemcitabine group. Pain (3.7 vs 7.9 months; P = 0.0493), KPS (3.4 vs 4.6 months; P = 0.0111) and weight (2.3 vs 3.8

Table 2. Median survival times and quality of life results of various types of chemotherapy versus gemcitabine (*Continued*)

			months; P = 0.0203). QoL measured with QLQ-C3 and QLQ-PAN26 were similar in the 2 groups

5FU: 5-Fluorouracil; **FOLFIRINOX**: 5-fluorouracil + irinotecan + oxaliplatin; **QoL**: quality of life; **QLQ-C30** and **QLQ-PAN26:** general and pancreatic cancer specific QoL questionnaire.

Table 3. Median survival times and quality of life results of gemcitabine combinations versus gemcitabine alone

Study	Gemcitabine combination details	Median survival:gemcitabine combination vs gemcitabine alone (months)	Quality of life
Platinum combinations			
Colucci 2002	Gemcitabine + cisplatin	7.5 vs 5.0	Not addressed
Colucci 2010	Gemcitabine + cisplatin	7.2 vs 8.3	The mean difference from baseline in global QoL (EORTC C30) was not significantly different between the 2 groups: 0.09 (gemcitabine/cisplatin) vs 6.20 (gemcitabine), P = 0.07
Heinemann 2006	Gemcitabine + cisplatin	7.5 vs 6.0	No difference was detected in the 2 groups with either the Spitzer index or the pain intensity score
Li 2004	Gemcitabine + cisplatin	5.6 vs 4.6	Clinical benefit (pain control, performance status, body weight gain) 29% vs 36% (P > 0.05); Quality adjusted life months 3.8 vs 5.6 (P < 0.001)
Louvet 2005	Gemcitabine + oxaliplatin	9.0 vs 7.1	Not addressed
Viret 2004	Gemcitabine + cisplatin	8.0 vs 6.7	Q-TWiST results did not differ significantly between the 2 arms (EORTC C30)
Wang 2002	Gemcitabine + cisplatin	7.2 vs 9.1	Not addressed
Fluoropyrimidine combinations			
Berlin 2002	Gemcitabine + 5FU (weekly)	6.7 vs 5.4	Not addressed

Table 3. Median survival times and quality of life results of gemcitabine combinations versus gemcitabine alone (*Continued*)

Cunningham 2009	Gemcitabine + capecitabine	7.1 vs 6.2	89% of people completed QoL questionnaires (EORTC QLQ-C30 + ESPAC). No differences seen at baseline between the 2 groups and no differences across treatment groups at 3 or 6 months
Di Costanzo 2005	Gemcitabine + daily 5FU	7.5 vs 7.75	No differences were seen between the 2 groups in mean disturbed days after cycle 1 or 2 or mean of days a person would like to cancel treatment in cycle 1 or 2
Herrmann 2007	Gemcitabine + capecitabine	8.4 vs 7.2	CBR seen in 29% of people in combination arm and 20% of people in gemcitabine arm. Median duration of response 9.5 and 6.5 weeks, respectively (P < 0.02) . No differences in QoL as measured by LASA
Lee 2017	Gemcitabine + capecitabine	10.3 vs 7.5	Not addressed
Ohkawa 2004	Gemcitabine + UFT	Not stated	Not addressed
Ozaka 2012	Gemcitabine + S1	13.7 vs 8.0	Not addressed
Riess 2005	Gemcitabine + 5FU (24 hour infusion) + FA	Not stated	Not addressed
Scheithauer 2003	Gemcitabine + capecitabine	9.5 vs 8.2	The gemcitabine + capecitabine arm had an improvement in pain (35.5 vs 20%), KPS (41.9 vs 27%) , but not weight (9.7 vs 17%)
Ueno 2013	Gemcitabine + S1	10.1 vs 8.8	The gemcitabine + S1 group showed an improvement in QALYs 0.525 vs 0.401, P < 0.001
Topoisomerase combinations			
Abou-Alfa 2006	Gemcitabine + exatecan	6.2 vs 6.7	Not addressed
Rocha Lima 2004	Gemcitabine + irinotecan	6.3 vs 6.5	FACT-Hep questionnaires were completed by 80% of people in irinotecan/gemcitabine group and 73% of the gemcitabine group during the first 30 weeks of

