Chemotherapy and radiotherapy for inoperable advanced pancreatic cancer (Review)

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ABSTRACT

Background
Pancreatic cancer has a poor prognosis. The benefit of chemotherapy, radiotherapy or both as a palliative treatment of advanced or relapsed disease is uncertain.

Objectives
To assess the effects of chemotherapy and/or radiotherapy in the management of pancreatic adenocarcinoma in people with inoperable advanced disease.

Search strategy
We searched the Cochrane Central Register of Controlled Trials (CENTRAL), which includes the Cochrane Upper Gastrointestinal and Pancreatic Diseases (UGPD) Group Trials Register (The Cochrane Library 2005, Issue 1); CANCERLIT (1975-2002); MEDLINE (1966 to January 2005); and EMBASE (1980 to January 2005). We handsearched reference lists from trials revealed by electronic searches to identify further relevant trials. We searched published abstracts from relevant conference proceedings. We contacted colleagues and experts in the field, and asked them to provide details of outstanding clinical trials and any relevant unpublished materials.

Selection criteria
Randomised controlled trials (single- or double-blind) in patients with advanced inoperable pancreatic cancer, in which one of the intervention types (chemotherapy or radiotherapy) was contrasted with either placebo or another type of intervention. Studies comparing non-chemotherapy agents such as biological agents, hormones, immunostimulants, vaccines and cytokines were excluded.

Data collection and analysis
Studies were assessed for eligibility and quality. Data were extracted by groups of two independent reviewers, with conflicts resolved by a third reviewer. Study authors were contacted for more information.

Main results
Fifty trials (7043 participants) were included. Chemotherapy significantly reduced the one-year mortality (odds ratio (OR) 0.37, 95% confidence interval (CI) 0.25 to 0.57, P value < 0.00001) when compared to best supportive care. Also, chemoradiation improved one year survival (0% versus 58%, P value 0.001) when compared to best supportive care. There was no significant difference in one-year mortality for 5FU alone versus 5FU combinations (OR 0.90, 95% CI 0.62 to 1.30); single-agent chemotherapy versus gemcitabine (OR 1.34, 95% CI 0.88 to 2.02, P value 0.17); or gemcitabine alone versus gemcitabine combinations (OR 0.88, 95% CI 0.74 to 1.05). However, subgroup analysis showed that platinum-gemcitabine combinations reduced six-month mortality compared to gemcitabine alone (OR 0.59, 95% CI 0.43 to 0.81, P value 0.001). A qualitative overview suggested that chemoradiation produced better survivals than either best supportive care or radiotherapy. Chemoradiation treatment was associated with more toxicity.

Authors' conclusions
Chemotherapy appears to prolong survival in people with advanced pancreatic cancer and can confer clinical benefits and improve quality of life. Combination chemotherapy did not improve overall survival compared to single-agent chemotherapy. Gemcitabine is

an acceptable control arm for future trials investigating scheduling and combinations with novel agents. There is insufficient evidence to recommend chemoradiation in patients with locally advanced inoperable pancreatic cancer as a superior alternative to chemotherapy alone.

PLAIN LANGUAGE SUMMARY

Chemotherapy and radiotherapy may improve survival and quality of life in people with advanced pancreatic cancer

Advanced pancreatic cancer is incurable. Symptoms affect quality of life, and life expectancy is reduced. This review investigated the effect of chemotherapy and radiotherapy on survival and symptoms, and found that having chemotherapy (compared to no chemotherapy) improved survival, and sometimes symptoms and quality of life. Chemotherapy using drug combinations did not improve life expectancy compared to treatment with individual drugs. Combining chemotherapy with radiotherapy is better, in terms of survival, for fit people (with inoperable pancreatic cancer, that has not spread to other organs), than radiotherapy alone, or no treatment. There is insufficient evidence of superior benefit of chemoradiation over chemotherapy alone.

BACKGROUND

Pancreatic carcinoma is the eighth commonest cause of cancer-related death worldwide, but the 13th most common tumour type (Parkin 2005). The reported incidence is higher in developed countries (pancreatic cancer is the fourth leading cause of cancer death in the US (Jemal 2005)), probably as a result of more accurate diagnosis, rather than aetiology (cause of disease) (Parkin 2005). Approximately 20% of people diagnosed with pancreatic carcinoma present with early disease, and are able to undergo resection (surgical treatment) with curative intent. However, after surgical resection, the risk of relapse is still high, with only 10% to 25% of people surviving for five years (Conlon 1996; Geer 1993; Shahrudin 1997; Trede 1990; Wagner 2004; Yeo 1997). More recent data suggest that outcomes may be improving over time. An overview of 100,313 pancreatic cancer patients reported to the National Cancer Database of the United States found a 23.4% five-year survival with pancreatectomy (removal of the pancreas), and 5.2% in those who had not received cancer-directed treatment (Sener 1999). In a retrospective population-based study of patients receiving treatment with curative intent in the US between 1991 and 1996, the three-year survival was 34% (Lim 2003). Attempts at improving survival by targeting micrometastatic residual disease (microscopic secondary tumours) with adjuvant (additional) therapies have been trialed. An individual patient meta-analysis (Stocken 2005) and a large randomised study (Neoptolemos 2004) have suggested that adjuvant chemotherapy following surgical resection conferred a benefit, while chemoradiation was detrimental. The benefit of chemotherapy, radiotherapy, or the combination of both, as a palliative treatment for advanced or relapsed disease is uncertain. Response rates with chemotherapy agents tested have generally been low and the benefits must be weighed up against treatment-related toxicities.

OBJECTIVES

The primary objective was to conduct a systematic review of the published and unpublished literature to assess the effect of chemotherapy, radiotherapy or combined chemoradiotherapy on overall survival in people with pancreatic carcinoma. We examined these effects in the setting of inoperable advanced (including locally-advanced and metastatic) or relapsed disease. Adjuvant therapy for prevention of recurrence in curatively resected patients was not examined in this review.

Comparisons were as follows:
(1) Treatment modality against best supportive care or a no treatment arm.
(2) Comparisons between modalities or types of chemotherapy regimens against each other.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomised controlled trials with a single-blind or double blind design, in which one of the intervention types (chemotherapy or radiotherapy) was contrasted with either placebo or another type of intervention. Both published and unpublished studies were identified and assessed for inclusion.

Types of participants

Patients with a diagnosis of pancreatic adenocarcinoma established by either histological or cytological findings (investigations on body tissue or cells).

Trials enrolling patients with advanced locally-advanced/unresectable and recurrent disease (testing "palliative or non-curative chemotherapy") were eligible for inclusion.

Types of intervention

Chemotherapy
Eligible interventions included both single-agent and combination chemotherapy. Chemotherapy with all cytotoxic or antineoplastic drug treatments, but excluding hormonal and biological therapies (e.g. interferon, somatostatin), was eligible regardless of dose or schedule.

Radiotherapy
Eligible interventions included external-beam radiotherapy (cobalt source and megavoltage external-beam) and brachytherapy (radioactive materials placed in direct contact with tissue being treated).

Combined chemoradiotherapy
Concurrent or sequential administration of chemotherapy and radiotherapy.

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

Types of outcome measures

The primary outcome measure was duration of overall survival on an intention-to-treat analysis measured by the median survival time and one-year survival rate. Secondary outcomes of interest were survival rate at six months, time to progression, overall tumour response, and quality of life or clinical benefit measurements.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Upper Gastrointestinal & Pancreatic Diseases Group methods used in reviews.

The authors aimed to complete searches that would identify all relevant published and unpublished randomised controlled trials. Articles published in any language were eligible for inclusion. Trials were identified by searching the following electronic databases - The Cochrane Central register of Controlled Trials - CENTRAL (which includes the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group Trials Register) on The Cochrane Library (Issue 1 2005) MEDLINE (1966 to January 2005) and EMBASE (1980 to January 2005). Searches were also conducted on CANCERLIT from 1999 to 2002. Subsequent searches have not been undertaken as the database has been merged into PUB MED from 2002 onwards.
To identify randomized controlled trials, the following search was combined with the Cochrane highly sensitive search strategy phases one, two and three as contained in the Reviewer's Handbook (Higgins 2005).

MEDLINE search strategy
exp pancreas/
pancrea$.tw.
exp pancreatic neoplasms/
(pancrea$ adj5 neoplasm$).tw.
(pancrea$ adj5 cancer$).tw.
(pancrea$ adj5 carcinoma$).tw.
(resect$ adj5 pancrea$).tw.
exp pancreatectomy/
exp Pancreaticoduodenectomy/
or/30-38
exp drug therapy/
exp chemotherapy adjuvant/
chemotherap$.tw.
chemoradiotherap$.tw.
(combin$ adj5 chemotherap$).tw.
(concurrent adj5 chemoradiotherap$).tw.
(preoperative adj5 chemotherap$).tw.
(postoperative adj5 chemotherap$).tw.
or/40-47
(best adj3 supportive adj3 care).tw.
(palliat$ adj5 surg$).tw.
or/49-50
exp radiotherapy/
exp radiotherapy adjuvant/
radiotherapy.tw.
(postoperative adj5 radiotherapy).tw.
(preoperative adj5 radiotherapy).tw.
exp drug therapy combination/
or/52-57
48 or 51 or 58
39 and 59
29 and 60
Reference lists from trials and review articles selected by electronic searching were handsearched to identify further relevant trials.
Published abstracts from the following conference proceedings were handsearched:
American Gastroenterological Association (AGA) 1994-2004.
American Society of Clinical Oncology (ASCO) 1996-2005.
American Association of Cancer Research (AACR) 1957-2004.
American Pancreatic Association (APA) 2001-2004.
Digestive Disease Week (DDW) 1994-2004.
European Cancer Conference (ECCO) 1997, 1999, 2001, 2003.
European Society of Medical Oncology (ESMO) 1998, 2000, 2002, 2004.
European Pancreatic Club (EPC) 2000-2004.
United European Gastroenterology Week (UEGF) 1960-2005.
The following information resources were also searched:
National Cancer Institute Physician Data Query
UK Co-ordinating Committee on Cancer Research and National Clinical Trials Registry: Cancer Trials (Australia)
National Research Register
Medical Research Council

Clinicaltrials.gov
Current Controlled Trials
Trialscentral
Center Watch
World Wide Web search using Internet search engine Google.
In addition, we contacted members of the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group, and experts in the field, and asked them to provide details of outstanding clinical trials and any relevant unpublished materials that were known to them.

METHODS OF THE REVIEW

Trial selection and quality assessment

Trials were selected for inclusion by pairs of independent authors (CK and DG, AS and CS), with disagreements resolved by a third author (DY). Methodological quality was assessed independently by three authors using a standardised checklist to assess the degree to which each study minimised the potential for bias due to differences between treatment groups. Concealment, defined as the process used to prevent foreknowledge of group assignment, was graded. Methods of assignment such as date of birth and case record numbers (see quasi-random allocation) are open to manipulation and were considered inadequate. Methods of allocation concealment considered adequate included: centralised randomisation schemes; randomisation schemes controlled by a pharmacy; numbered or coded containers in which capsules from identical-looking, numbered bottles are administered sequentially; on-site computer systems, where allocations are in a locked unreadable file; and sequentially-numbered opaque, sealed envelopes. Data were extracted from published reports by pairs of reviewers using standardised forms, with disagreements resolved by discussion with the additional reviewer (DY). The authors were not blinded to the sources of data. We attempted to collect missing information, where possible, by contacting investigators involved with the studies. Individual patient data meta-analysis was not attempted.

Statistical analyses

Survival data were extracted by reading from the survival curves at six months and 12 months, by recording median survival times, and by recording published P values for comparisons of survival curves based on Mantel Cox log rank test, Cox model (univariate) or similar statistical tests. Data from individual trials were summarised by:
(1) comparing the median survival in the treatment arm to the median survival in the control arm;
(2) the reported P value for an unadjusted comparison of the survival curves; and,
(3) the odds ratios (OR) for one year survival rates for advanced disease.

Median survivals that could not be combined in a meta-analysis were recorded in a table and discussed in the text. Fixed-effect meta-analyses (Mantel-Haenszel) were used to pool results for survival at six months and 12 months, where appropriate, as this method gave more weight to larger studies than smaller ones. Exploratory subgroup analysis was performed where comparator drugs were identical, or of the same class of chemotherapy agents.

Heterogeneity was assessed with chi-squared tests as well as funnel plots, and supplemented by the I^2 test for inconsistency. Random-effects models were also examined as part of sensitivity analysis. Analyses were based on intention-to-treat data, as far as allowed by the published data.

DESCRIPTION OF STUDIES

The literature review identified one published meta-analysis (Fung 2003). This Japanese language paper reviewed randomised trials published between 1974 and 2003 and identified 43 studies. However, the authors were not strict in excluding trials that were not prospectively randomised. As a result trials were included that used matched population controls, or in which treatment allocation was not properly randomised.
Fifty reported trials fulfilled the inclusion criteria and were included in our review. Nine of these reports were in the form of conference abstracts (Cheverton 2004; Heinemann 2003; Herrmann 2005; Levi 2004; Li 2004; O'Reilly 2004; Ohkawa 2004; Riess 2005; Stathopoulos 2005). For most of these, further details on the trials were obtained from the associated PowerPoint presentations or posters posted on the conference websites.
Fifty-eight trials identified through searching were not included in the review. Reasons for their exclusion are given in the Characteristics of excluded studies table. The included trials were divided into three groups for analysis:
Best supportive care versus chemotherapy in advanced pancreatic cancer

A number of studies examining best supportive care were excluded for the following reasons: one study did not present survival data (Klapdor 1982); two studies assessed patients who had not responded to prior chemotherapy (Jacobs 2004; Ulrich-Pur 2003); four trials compared best supportive care to the biological agents octreotide (Cascinu 1995), G17DT immunogen (Gilliam 2004), and gastrazole (Chau 2003) which were not within the scope of this review. A study (Shinchi 2002) of best supportive care versus chemoradiotherapy is discussed in the section on radiotherapy with or without chemotherapy for locally-advanced disease.

Eight studies compared best supportive care to chemotherapy in advanced pancreatic carcinoma and met the inclusion criteria (Andersen 1981; Andren-Sandberg 1983; Frey 1981; Glimelius 1996; Huguier 2001; Mallinson 1980; Palmer 1994; Takada 1998). Best supportive care included surgical intervention (e.g. biliary bypass

or palliative resection) in some of the trials (Andersen 1981; Andren-Sandberg 1983; Frey 1981; Takada 1998). All patients had histological or cytological confirmation of pancreatic cancer except those in the Mallinson study (Mallinson 1980). Two trials included biliary tract cancers but separate data were available for the pancreatic cancer patients (Glimelius 1996; Takada 1998). The chemotherapy schedules used in the treatment arms were all 5-fluorouracil (5FU) combination regimens that included the cytotoxics BCNU (carmustine), CCNU (lomustine), vincristine, adriamycin, etoposide and mitomycin C. All trials enrolled both locally-advanced (inoperable cancer that has not spread to other organs) and metastatic (cancer that has spread to other organs) pancreatic cancer patients.

Quality of life (QOL) was measured in several studies. Mallinson (Mallinson 1980) scored symptoms of pain, nausea, stool frequency, hair loss and analgesic requirement on the basis of severity. Patients also rated their own well-being and body weight. Andren-Sandberg (Andren-Sandberg 1983) assessed QOL by means of the Karnofsky performance score, and Anderson (Andersen 1981) by an estimate calculated from number of hospital days, need for analgesia and rate of weight loss. Glimelius used the European Organisation for Research and Treatment of Cancer (EORTC) QLC C30 questionnaire (Glimelius 1996), while Palmer (Palmer 1994) used the Hospital Anxiety and Depression (HAD) questionnaire to measure psychological status. Takada (Takada 1998) measured 'clinical effects' by changes in performance status and body weight.

Comparative studies of chemotherapy in advanced pancreatic cancer

(1) 5-fluorouracil (5FU) versus another chemotherapy

One trial that compared 5FU with a biological agent, gastrazole (Chau 2003), was excluded. Four studies compared single-agent 5FU with another single chemotherapy agent. These drugs were BCNU (Kovach 1974), gemcitabine (Burris 1997; Cantore 2004) and oxaliplatin (Ducreux 2004). The Kovach and Ducreux trials also had third arms that compared the combination of the two drugs being tested, and both had early closure of one or more of the arms due to inferior results at interim analysis. Infusional 5FU was used in the Ducreux trial, and bolus dosing in the other three. 5FU was modulated with leucovorin in the Cantore trial. Clinical benefit response was measured in the Burris, Cantore and Ducreux trials. Clinical benefit was defined as a composite endpoint of pain, performance status and weight loss.