Table 3. Median survival times and quality of life results of gemcitabine combinations versus gemcitabine alone (*Continued*)

			the study. There were no differences between the 2 groups
Stathopoulos 2006	Gemcitabine + irinotecan	6.4 vs 6.5	Not addressed
Taxane combinations			
Von Hoff 2013	Gemcitabine + nab-paclitaxel	8.5 vs 6.7	Not addressed
Other combination chemotherapy including gemcitabine			
Petrioli 2015	Gemcitabine + oxaliplatin + capecitabine (GEMOXEL)	11.9 vs 7.1	The global QoL score was higher in the combination chemotherapy group at 2 months (61 vs 56) and 4 months (72 vs 66)
Reni 2005	Cisplatin/epirubicin/ gemcitabine/5FU (PEFG)	Not stated	The EORTC-QLQ Pan 26 questionnaire was done but the sample size was insufficient to obtain adequate statistical power to reliably detect differences between groups for multiple comparisons. People in PEFG group 20% to 44% more likely to have improvement in emotional functioning, overall quality of life, cognitive measures, pain, fatigue, indigestion, dyspnoea, appetite loss and flatulence. However, people in gemcitabine group had better scores for sexual function and body image
Other agents in combination with gemcitabine			
Gansauge 2002	Gemcitabine + Ukrain	10.4 vs 5.2	Not addressed
Meng 2012	Gemcitabine + huachansu	5.2 vs 5.3	No significant differences were seen between the treatment groups with either the FACT-G or MDASI assessments
Oettle 2005	Gemcitabine + pemetrexed	6.2 vs 6.3	People in the gemcitabine group had better financial difficulties score, better physical functioning score and better cognitive functioning score. People in the gemcitabine/pemetrexed group had better pain scores. Performance status improvements was seen

Table 3. Median survival times and quality of life results of gemcitabine combinations versus gemcitabine alone (*Continued*)

			in 11.4% of gemcitabine/pemetrexed group and 9.4% of gemcitabine group. Weight gain was seen in 10.2% of gemcitabine/pemetrexed group and 5.7% of gemcitabine group
Ueno 2013 - EPA study	Gemcitabine + EPA	8.2 vs 9.7	Not addressed

5FU: fluorouracil; **CBR**: clinical benefit response; **ESPAC**: European Study Group for Pancreatic Cancer; **EORTC**: European Organisation for Research and Treatment of Cancer; **FACT-G**: Functional Assessment of Cancer Therapy; **FA**: folinic acid; **KPS**: Karnofsky performance status; **LASA**: linear-analog self-assessment indicators; **MDASI**: MD Anderson Symptom Inventory; **QALY**: quality-adjusted life year; **QLQ-C30**: quality of life questionnaire for cancer patients; **QoL**: quality of life; **Q-TWiST**: quality-adjusted time without symptoms or toxicity.

Table 4. Median survival times and quality of life results for fluoropyrimidine combinations versus fluoropyrimidine alone

Study	Fluoropyrimidine combination details	Median survival:fluoropyrimidine combination vs fluoropyrimidine alone (months)	Quality of life
Ducreux 2004	5FU + oxaliplatin	3.7 vs 3.4	Not addressed
Kovach 1974	5FU + BCNU	Not stated	Not addressed
Maisey 2002	5FU + MMC	6.5 vs 5.1	EORTC-QLQ C30 showed that at 24 weeks, global QoL was superior in the combination arm compared to baseline (P = 0.035), and the pain score was also improved (P = 0.048). There was less dyspnoea at 12 weeks in the combination arm when compared to baseline (P = 0.033)
Moertel 1979	5FU + streptozocin	4.5 vs 5.25	Not addressed

5FU: fluorouracil; **BCNU**: bis-chloroethylnitrosourea (carmustine); **EORTC QLQ-C30**: European Organisation for Research and Treatment of Cancer quality of life questionnaire for cancer patients; **MMC**: 5FU+doxorubicin + mitomycin C; **QoL**: quality of life.

Table 5. Results of studies addressing unique treatment comparisons

Study	Treatment arms/no. of participants	Survival outcomes	Response rates	Adverse events	Quality of life
Multi-armed studies					
Boeck 2008	Capecitabine/ oxaliplatin (n = 61) versus capecitabine/ gemcitabine (n = 64) versus modified gemcitabine/oxaliplatin (n = 63)	OS: 8.1 vs 9.0 v 6.9 months PFS 4.2 vs 5.7 v 3.9 months	PR 13% vs 25% vs 13% SbD: 36% vs 39% vs 43%	Haematological AEs more common in the gemcitabine containing arms	Not studied
Cullinan 1985	5FU (n = 50) versus 5FU/doxorubicin (n = 44) versus 5FU/ doxorubicin/mitomycin C (n = 50)	Median survival of 22 weeks in all treatment groups	30% vs 30% vs 7.7%	Haematological AEs more common in the 5FU and 5FU/doxorubicin arm, however the subgroup with PC were not reported separately	Not studied
Cullinan 1990	5FU (n = 64) versus 5FU/cyclophosphamide/methotrexate 'Mallinson Regimen' (n = 61) versus 5FU/doxorubicin/cisplatin 'FAP' (n = 59)	OS: 3.5 vs 4.5 vs 3.5 months respectively PFS: 2.5 vs 2.5 vs 2.5 months	7% vs 21% vs 15%	More AEs reported in the combination arms compared with 5FU alone	Not studied
Kulke 2009	Gemcitabine (fixed dose rate) (n = 64) versus infusional gemcitabine + cisplatin (n = 66) versus infusional gemcitabine + docetaxel (n = 65) versus infusional gemcitabine + irinotecan (n = 60)	OS: 6.4 vs 6.7 vs 6.4 vs 7.1 months, respectively. Time to progression: 3.3 vs 4.5 vs 4.1 vs 4.0 months	14 vs 12.5 vs 12 vs 14%	Neutropenia and fatigue most common AE and same in all groups	Not studied
Other studies					
Afchain 2009	Gemcitabine/oxaliplatin (n = 20) vs simplified gemcitabine/oxaliplatin (n = 37)	OS: 3.2 vs 7.6 months PFS: 2.5 vs 4.0 months	PR: 10% vs 27% SbD: 45% vs 43%	Peripheral neuropathy more common in the simplified GemOx arm	Not studied

Table 5. Results of studies addressing unique treatment comparisons (*Continued*)

Bukowski 1983	Mitomycin C/5FU (MF) (n = 73) vs Streptozocin/mitomycin C/5FU (SMF) (n = 72)	OS: 17 vs 18 weeks	PR: 8% v 34%	More gastrointestinal and renal toxicity in the SMF arm	Not studied
Corrie 2017	Standard nab-paclitaxel and gemcitabine (n = 75) vs sequential nab-paclitaxel and gemcitabine (n = 71)	OS: 7.9 vs 10.1 months (HR 0.88) PFS: 4.0 vs 5.8 months (HR 0.66)	PR: 33% vs 50% SbD: 28% vs 42%	Neutropenia more common in the sequential arm	QoL score dropped by −12.1 points at 24 weeks in the standard arm vs −2.1 in the sequential arm
Hirao 2011	Gemcitabine 3-week schedule (n = 45) vs gemcitabine 4-week schedule (n = 45)	OS: 250 vs 206 days PFS: 114 vs 112 days	17.1% vs 14.2%	Thrombocytopenia more common in the 4-week schedule	Not studied
Kelsen 1991	Streptozocin/mitomycin C/5FU (SMF) (n = 42) vs cisplatin/ara-C/caffeine (CAC) (n = 40)	OS: 10 vs 5 months	10% vs 6%	Nausea and vomiting more common in CAC arm.	Not studied
Levi 2004	5FU constant infusion vs 5FU constant infusion/cisplatin versus 5FU chronomodulated infusion vs 5FU chronomodulated infusion/cisplatin (no cisplatin n = 55, with cisplatin n = 52)	OS: 5.4 vs 8.3 months (no cis vs cis) OS: 6.1 vs 6.7 months (continuous vs chronomodulated) PFS: 2.1 vs 3.2 months	Not reported	Cisplatin increased rates of haematological AEs. Chronomodulated regimen increased rates of mucositis	Not studied
Lutz 2005	Gemcitabine + docetaxel (n = 49) vs cisplatin + docetaxel (n = 47)	OS: 7.0 vs 7.5 months PFS: 3.9 vs 2.8 months	19.4% vs 23.5%	Febile neutropenia more common in the cisplatin/docetaxel arm	Not studied
Moertel 1977	Streptozocin + 5FU (n = 40) vs streptozocin + cyclophosphamide (n = 48)	OS: 13 vs 9 weeks	CR: 3 vs 6 PR: 2 vs 0 SbD: 9 vs 9	Haematological AEs more common in the cyclophosphamide arm	Not studied