(2) 5-fluorouracil versus 5-fluorouracil-based combinations

One study (Takada 1994) was excluded as it combined pancreatic and biliary cancer patients and separate results could not be obtained for each group. There were seven included trials that compared 5FU alone with 5FU chemotherapy combinations (Cullinan 1985a; Cullinan 1990a; Ducreux 2002; Ducreux 2004; Kovach 1974; Levi 2004; Maisey 2002). Three of the trials enrolled patients with gastric (Cullinan 1985a; Kovach 1974) and ampullary cancers (Ducreux 2002), but data on pancreatic cancer patients were available separately. All patients had pathological confirmation of pancreatic cancer except for the Ducreux 2002 trial, which enrolled eight patients without this confirmation. The Kovach trial was conducted before CT scanning became available and enrolled 33 patients whose histology of metastases, clinical presentation and negative barium studies were suggestive of pancreatic cancer. Survival data could not be obtained, so these patients were excluded from the analyses. Patients with locally-advanced and metastatic disease were enrolled in all of these studies.

Two of the trials (Cullinan 1985a; Cullinan 1990a) ran two comparative combination chemotherapy arms. The Kovach trial (Kovach 1974) compared 5FU to single-agent BCNU as well as 5FU in combination with BCNU. The Ducreux 2004 study (Ducreux 2004) compared 5FU to a single agent, oxaliplatin, as well as 5FU plus oxaliplatin. Three studies used infusional 5FU as the control (Ducreux 2004; Levi 2004; Maisey 2002); the rest used bolus 5FU. These three studies also used protracted infusional 5FU in the comparative combination arms with mitomycin C, cisplatin and oxaliplatin, respectively, as did Ducreux (Ducreux 2002) with cisplatin. The Levi study (Levi 2004) also incorporated a randomisation between constant and chronomodulated administration of escalating dose 5FU. Two trials (Ducreux 2002; Maisey 2002) measured quality of life, while another assessed clinical benefit response (Ducreux 2004).

(3) Gemcitabine versus other chemotherapy

Three trials were excluded because they compared gemcitabine to the biological agents BAY 12-9566 (Moore 2003), marimastat (Bramhall 2001), and imatinib mesylate (Chen 2006). Four randomised trials were included in this group. These trials compared gemcitabine to 5FU (Burris 1997), 5FU/folinic acid (Cantore 2004), exatecan (Cheverton 2004) and NSC-631570 (Gansauge 2002).

The Cantore study had two comparator arms against gemcitabine: FLEC (fluorouracil, leucovorin, epirubicin and carboplatin) which was administered intra-arterially and 5FU/leucovorin given intravenously. The 5FU/leucovorin arm terminated early and was not reported in the two associated publications (Cantore 2004). Unpublished individual patient data were obtained from the principal author and analysis was performed. The Gansauge trial (Gansauge 2002) was also a three-armed trial incorporating a combination arm of gemcitabine and NSC-631570. All four trials enrolled both locally-advanced and metastatic pancreatic cancer patients and also assessed clinical benefit response.

(4) Gemcitabine versus gemcitabine combination chemotherapy
Sixteen studies were identified in this group (Berlin 2002; Colucci 2002; Gansauge 2002; Heinemann 2003; Herrmann 2005; Li 2004; Louvet 2005; O'Reilly 2004; Ohkawa 2004; Reni 2005; Oettle 2005b; Riess 2005; Rocha Lima 2004; Scheithauer 2003; Stathopoulos 2005; Wang 2002). Seven of these were final pub-

lications (Berlin 2002; Colucci 2002; Louvet 2005; Reni 2005; Rocha Lima 2004; Scheithauer 2003; Wang 2002;Wang 2002) and the rest were conference abstracts.

Seven studies were excluded because they compared the addition of the following biological agents to gemcitabine: SCH 66336 (Lersch 2001), marimastat (Bramhall 2002), C1-994 (Richards 2002), tipifarnib (Van Cutsem 2004), BAY 12-9566 (Moore 2003), G17DT immunogen (Shapiro 2005), and erlotinib (Moore 2005).

All studies except the Scheithauer study, which included only metastatic patients (Scheithauer 2003), enrolled both locally-advanced and metastatic pancreatic cancer patients. The Gansauge trial (Gansauge 2002) included only two locally-advanced pancreatic cancer patients. The control arm of most of the studies used either the Burris regimen (intravenous gemcitabine 1000mg/m^2 over 30 minutes) weekly for seven weeks out of the first eight and then three out of four weeks, or weekly for three weeks out of four from the start. The Scheithauer trial used a biweekly schedule of high dose gemcitabine (2200 mg/m^2), while Stathopoulos (Stathopoulos 2005) used a three-out-of-four week schedule of gemcitabine (900 mg/m^2). The gemcitabine dose or scheduling varied in the test arm in several trials. Rocha Lima (Rocha Lima 2004) and Stathopoulos (Stathopoulos 2005) both used a two out of three week schedule with irinotecan; Louvet (Louvet 2005) used a fortnightly schedule of fixed dose rate gemcitabine as described by Tempero (Tempero 2003) given in combination with the oxaliplatin; Reni (Reni 2005) used 600 mg/m^2 of gemcitabine to allow it to be combined with three other cytotoxics; and Richards (Oettle 2005b) used a higher dose of 1250 mg/m^2 given in a two out of three schedule in combination with pemetrexed. Four of the trials (Colucci 2002; Heinemann 2003; Li 2004; Wang 2002) compared gemcitabine with gemcitabine-cisplatin.

(5) Other comparative chemotherapy trials

Six trials compared a variety of 5-fluorouracil based combinations (Bukowski 1983; Buroker 1979; Horton 1981; Kelsen 1991; Oster 1986; Topham 1991). All enrolled both locally-advanced and metastatic pancreatic cancer patients.

Radiation therapy in locally advanced pancreatic cancer

Ten randomised trials were identified in this group (Childs 1965; Earle 1994; GITSG 1985b; GITSG 1988; Hazel 1981; Klaassen 1985; Li 2003; Moertel 1969; Moertel 1981; Shinchi 2002). Two trials were excluded: one because it utilised a radiosensitizer (PR-350), rather than a cytotoxic chemotherapy agent (Sunamura 2004), and the other (McCracken 1980) because it tested a hormonal agent (testolactone) combined with chemoradiotherapy.

METHODOLOGICAL QUALITY

The quality of randomisation was assessed according to method of generation, and concealment, of the allocation sequence. Grade A was awarded for trials where these were clearly adequate, grade B where these were possibly adequate, and C where these were clearly inadequate (see Characteristics of included studies table). It was not possible to assess accurately the quality of randomisation used in most studies, due to the lack of information in the published articles. Only three studies utilised a placebo control (Andersen 1981; Childs 1965; Moertel 1969). The Andersen trial was placebo-controlled and triple-blinded (doctor, patient and pharmacist blinded to treatment allocation).

Description and meta-analysis was restricted to those trials from which suitable data could be extracted. Tumour measurements in some early studies were by clinical measurements only because of the unavailability of computed tomography. More recent studies have used World Health Organization (WHO) and response evaluation criteria in solid tumours (RECIST) objective radiological criteria for determining response. Response rates are listed as being percent of evaluable patients who achieved either partial or complete tumour response. Reporting of quality of life and clinical benefit response varied between the trials according to whether they were used as an endpoint, what instruments were used, the way they were analysed and compliance with assessments. It was not possible to analyse this quantitatively.

RESULTS

Chemotherapy versus best supportive care

Mortality data at six and 12 months were obtained for seven of the eight studies (not available for Andren-Sandberg (Andren-Sandberg 1983) trial). Pooled data of mortality at 12 months for chemotherapy versus best supportive care resulted in an odds ratio (OR) of 0.37 (95% confidence interval (CI) 0.25 to 0.57, P value < 0.00001) using the fixed-effect model. There was no evidence of serious heterogeneity (chi-squared test P value 0.33) or inconsistency (I^2 = 12.6%). Pooled mortality at six months gave an OR of 0.46 (95% CI 0.25 to 0.84, P value 0.01). The chi-squared test for heterogeneity was significant at this timepoint (chi-squared P value 0.02) and confirmed by I^2 = 71.5%. Sensitivity analysis was performed using a random-effects model and the findings remained significant, OR 0.35 (95% CI 0.14-0.85, P value 0.02). On the forest plot, two studies (Mallinson 1980; Palmer 1994) lay to the very left of the plot with highly significant results in favour of chemotherapy, while two other trials lay to the right of the line of no difference with non-significant difference in favour of best supportive care. See Figure 01.