Table 5. Results of studies addressing unique treatment comparisons (*Continued*)

Reni 2012	Capecitabine + cisplatin + gemcitabine + docetaxel (PDXG) (n = 53) vs capecitabine + cisplatin + gemcitabine + epirubicin (PEXG) (n = 52)	OS: 10.7 vs 11 months PFS: 7.4 vs 7.6 months	CR: 2 vs 4% PR: 58 vs 33%	Neutropenia more common in the PEXG arm	Not studied
Topham 1991	Epirubicin (n = 32) vs 5FU + epirubicin + mitomycin C (n = 30)	1 year survival rates 15.4 vs 23.2%	8% vs 11%	AEs were similar in both arms	Not studied

5FU: fluorouracil; **AE**: adverse event; **CR**: complete response; **OS**: overall survival; **PC**: pancreatic cancer; **PR**: partial response; **SbD**: stable disease.

APPENDICES

Appendix 1. Glossary of terms

Adenocarcinoma: cancer arising from glandular tissue
Analgesia: medication used to relieve pain
Anti-neoplastic: stopping or preventing the growth and spread of cancerous cells
Antibody: a protein produced to neutralise another protein. In the case of cancer treatment, these proteins block particular cancer pathways
Aortic: the large artery that originates in the heart and supplies the body with blood
Biliary: related to the structures that carry bile (a substance which is produced by the liver and responsible for helping the digestion of fats)
Cobalt source: radioisotope from which radiation is emitted
Coeliac abutment: when tumour touches but does not invade the coeliac vessels, the blood supply around the pancreas
Complete response: when a tumour is no longer seen on imaging in response to treatment
Cytotoxic: chemicals or drugs capable of killing cells
Dyspnoea: difficulty breathing
Epigastric: the top, middle part of the abdomen, the area around the stomach
Flatulence: gas
Insomnia: difficulty sleeping
Jaundice: the yellowing of the skin, whites of of the eyes and mucous membranes due to high levels of bilirubin
Lethal: capable of causing death
Mesenteric vein: one of the two veins responsible for draining the intestines
Neutropenia: low white cell count. Can pre-dispose patients to getting serious infections
Nodal: related to lymph nodes
Palliative: treatment with the intention of improving symptoms, not cure
Partial response: when a tumour shrinks on imaging in response to treatment
Placebo: sham or fake treatment

Portal occlusion: the blockage of the portal vein, a large vein in the abdomen
Resection: surgical removal
Stable disease: when tumour growth stabilises in response to treatment (does not change in size between scans)
Stent: a small tube used to relieve blockages
Thrombocytopenia: low platelet count. Can pre-dispose patients to serious bleeding
Thromboembolic: blood clots in the calf or lung veins
Toxicities: side effects