Mallinson found, in a non-parametric analysis of the clinical measurements, that the only difference between the two groups was in nausea, which was increased in treated patients. In the Andren-Sanberg study, there was no difference in maintenance of Karnofsky performance status between arms of the study (Andren-Sandberg 1983), and no statistical difference in their quality of life

measurement. Takada (Takada 1998) also did not observe any statistical difference in improvements in body weight or performance in both arms. Palmer found that people in the best supportive care arm of his study had similar levels of anxiety but were more depressed than those in the treatment arm. This difference persisted at two months. Quality of life measured in the Glimelius study (Glimelius 1996) using the EORTC QOL C30 questionnaire found statistically better scores in pain, fatigue, appetite and dyspnoea in the treatment group compared to best supportive care. Average quality- adjusted survival (another quantitative measure of quality of life whereby survival time is weighted by utility of quality of life experienced) was also longer.

These trials are summarised in Table 01.

Comparative studies of chemotherapy in advanced pancreatic cancer

(1) 5-fluorouracil versus another chemotherapy agent

The four studies provided mortality data at six and 12 months. Pooled data of mortality at six months for another chemotherapy agent versus 5-fluorouracil (5FU) resulted in OR 0.58 (95% CI 0.37-0.92, P value 0.02) and at 12 months OR 0.67 (95% CI 0.34-1.31, P value 0.24). Chi-squared tests for heterogeneity were not significant at these points (P value 0.07, I2 = 57.9%; and P value 0.06, I^2 = 60%, respectively).

The Kovach trial (Kovach 1974) randomised 31 patients to 5FU and 21 to BCNU with another 30 to the combination of both drugs. Overall response rates were not reported separately for each arm. Median survivals estimated from Kaplan Meier curves of 5FU compared with BCNU were 5.4 versus 5.1 months (no difference), with one-year survival being 10% and 23% respectively.

The Burris trial (Burris 1997) randomised 126 patients to receive either 5FU, as a weekly bolus, or treatment with gemcitabine. This found an improvement in median survival from 4.41 months to 5.65 months (P value 0.025), with the 12-month survival being 2% and 18% respectively. However, the primary endpoint of the study was clinical benefit response, which was a composite of pain measurements (including analgesic consumption and pain intensity), Karnofsky performance status and weight. Of the patients in the gemcitabine arm 23.8% experienced an improvement in clinical benefit compared with 4.8% for the 5FU arm. Of the 56 gemcitabine patients with bidemensionally measurable disease on enrolment, three achieved objective tumour response (shrinkage of at least 50% of the product of bidimensional measurements on imaging) giving rise to a overall response rate of 5.4% compared to 0% for the 57 5FU patients with measurable disease. The Cantore study (Cantore 2004), which incorporated a 5FU/folinic acid and a gemcitabine arm, is discussed below in section (3).

The Ducreux trial (Ducreux 2004) randomised 15 patients to infusional 5FU, 17 patients to oxaliplatin and 31 to a combination of the two. Objective tumour responses in both the single-agent arms of the trial were 0%. Comparison of 5FU to oxaliplatin showed that median survivals were 2.4 months and 3.4 months, six-month survival was 20% versus 40%, and one-year survival was 6% versus 6%, respectively. Only 51% of the patients in the study were evaluable for clinical benefit response due to poor compliance. The results were 0% versus 14%, respectively.

(2) 5-fluorouracil versus 5-fluorouracil based chemotherapy combinations

Six out of the eight included studies provided mortality data at six and 12 months. Pooling mortality data for 5FU combination chemotherapy versus 5FU alone at 12 months resulted in an OR of 0.90 (95% CI 0.62-1.30, P value 0.57). Pooled analysis of mortality at six months resulted in an OR of 0.79 (95% CI 0.59-1.05, P value 0.10). The chi-squared test was not significant for heterogeneity (P value 0.06, I^2 = 47.7%; and P value 0.32, I^2 = 13.7%, respectively). Median survival times were available for all the trials and these are listed in Table 02.

Four of the trials found a better tumour response rate with the 5FU combination regimens (Ducreux 2002; Ducreux 2004; Kovach 1974; Maisey 2002). Measurement of quality of life (QOL) with the EORTC QLQ C30 questionnaire found no difference between the study arms in the Maisey trial (Maisey 2002). In another study (Ducreux 2002), measurement of QOL with the Spitzer index found a significant treatment effect in favour of the combination therapy arm. Clinical benefit response was also better with the combination of oxaliplatin and 5FU versus 5FU alone in a third trial (Ducreux 2004).
These studies are listed in Table 02.

(3) Gemcitabine versus another type of chemotherapy.

The four trials provided mortality data at six and 12 months. Pooled analysis for mortality at 12 months for gemcitabine versus another type of chemotherapy resulted in an OR of 1.34 (95% CI 0.88 to 2.02, P value 0.17), and at six months in an OR of 1.10 (95% CI 0.80 to 1.51, P value 0.55). The chi-squared test was significant for heterogeneity at six months (P value 0.006, I2 = 76%), but not at 12 months (P value 0.03, I2 = 79.7%). A sensitivity analysis using a random-effects model confirmed there was no statistical significance.

The Cheverton study (Cheverton 2004) compared gemcitabine with exatecan (DX-8951f) in 339 patients. Gemcitabine was found to be superior to exatecan for time to progression (3.8 versus 2.8 months, P value < 0.0001), and six month and 12-month survival (51.1% versus 44.1%, and 22.1% versus 17.9%, respectively). The overall tumour response rate was higher with gemcitabine (7.7% versus < 1%), and the time to worsening of weight loss and pain was also better.

Gansauge (Gansauge 2002) randomised 90 patients to gemcitabine, NSC-631570 or a combination of both. Six-month and 12-month survival rates were 26% versus 65%, and 13% versus

29%, for the gemcitabine and NSC-631570 arms, respectively. The median survival times were 5.2 versus 7.9 versus 10.4 months respectively. The significance values for survival in subjects receiving gemcitabine compared to NSC 631570 and to the combination were both P value < 0.01. Tumour response rates in assessable patients were 4%, 10% and 40% respectively.

Two trials compared 5FU with gemcitabine. The Burris trial (Burris 1997) randomised 126 patients to either bolus weekly 5FU or treatment with gemcitabine. This found an improvement in median survival from 4.41 months to 5.65 months (P value 0.025) by the use of gemcitabine with the 12-month survival being 2% and 18% respectively. The primary endpoint of the study, however, was clinical benefit response, which consisted of a composite score of measurements of pain (analgesic consumption, pain intensity), Karnofsky performance status (KPS) and weight. More patients in the gemcitabine arm experienced an improvement in clinical benefit (23.8%), than did in the 5FU arm (4.8%). Cantore (Cantore 2004) randomised 175 patients to receive gemcitabine, intra-arterial FLEC with filgrastim support, or 5FU/leucovorin. The median survivals were 5.8 months, 7.9 months and 6.4 months respectively. Six-month survival was 7% versus 62% versus 51%, and 12-month survival 21% versus 35% versus 17%. Median times to disease progression were 4.2 months for patients receiving gemcitabine versus 5.3 months for patients on FLEC. Insufficient data on time to progression were collected in the 5FU/leucovorin arm to permit analysis. Clinical benefit responses were 17.9% versus 26.7% versus 13%, and overall tumour response 5.9%, 14% and 5% of those assessable. The overall survival and time to progression were statistically better in the FLEC arm compared to gemcitabine (P values 0.036 and 0.013 respectively). There was no statistically significant survival benefit of gemcitabine versus 5FU/leucovorin (P value 0.82). FLEC was associated with the most grade-3 and -4 toxicities. Pooled subgroup analysis was performed with these two trials to compare the 5FU and gemcitabine arms. Six-month pooled survival analysis showed an OR of 1.30 (95% CI 0.76 to 2.23, P value 0.34) and at 12- months OR 2.29 (95% CI 0.99 to 5.27, P value 0.05).

(4) Gemcitabine versus gemcitabine combination chemotherapy

Six-month pooled mortality data for gemcitabine combination chemotherapy regimens versus gemcitbine alone using the fixed effect model from 14 of the 16 trials was not significant, with an OR of 0.88 (95% CI 0.77 to 1.02, P value 0.08). There was significant evidence of heterogeneity (chi-squared P value 0.009, I^2 = 53.7%) at this time point. Examination of the funnel plot showed asymmetry with two small trials (Gansauge 2002; Wang 2002) to the far left of the plot in favour of combination therapy (see Figure 02). Sensitivity analysis using the random-effects model showed that the difference remained non-significant at P value 0.06. One-year survival data were available for all except one (Ohkawa 2004) of the 16 studies. Pooled data of mortality from these trials at 12 months for gemcitabine combination chemotherapy regimens versus gemcitabine alone resulted in an OR of 0.89 (95% CI 0.76 to 1.05, P value 0.17) which was also not significant. The chi-squared test was not significant for heterogeneity (P value 0.64, I2 = 0%).