Appendix 2. CENTRAL search strategy

1. exp Pancreas/
2. (carcin$ or cancer$ or neoplas$ or tumour$ or tumor$ or growth$ or adenocarcin$ or malig$).mp.
3. 1 and 2
4. Carcinoma, Pancreatic Ductal/
5. Pancreatic Neoplasms/
6. or/3-5
7. Antineoplastic Protocols/
8. chemotherap*.tw.
9. Radiotherapy/
10. chemoradiotherap*.tw.
11. chemo-radiotherap*.tw.
12. radiochemotherap*.tw.
13. radio-chemotherap*.tw.
14. Biological Therapy/
15. Immunotherapy, Adoptive/
16. exp Immunotherapy, Active/
17. cetuximab.tw.
18. erlotinib.tw.
19. bevacuzimab.tw.
20. panitumumab.tw.
21. trastuzumab.tw.
22. Protein-Tyrosine Kinases/ai [Antagonists & Inhibitors]
23. tyrosine kinase inhibitor*.tw.
24. interleukins.tw.
25. exp Interleukins/
26. Cancer Vaccines/
27. Antibodies, Monoclonal/
28. exp Interferons/
29. Molecular Targeted Therapy/
30. or/7-29
31. 6 and 30

Appendix 3. MEDLINE search strategy

1. exp Pancreas/
2. (carcin$ or cancer$ or neoplas$ or tumour$ or tumor$ or growth$ or adenocarcin$ or malig$).mp.
3. 1 and 2
4. Carcinoma, Pancreatic Ductal/
5. Pancreatic Neoplasms/
6. or/3-5
7. Antineoplastic Protocols/
8. chemotherap*.tw.
9. Radiotherapy/
10. exp Chemoradiotherapy/
11. chemoradiotherap*.tw.
12. chemo-radiotherap*.tw.
13. radiochemotherap*.tw.
14. radio-chemotherap*.tw.
15. Biological Therapy/
16. Immunotherapy, Adoptive/
17. exp Immunotherapy, Active/
18. cetuximab.tw.
19. erlotinib.tw.
20. bevacuzimab.tw.
21. panitumumab.tw.
22. trastuzumab.tw.
23. Protein-Tyrosine Kinases/ai [Antagonists & Inhibitors]
24. tyrosine kinase inhibitor*.tw.
25. interleukins.tw.
26. exp Interleukins/
27. Cancer Vaccines/
28. *Antibodies, Monoclonal/
29. exp Interferons/
30. Molecular Targeted Therapy/
31. or/7-30
32. 6 and 31
33. randomized controlled trial.pt.
34. controlled clinical trial.pt.
35. randomized.ab.
36. placebo.ab.
37. clinical trials as topic.sh.
38. randomly.ab.
39. trial.ti.
40. or/33-39
41. exp animals/ not humans.sh.
42. 40 not 41
43. 32 and 42

Appendix 4. EMBASE search strategy

1. exp Pancreas/
2. (carcin$ or cancer$ or neoplas$ or tumour$ or tumor$ or growth$ or adenocarcin$ or malig$).mp.
3. 1 and 2
4. Carcinoma, Pancreatic Ductal/
5. Pancreatic Neoplasms/
6. or/3-5
7. Cancer chemotherapy/
8. Cancer radiotherapy/
9. exp Chemoradiotherapy/
10. chemoradiotherap*.tw.
11. chemo-radiotherap*.tw.
12. radiochemotherap*.tw.
13. radio-chemotherap*.tw.
14. Biological Therapy/
15. exp Immunotherapy, Active/
16. vaccine/ or cancer vaccine/ or tumor cell vaccine/ or tumor vaccine/
17. active immunization/
18. antineoplastic agent/
19. cetuximab/
20. erlotinib/
21. bevacizumab/
22. panitumumab/
23. trastuzumab/
24. protein tyrosine kinase inhibitor/
25. interleukin derivative/
26. cancer vaccine/
27. monoclonal antibody/
28. exp interferon/
29. immunotherapy/ or adoptive immunotherapy/ or cancer immunization/
30. molecularly targeted therapy/
31. or/7-30
32. 6 and 31
33. random:.tw. or placebo:.mp. or double-blind:.tw.
34. 32 and 33

HISTORY

Protocol first published: Issue 6, 2013

Review first published: Issue 3, 2018

Date	Event	Description
30 October 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

VC: protocol design, sourcing articles, reviewer one, data entry, analysis, results, discussion and conclusion, preparation of manuscript.