The drugs combined with gemcitabine were divided into the following subgroups: fluropyrimidines, irinotecan, platinums and other combinations. None of these subgroups showed a statistically significant difference for gemcitabine compared with the combinations for 12-month mortality. However, there was a suggestion of a statistically significant improvement in the six-month mortality figures in favour of the five platinum-gemcitabine combination regimens (OR 0.59 (95% CI 0.43 to 0.81, P value 0.001). This significant subgroup benefit persisted even when the Wang study (Wang 2002) was excluded on a sensitivity analysis (P value 0.003). Although it was small, this trial lay at the extreme of the forest plot indicating heterogeneity. Furthermore, omission of this study from the 12-month analysis did not affect the non-significance of the subgroup comparison.

Median survival times were available for all studies and only the Gansauge trial (Gansauge 2002) showed a statistically significant difference between single-agent gemcitabine and a gemcitabine combination. Progression-free survivals were statistically superior with the combination arms in five studies (Berlin 2002; Colucci 2002; Heinemann 2003; Louvet 2005; Reni 2005).

Tumour response rates were superior with gemcitabine combinations in a number of studies (Colucci 2002; Gansauge 2002; Louvet 2005; Reni 2005; Oettle 2005b; Rocha Lima 2004). Clinical benefit response was better in the combination arms in three studies (Louvet 2005; Reni 2005; Scheithauer 2003). Reni measured quality of life with the EORTC QLQ C30 and PAN26 scales (Reni 2004b). Clinically relevant improvements from baseline were seen but there were no statistically significant differences between the arms. Although there was no difference in clinical benefit response in the O'Reilly study (O'Reilly 2004), patients in the combination arm experienced improvement in time to deterioration of analgesic consumption and performance status.

These studies are summarised in Table 03.

(5) Other comparative chemotherapy trials

The trials were heterogeneous with regard to the different combinations of chemotherapy regimens tested, and a pooled analysis was not performed. Most of the trials presented data on tumour response and median survival. In this group of studies only one trial found an advantage of one regimen over another. This was the Kelsen trial (Kelsen 1991), which found a statistically significant survival benefit of SMF (streptozocin, mitomycin and fluorouracil) over CAC (cisplatin/Ara C and caffeine), but the trial enrolled only 28 people. In another trial where SMF was compared to FAM (5-fluorouracil, adriamycin and mitomycin C) (Oster 1986), the differences in response rates and survival were not statistically significant. In addition, in a third trial, the SMF reg-

imen performed no better than mitomycin and 5FU in terms of survival, and had a higher toxicity (Bukowski 1983).

When mitomycin/5FU was compared to mitomycin/CCNU (Buroker 1979) the higher response rate (22% versus 5%) obtained did not translate into a better survival. Horton (Horton 1981) found no differences in survival on comparing melphalan with 5FU/CCNU and 5FU/CCNU/streptozocin. Tumour response assessment in these two trials was not reliable, as the investigators used clinical measurements rather than radiological assessments. Another study (Topham 1991) compared single-agent epirubicin with 5FU/epirubicin/mitomycin C. We have presumed, although we have been unable to confirm with the authors, that a subsequent publication (Topham 1993) is a preliminary publication of the same trial. No statistical difference was found with respect to response rate or survival. No combination schedule was clearly superior to others. These trials are summarised in Table 04.

Radiation therapy in locally advanced pancreatic cancer

The randomised studies identified in this part of the review were, once again, very heterogeneous in terms of study design, radiation schedules and techniques, as well as chemotherapy employed. A pooled analysis was not possible. A qualitative overview was performed. The studies are summarised in Table 05.

(1) Radiation therapy with or without chemotherapy in locally advanced pancreatic cancer

The first trial to examine the role of chemoradiation in detail was a placebo-controlled study by Childs (Childs 1965), where 25 locally-advanced pancreatic cancer patients were randomised to receive either saline with radiotherapy, or 5FU with radiotherapy. Six-month survival was 48% and 77% respectively, and 12-month survival 12% and 31%, although these were not statistically significant because of the small number of participants. In 1967, Moertel and colleagues (Moertel 1969) randomised 64 patients with locally-advanced pancreatic cancer to radiation alone or radiation with concurrent 5FU. There was an increase in median survival from 6.3 to 10.4 months (P value < 0.05) and one-year survival improved from 5% to 25%. Both these trials also enrolled patients with colon and gastric cancer. In 1981 Moertel reported the final results of a GITSG (Gastrointestinal Tumor Study Group) trial (Moertel 1981) with 194 patients randomised to either high dose radiation alone, or high dose radiation plus 5FU, or lower dose radiation plus 5FU. The median survival for combined modality was 42 weeks versus 23 weeks for radiation and one-year survival 40% versus 12% (P value < 0.01). There was no statistically significant difference between the two chemoradiation arms. A further study, reported in 1994 (Earle 1994), randomised 87 patients to radiation plus 5FU, or radiation plus an antishistosomal drug hycanthone used as a radiosensitizer to potentiate the radiotherapy. No statistical differences were seen in relapse-free survival (P value 0.27), median survival (both arms 34 weeks) or one-year survival (35% versus 28%). Quality of life were not measured in these trials but the toxicity of combined modality was greater than with radiation alone.

Another Gastrointestinal Tumor Study Group study (GITSG 1985b) randomised 157 patients to receive radiation therapy combined with either adriamycin or 5FU. No difference was seen with respect to survival (P value > 0.8), but adriamycin caused much more toxicity. Both the proportion of patients who experienced alleviation of pain, and the average amount of weight loss, were similar in both arms at 10 to 12 weeks into the study. The most recent study (Li 2003) randomised 34 patients to radiation (three-dimensional conformal radiotherapy) plus weekly gemcitabine, or to radiation (as before) plus 5FU as a continuous infusion. All patients received maintenance gemcitabine after radiation until progression. This study showed an improvement in median survival from 6.7 months to 14.5 months (P value 0.019), and time to progression from 2.7 to 7.1 months (P value 0.027), for those in the gemcitabine arm. Response rate was also better with concurrent gemcitabine (50% versus 12%), as were pain control (6% versus 39%), performance status, and quality adjusted life months.

A recent study from Japan (Shinchi 2002) has looked at the question of combined-modality therapy (radiation plus concurrent 5FU infusion with weekly 5FU maintenance post radiation) versus best supportive care. It randomised 31 patients and showed a median survival of 13.2 months for treatment versus 6.4 months (P value 0.001) with supportive care, and one-year survival of 53% versus 0% (P value 0.009) respectively. A quality of life benefit was found with treatment measured by maintenance of performance status.

(2) Chemotherapy with or without radiation therapy in locally advanced pancreatic carcinoma

Three studies compared chemoradiotherapy with chemotherapy alone. Hazel (Hazel 1981) randomised patients either to combination chemotherapy with 5FU and CCNU, or to radiation with 5FU followed by CCNU. No difference in survival between the two groups of 15 patients in each arm was noted (median survival 7.8 months). The Eastern Cooperative Oncology Group (ECOG) study (Klaassen 1985) reported upon 91 patients randomised to weekly maintenance 5FU until progression, or radiation therapy with 5FU. The results included: median survival of 8.2 versus 8.3 months; median time to treatment failure of 4.4 months versus 4.2 months; and one-year survival of 28% versus 30%. This trial enrolled patients with gastric cancer as well, and the randomisation was stratified on the basis of tumour aneuploidy, but not tumour site. There was a high rate of patients (22%) who were ineligible or cancelled in the trial, and the trial closed early due to poor accrual. In 1988 the Gastrointestinal Tumor Study Group trial (GITSG 1988) compared combination chemotherapy, using streptozotocin, methotrexate and 5FU, to the same regimen plus radiation in 42 patients who experienced median survival of 32 versus 42 weeks and one-year survival of 19% versus 41% (P value < 0.05) respectively. This trial closed early due to lack of funding.

None of these studies incorporated formal assessments of quality of life, however, the toxicities of treatment were higher in the arms evaluating combined modalities.

DISCUSSION

Best supportive care versus chemotherapy

A survival benefit was seen in the pooled results of combination chemotherapy against best supportive care studies at 12 months and six months. These trials all used old style chemotherapy combination regimens and none involved the use of gemcitabine which is discussed further below. Only one study (Glimelius 1996) used a validated measure of quality of life in the form of the EORTC QLC C30 questionnaire and found a clinical benefit with the use of chemotherapy.

Comparative studies of chemotherapy in advanced pancreatic cancer

5-Fluorouracil (5FU) has been the most studied agent in advanced pancreatic cancer. Pooled analysis of 5FU found it to be inferior to other single-agent chemotherapy with respect to six-month survival. When 5FU was compared against 5FU combination regimens, pooled analysis did not demonstrate a survival advantage for the 5FU combination regimens compared to 5FU alone. Although, in some trials, the objective tumour response rates were higher with the combination regimens, this did not correlate with better survival, but was usually associated with increased toxicity. This is in contrast to advanced breast cancer (Bruzzi 2002) and colon cancer (Buyse 2000) where higher response does seem to correlate with better survival. Despite this, two trials(Ducreux 2002; Ducreux 2004) did find a better clinical benefit with the combination regimen. Various 5FU combinations have been tested and there is no regimen that is clearly superior.

The Burris study (Burris 1997) introduced the concept of measurement of clinical benefit as a primary endpoint when comparing gemcitabine to 5FU. Gemcitabine exhibited superior survival and improvement in clinical benefit to 5FU, and became the standard treatment for advanced pancreatic cancer. The subsequent three-armed Cantore study (Cantore 2004) included gemcitabine and 5FU/folinic acid arms; these showed no difference in survival, but the latter arm terminated early and the resulting cross-over of patients onto the other arm may have diluted any survival difference. The Cantore study also enrolled a larger proportion of patients with locally-advanced disease than Burris. The two 5FU schedules differed, with Burris employing a weekly schedule, and Cantore a monthly five-day regimen in combination with folinic acid. The intrahepatic FLEC arm of this trial demonstrated superiority in survival over gemcitabine, but at a cost of significantly higher toxicity. Pooled subgroup analysis of these two studies showed a borderline reduction effect in one-year mortality rate of gemcitabine over 5FU, with wide confidence intervals, so evidence of superiority is inconclusive. Pooled analysis of single-agent chemotherapy versus gemcitabine did not show any statistically significant differences in 12- or six-month mortality.

A large number of trials compared gemcitabine combination chemotherapy regimens to gemcitabine alone. The pooled results for one-year and six-month survival showed no statistically significant differences. Subgroup analysis showed that six-month survival is better with the platinum-gemcitabine combinations. Once again, increased response rates seen in some of the gemcitabine combinations do not seem to correlate with improvements in survival. Several studies do show an improvement in progression-free survival with the use of combination therapy. The one-year survival rates in these studies are increasingly in excess of 20%, which may reflect either better supportive care, or an increased use of second-line therapies following initial treatment failure that may dilute the overall survival differences.

Tumour response rate is a surrogate endpoint for clinical trials, which is subject to investigator bias. Some trials in the review were completed before computed tomography (CT) imaging became available. Despite the current availability of CT imaging, response in advanced pancreatic cancer can be difficult to assess because of the high incidence of peritoneal disease that does not image well, and because of desmoplastic stromal activity around the primary site. The response rates in the trials were based on the number of patients who were evaluable and not necessarily the number randomised. Combination chemotherapy regimens may be useful in rare situations, for example, where a locally-advanced pancreatic cancer could be sufficiently reduced in size to enable curative surgical resection, or when combination with radiation treatment is aimed at achieving high response rate with a view to downstaging tumours again for curative surgery (Wilkowski 2005). At present, no randomised trials support the benefit of downstaging treatment in pancreatic cancer, however, single arm studies that have shown that inoperable patients may be rendered operable, suggest a need for trials in this area.

Clinical benefit or quality of life was measured in twelve of the sixteen gemcitabine combination studies. Only three of these (Louvet 2005; Reni 2005; Scheithauer 2003) found a superiority with the combination regimens. Importantly, one study (Li 2004) found an adverse effect of combination chemotherapy on quality adjusted life months compared to single agent.

Radiation therapy in locally-advanced pancreatic cancer

Locally unresectable pancreatic cancer represents an under-researched area in which management is based more upon opinion than evidence. A series of small trials performed several decades ago continues to provide the only randomised data upon which current management decisions are made. Some of these trials were conducted before computed tomography became available, so assessment of the stage of the disease was suboptimal. Amongst these

trials, there is a clear separation between those that offer identical treatment to patients with both metastatic disease or locally-advanced disease stating that the outcome is identical, and those that believe that a longer natural history, a longer median survival and a differential response to radiation merit the use of combined-modality therapy in locally advanced disease.

In one small study (Shinchi 2002), chemoradiation therapy showed a benefit in both survival and quality of life when compared to best supportive care in locally-advanced pancreatic cancer. It also produced better survival in two relatively small, randomised trials (Moertel 1969; Moertel 1981) where it was compared to radiation alone, and in another small study (GITSG 1988), that was terminated early, in which it was compared to combination chemotherapy alone. The toxicity of chemoradiation is higher than with single-modality treatment. 5FU is the drug that has been used in all of the studies of concurrent chemoradiation. One small study (Li 2003) compared concurrent gemcitabine to 5FU showing a better outcome with the gemcitabine. Most of the trials were conducted before the availability of conformal radiotherapy techniques, that have reduced the toxicity of radiation treatment.

The consistent difference in median survival times of 10 to 14 months for combined treatment groups, compared to half that for groups receiving radiation alone, and one-year survivals of 28% to 50% is most interesting. This suggests, firstly, that optimising chemoradiation protocols is justified in this condition, and, secondly, that people with locally-advanced disease should not be studied with those with metastatic disease in any new randomised studies, unless there is equal stratification across the arms of the study. The need to standardise tests to exclude metastatic disease makes such studies difficult and suggests that only careful, prospective, well controlled studies can provide a definitive answer to the management of this subgroup of pancreatic carcinoma. Such a study has been completed and results are expected in 2006 (ECOG-4201;assessing gemcitabine with or without radiation). In the meantime, it remains unclear whether chemotherapy alone would produce equivalent outcomes in locally-advanced disease compared to a more complex, and potentially more toxic, regimen of chemotherapy and radiation.

AUTHORS' CONCLUSIONS

Implications for practice

Systemic chemotherapy appears to improve survival and quality of life in patients with advanced (metastatic and locally-advanced) pancreatic cancer when compared to best supportive care.

Gemcitabine alone is an acceptable palliative treatment for patients with locally-advanced or metastatic pancreatic cancer. Superiority of survival over 5FU is inconclusive, but for clinical benefit gemcitabine is better. Combination regimens with gemcitabine can produce a higher response rate, but this does not appear to translate into a survival advantage.

Chemoradiation appears to have a benefit over best supportive care, or radiation alone. There is insufficient evidence to recommend chemoradiation as a superior alternative to chemotherapy alone in fit individuals with locally advanced inoperable pancreatic cancer

Implications for research

Trial reporting and design

Survival results are still poor even with the best-studied regimens. Clinical trials need to be adequately powered to detect clinically significant differences in survival, and report on meaningful endpoints such as: time to progression, toxicities and quality of life (using validated instruments). Pharmacoeconomics data and cost effectiveness will also be important considerations. Chemotherapy studies in advanced pancreatic cancer should stratify patients with locally-advanced and metastatic disease.

Agents to compare in future trials

Gemcitabine is still an acceptable control arm in clinical trials, which should continue to explore scheduling and combinations with novel agents. There is a need to avoid further chemotherapy combinations unless a new drug has shown substantial survival benefit in a second-line setting, or has shown improvement in the expected median and 12-month survivals in a phase II setting. Improvements are unlikely to be achieved through trials that examine existing chemotherapy drug combinations and it is inadvisable to test more versions of the same classes of agents.

The impact of second-line therapies on outcome, and their possible influence on diluting the survival gains of combination therapy, needs to be quantified. A legitimate area of trials research would be the influence of second-line therapies on outcomes, with more rigorous identification of active second line drug regimens and quantification of the degree of benefit, as well as identification of predictive factors to segregate the groups most likely to gain from such treatment(s). The issue of sequential, as opposed to combination therapy, is also a legitimate area to explore in order to maximise quality of life without compromising survival.

Further chemoradiation studies employing modern conformal 3-D planning techniques to determine optimal chemoradiation schedules are required.

Randomised trials are also required in people with locally-advanced unresectable pancreatic cancer to determine whether there is any advantage to adding radiation to chemotherapy and to identify the best means of downstaging tumours for resection, as well as whether this provides sustained benefits.

Clinicians and patients should be encouraged to participate in high quality clinical trials in advanced pancreatic cancer.

Future updates of this review

At the time of protocol conception, biological therapies such as cytokines, signal transduction inhibitors and monoclonal antibodies were excluded from this review, and it was decided to focus on cytotoxic chemotherapy and radiotherapy. However, since phase III trials of a number of these agents have either been completed or are ongoing, the next update of this review will include these therapies, and also randomised second line treatment studies.