AN: protocol design, reviewer two, analysis, statistics support, reviewing of manuscript.

KS: protocol design, statistics support, reviewing of manuscript.

CO: protocol design, radiotherapy trials/methodology support, reviewing of manuscript.

LC: protocol design, reviewing of manuscript.

AB: protocol design, reviewing of manuscript.

RS: data analysis and statistical support, reviewing of the manuscript.

DY: author of previous version of this review, protocol design, methodological support, reviewer three, reviewing of manuscript.

DECLARATIONS OF INTEREST

VC: Venessa Chin received scholarship funding from the Research and Education Foundation of the Royal Australasian College of Physicians, Pancare Australia, Sydney Catalyst, National Health and Medical Research Council, and the Garvan Institute of Medical Research for work related to this review.

AN: none known.

KS: Katrin Sjoquist received programme grant funding from the National Health and Medical Research Council for work related to this review. She has received consultancy fees, fees for expert testimony and travel support for work unrelated to this review.

CO: none known.

LC: Lorraine Chantrill is employed (part-time) by NSW Health as a staff specialist in medical oncology and enrolled full-time in PhD studies supported by the Australian Federal Government. She has been paid as an advisory board member in relation to chemotherapy for pancreas cancer and has been paid for formulating educational materials and presentations. She has received grants for the practice of clinical trials in pancreas and other cancers.

AB: Andew Biankin received grant funding from the Cancer Institute NSW for work related to this review. He also received consultancy fees from Celegene and Clovis Oncology for work unrelated to this review. His institution received consultancy fees from Roche for work unrelated to this review.

RS: Rob Scholten's institution has received grant funding from the Belgian Health Care Knowledge Centre for work related to this review. His institution has also received funding from the WHO and World Federation of Haemophilia for travel and consultancy unrelated to this review.

DY: Advisory Board Member, Specialised Therapeutics.

SOURCES OF SUPPORT

Internal sources

- The Garvan Institute of Medical Research, Australia.

PhD stipend top up for Venessa Chin

External sources

- The Royal Australasian College of Physicians, Australia.

PhD stipend for Venessa Chin

- National Health and Medical Research Council, Australia.

PhD stipend for Venessa Chin

- Pancare Australia, Australia.

PhD stipend for Venessa Chin

- Sydney Catalyst, Australia.

PhD stipend for Venessa Chin

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Biological agents, second line therapies, locally advanced PC

The original protocol included studies addressing biological therapies, studies addressing second-line treatment and people with locally advanced disease. We felt that due to the large number of comparisons, the review became unmanageable. We therefore decided to split the review and concentrate on chemotherapy and radiotherapy in the advanced setting. Separate reviews will report on biological and immunological agents, second-line therapies and studies dealing exclusively with people with non-metastatic, locally advanced disease.

Outcomes

The original protocol did not include adverse events, response rates and quality of life as secondary outcomes. Prior to data extraction, the review authors added those as secondary outcomes. We deleted disease-specific survival as a secondary outcome.

Measures of treatment effect

The original protocol stated that fixed-effect model meta-analyses would be used to pool results for survival at 6 months and 12 months. It was never our intention to use 6- and 12-month survival as endpoints in this review. We instead used HRs for overall and progression-free survival. We employed random-effect models for most analyses given the experimental arms were often very different within each comparison.

Dealing with multi-armed studies

In such cases where studies reported the event rates for all arms, we divided the control arm accordingly and entered all arms of the studies into the analysis as appropriate. Where the event rates were not available, if the study had two arms that fell into a subgroup analysis, then we analysed only these two arms. We described any study that we could not analyse in the above two scenarios in table form only.

Number needed to treat (NNT) as a secondary endpoint

We replaced this outcome with GRADE 'Summary of findings' tables.