POTENTIAL CONFLICT OF INTEREST

Desmond Yip has received consultancy fees from Eli Lilly for being an independent advisor in a clinical trial and was an investigator in the Shapiro 2005 and Chau 2003 studies. Andrew Strickland and Christopher Steer have received travel grants from Eli Lilly. David Goldstein has acted as an advisor for Eli Lilly, Pharmacia/Pfizer, Roche, Merck AG and Novartis. He was a principal investigator in the Moore 2005 trial and an investigator in the Van Cutsem 2004 trial. No payments of any kind have been received for preparation of this review.

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Cunningham 2005

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CALGB-89904

Phase II randomised study of gemcitabine alone vs gemcitabine with cisplatin vs gemcitabine with Docetaxel vs gemcitabine with irinotecan in patients With metastatic pancreatic cancer. Ongoing study Starting date of trial not provided. Contact author for more information.

ECOG-4201

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ECOG-6201

Phase III randomised study of standard infusion gemcitabine vs prolonged infusion gemcitabine with or without oxaliplatin patients with locally advanced or metastatic pancreatic cancer.. Ongoing study 03/2003.

ECOG-E8200

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EORTC 40033

Phase III trial of docetaxel/gemcitabine vs gemcitabine in advanced pancreatic cancer.. Ongoing study Starting date of trial not provided. Contact author for more information.

EORTC-05962

Phase III randomised multicentre trial of infusional fluorouracil with or without cisplatin and with or without chronomodulation against locally advanced or metastatic pancreatic cancer.. Ongoing study Starting date of trial not provided. Contact author for more information.

FRE-GERCOR-GEM-GEMOX

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MRC PANRAD

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NCI-6580

Phase II randomised study of bevacizumab and gemcitabine with either cetuximab or erlotinib in patients with advanced adenocarcinoma of the pancreas.. Ongoing study Starting date of trial not provided. Contact author for more information.

NCT00051467

A randomised, phase II, study of TNFerade™ biologic with 5-FU and radiation therapy for first-line treatment of unresectable locally advanced pancreatic cancer. Ongoing study Starting date of trial not provided. Contact author for more information.

RTOG-PA-0020

Randomised phase II trial to compare the effectiveness of gemcitabine, paclitaxel, and radiation therapy with or without tipifarnib in treating patients who have locally-advanced pancreatic cancer.. Ongoing study Starting date of trial not provided. Contact author for more information.

SWOG S0205

Phase III randomised open label study comparing gemcitabine with cetuximab vs gemcitabine as first line therapy of patients with advanced pancreatic carcinoma.. Ongoing study Starting date of trial not provided. Contact author for more information.

TBC-PAN-003

Phase III randomised controlled study to evaluate the safety and efficacy of PANVAC-VF in combination with GM-CSF vs best supportive care or palliative chemotherapy in patients with metastatic adenocarcinoma of the pancreas who have failed a gemcitabine containing chemotherapy regimen.. Ongoing study 06/2004.

TC-CR-302

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* *Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	**Andersen 1981**
Methods	Randomised controlled trial Single centre study Recruitment period: August 1974-January 1978 Funding not stated
Participants	Inclusion criteria: microscopically-proven pancreatic carcinoma. Exclusion criteria: terminal disease; previous chemotherapy; concomitant disease precluding evaluation of response. Total patients enrolled: 40 (A: 20, B:20). Median age: 67 y (range 34-81y) M:F ratio: 16:24. Disease extent: locally advanced and metastatic or relapsed: A: 19:1, B. 18:2.
Interventions	A. Best supportive care+ placebo (isotonic saline). B. Best supportive care+ 5FU 10 mg/kg+ BCNU 40 mg/sqm days 1-5.
Outcomes	Median survival One year survival
Notes	'Triple blind' randomised scheme.
Allocation concealment	A – Adequate

Study	**Andren-Sandberg 1983**
Methods	Randomised controlled trial,

Characteristics of included studies (*Continued*)

	single-centre study, Recruitment period not stated Funding not stated.
Participants	Inclusion criteria: inoperable pancreatic cancer with pathological confirmation, age <71 years, no prior chemotherapy. Number randomised: 47 (A: 22, B:25). Median age: A: 61y (range 40-69 y), B: 60 (range 28-78 y) M M:F ratio: A: 15:7, B: 15:10. Locally-advanced: metastatic: A: 10:12, B: 14:11.
Interventions	A. Best supportive care. B. Vincristine 1 mg/sqm IVI d1, 5FU 500mg PO d2-5+CCNU PO d2-3 q six weekly
Outcomes	Median survival QOL (Karnofsky scale)
Notes	Randomisation not assessable In control group, 16 had undergone gastroenterostomy and two had percutaneous biliary stents In the treatment group 18 had undergone gastroenterostomy and 4 had percutaneous biliary stents.
Allocation concealment	B – Unclear

Study	**Berlin 2002**
Methods	Randomised controlled trial, multicentred government-funded Recruitment period: April 1998- November 1999. Planned enrolment: 320.
Participants	Inclusion criteria: microscopically-confirmed pancreatic cancer not amenable to resection; >18 y; ECOG performance status 0-2; no active malignancy or active disease; adequate organ function Exclusion criteria: prior chemotherapy for advanced disease; pregnant or lactating female. Total patients randomised:322 (A: 162, B: 160). Mean age: A: 64 y (33-85 y), B 65 (28-84 y) M:F ratio: A: 87:75, B: 83:77. Locally-advanced:metastatic: A: 16:145 B: 17:143.
Interventions	A. Gemcitabine 1g/sqm IV weekly for 3 weeks out of 4. B. Gemcitabine 1g/sqm +5FU 600mg/sqm IV for 3 weeks in 4
Outcomes	Median survival. Progression free survival. Overall survival at 6 and 12 months.
Notes	Prior radiotherapy allowed if >4 weeks prior, and adjuvant chemotherapy allowed if >6 months prior Survival figures obtained from survival curve.
Allocation concealment	A – Adequate

Study	**Bukowski 1983**
Methods	Randomised controlled trial, multicentre government -funded trial. Recruitment period: not stated.
Participants	Inclusion criteria: histologically confirmed adenocarcinoma of pancreas; no prior chemotherapy or radiotherapy; adequate renal function. Total number randomised: 181 (A: 88, B:93). Bypass surgery: A: 27, B: 32.
Interventions	A. MF chemotherapy (5FU 1000 mg/sqm IV d1-4, 29-32, mitomycin C 20-30mg/sqm IV d1) every 56 days.

	B. SMF chemotherapy (5FU 1000mg/sqm IV d1-4, d29-32, mitomycin C 10-15 mg/sqm IV, streptozotocin 400mg/sqm d1-4, d29-32) every 56 days.
Outcomes	Median survival. 1-year survival. Response rate.
Notes	Patients stratified according to risk status, presence of measurable or non-measurable disease. Poor risk patients received the lower dose level of mitomycin C. Results given separately for measurable and non-measurable disease patients.
Allocation concealment	B – Unclear

Study	**Buroker 1979**
Methods	Randomised control trial, multicentre study (11 institutions), government funded. Recruitment period: March 1975-March 1977.
Participants	Inclusion criteria: histologically confirmed adenocarcinoma of pancreas; clinical evidence of gross locally recurrent or metastatic tumour; no prior chemotherapy; life expectancy >8 weeks; WCC>4000; platelets >1000; Cr< 1.5 mg/dL. Total enrolled (pancreatic): 144 Total eligible(pancreatic): 140 (A:69, B:71) Seven dropouts: 3 refused further therapy, one incomplete form, 3 lost to follow-up.
Interventions	A. 5FU 1g/sqm/day infusion for 4 days every 4 weeks + mitomycin C 15-20 mg/sqm IVon d1 every 8 weeks. B. 5FU 1g/sm/day infusion x 4 days every 4 weeks, MeCCNU 150-175 mg/sqm PO on d1 every 8 weeks.
Outcomes	Median survival. Response rate. Toxicity.
Notes	Trial enrolled both pancreatic and gastric cancers. Separate data available for pancreatic cancer. 3 patients ineligible in arm A and 1 on arm B. Patients stratified for presence or absence of measurable disease and liver metastases. Dose of mitomycin C reduced by 50% once 3rd course reached. Lower dose of MeCCNU used if age >65, concurrent radiotherapy or bilirubin > 2 times normal.
Allocation concealment	B – Unclear

Study	**Burris 1997**
Methods	Randomised controlled trial, multicentred (17 sites), pharmaceutical company funded (Eli Lilly). Planned enrolment: not stated, enrolment period: July 1992-March 1994.
Participants	Inclusion criteria: locally-advanced or metastatic pancreatic cancer with pathological diagnosis not amenable to curative resection; life expectancy > 12 months; Karnofsky score >50; Cr<1.5; WCC>3.5; Hb >9.5; AST and ALT <3 x upper limit of normal unless tumour involvement where <5x upper limit of normal. Exclusion criteria : prior chemotherapy, prior radiotherapy unless the only site of measurable disease. Number enrolled: 160. Number randomised: 126 (A:63,B:63). Median age: A: 61 y (36-77 y) and B: 62 y (37-79 y). M:F ratio: A: 34:29, B: 34:29. Metastatic: A: 76%, B: 72%. Dropouts prior to randomisation=34. Reasons: due to ineligibility (17), inadequate pain control (10), medical problems (4) and declined further evaluation (3).
Interventions	A. 5FU 600 mg/sqm IV bolus weekly until progression. B. Gemcitabine 1000 mg/sqm IV weekly for 7 weeks then 1 week off and weekly for 3 weeks out of 4 until progression.

Characteristics of included studies (*Continued*)

Outcomes	Clinical benefit (composite measure of pain, analgesic consumption, performance status, weight). Median survival. 1 year survival. Response rate.
Notes	Pain stabilisation lead in period of 2-7d prior to treatment commencement. Clinical benefit was the primary endpoint of trial.
Allocation concealment	A – Adequate

Study	**Cantore 2004**
Methods	Randomised controlled trial, multicentre (9 sites). Enrollment period: June 1997-June 2001. Funding not stated.
Participants	Inclusion criteria: histologically-proven adenocarcinoma of pancreas not suitable for curative resection; KPS>50; adequate bone marrow reserve; hepatic function and renal function. Exclusion criteria: peritoneal metastases; previous chemotherapy; radiotherapy or both; previous myocardial infarct; severe coagulopathy; second malignancy or pregnancy. Number enrolled and randomised: 175 (A: 67, B: 71, C: 37). Median age: A: 64 y (37-79 y), B: 61 y (38-76y), C:64 y (41-78 y). M:F ratio: A: 70:30, B: 63:37, C: 57:43. Locally advanced: metastatic: A: 48:52, B: 49:51, C 43: 57. Two patients lost to followup in Arm C.
Interventions	A. Gemcitabine 1g/sqm IV weekly for 7 weeks then 1 week off and weekly for 3 weeks out of 4. B. FLEC (Leucovorin 100 mg/sqm+ 5FU 1000mg/sqm+carboplatin 300 mg/sqm+epirubicin 60 mg/sqm) intra-arterial every 3 weeks for 3 cycles. C. 5FU 400 mg/sqm+ folinic acid 20 mg/sqm for d1-5 every 28 days x 6 cycles
Outcomes	Overall survival Time to treatment failure Clinical benefit response Response rate
Notes	FLEC arm received filgrastim (G-CSF) support for d10-d16 after treatment. Arm C terminated early in December 1998 by scientific committee due to reluctance of clinicians and patients to have patients randomised to this arm. Arm C data unpublished and provided by author.
Allocation concealment	A – Adequate

Study	**Cheverton 2004**
Methods	Randomised trial; multicentre (USA, Europe, South Africa). Pharmaceutical industry sponsored (Daiichi). Recruitment period: July 2001-January 2003.
Participants	Inclusion criteria: histologically or cytologically-proven locally advanced or metastatic adenocarcinoma of the pancreas; KPS>60%; no prior chemotherapy. Planned recruitment: 340. Number randomised: 339 (A: 170. B: 169). Number completing: 330. M: F ratio: A: 96:73, B: 100:70. Locally advanced: metastatic: A: 49:121, B: 51:118. 5 dropouts in A and 4 in B, reasons not given.
Interventions	A. Gemcitabine 1000 mg/sqm IV weekly for 7 weeks, 1 week break then for 3 weeks out of 4

Characteristics of included studies (*Continued*)

	B. Exatecan (DX-8951f) 0.5 mg/sqm daily for d1-5 every 3 weeks
Outcomes	Median survival. Survival at 6 months, 12 months and 21 months. Time to progression. Time to worsening of clinical benefit. Response rate. Time to marker progression.
Notes	
Allocation concealment	A – Adequate

Study	**Childs 1965**
Methods	Randomised double blind controlled trial. Single centre study supported in part by the American Cancer Society. 5FU supplied by Hoffman La Roche. No information on recruitment period or dropouts from study.
Participants	Inclusion criteria: inoperable histologically proven adenocarcinoma of the gastrointestinal tract; localised no distant metastases at operation; disease within 20 x 20 cm radiation field. Total enrolled (pancreatic only): 25 (A: 12 B: 13). Mean age: A: 59 y (range 47-74 y) B: 56 y (44-72 y). M:F ratio: A: 11:1 B: 8:5.
Interventions	A. Radiotherapy (3500-4000 rad 6 d per week, 900-1200 rad /week) +saline. B. Radiotherapy (3500-4000 rad 6 d per week, 900-1200 rad /week) + 5FU (15mg/kg/day on consecutive days until 40-50 mg/kg total dose reached).
Outcomes	Survival at 6 and 12 months. Median survival.
Notes	Placebo controlled study. Pharmacists made up solutions but clinicians blinded. Further radiotherapy and chemotherapy allowed on progression. Approximately equally distributed.
Allocation concealment	A – Adequate

Study	**Colucci 2002**
Methods	Randomised controlled trial, multicentred. Funding not stated. Enrolment period:not stated.
Participants	Inclusion criteria: histologically or cytologically diagnosed locally advanced and/or metastatic pancreatic carcinoma; bidimensionally measurable disease; no prior chemotherapy; radiotherapy or hormonal therapy; age 18-75 y, KPS>50; no congestive cardiac failure; serious arrhythmia or coronary heart disease; absence of severe uncontrolled metabolic; infectious; or neurological disease; absence of other malignant neoplasms except CIS of the uterine cervix and nonmelanotic skin cancers; geographic accessibility; adequate baseline bone marrow reserve; adequate hepatic function and adequate renal function. Exclusion criteria : brain metastases; pre-existing medical condition of sufficient severity to prevent full compliance with the study. Planned accrual:106. Total enrolled: 107 (A: 54, B: 53). M:F ratio: A: 50:50, B: 66:34. Median age: A: 63 y (43-75 y) B 60 (33-71 y). Metastatic: A: 50%, B 57%.
Interventions	A. Gemcitabine 1000 mg/sqm IV weekly for 7 weeks then for 3 out of 4 weeks for 2 cycles. B. Gemcitabine 1000 mg/aqm IV weekly for 7 weeks with cisplatin 25 mg/sqm IV d1,8,15,36,42, then weekly gemcitabine+cisplatin for 3 week out of 4 for 2 cycles

Characteristics of included studies (*Continued*)

Outcomes	Median survival. Survival at 6 and 12 months. Objective response rate. Time to progression. Toxicity.
Notes	
Allocation concealment	A – Adequate

Study	**Cullinan 1985a**
Methods	Randomised controlled trial; multicentred study (12 centres) funded by National Cancer Institute. Recruitment period uncertain Planned accrual: 300.
Participants	Inclusion criteria: unresectable or metastatic histologically proven pancreatic or gastric adenocarcinomas; minimum 3 weeks post major surgical procedure or 2 weeks post exploration and biopsy; ambulatory and capable of maintaining oral nutrition; ECOG status 0-3. Exclusion criteria: prior chemotherapy; active infectious process; leucopenia; (<4000), thrombocytopenia (<130; active heart disease; azotaemia or concomitant second primary cancer. Total randomised: 305. Patients with pancreatic cancer randomised: 144 (A: 50, B: 44, C: 50).
Interventions	A. 5FU alone chemotherapy (500 mg/sqm for d1-5) every 4 weeks for 3 cycles then every 5 weeks. B. Mallinson regimen: FA chemotherapy (5FU 400 mg/sqm for d1-4 + Adriamycin 40 mg/sqm d1) every 4 weeks for 3 cycles then every 5 weeks C. FAM chemotherapy (5FU 600 mg/sqm for d1,8,29,36+ doxorubicin 30 mg/sqm for d1,29+mitomycin C 10mg/sqm for d1) every 8 weeks. Maximal cumulative dose adriamycin= 500mg/sqm
Outcomes	Response rate. Median survival. Time to progression. Palliative effects (weight gain, symptoms and performance score).
Notes	Stratification within institution according to primary site, disease stage, presence of measurable disease and performance status. Survival figures obtained from survival curves. Cullinan 1985a and b are same trial. Arm B in pooled analysis.
Allocation concealment	B – Unclear

Study	**Cullinan 1985b**
Methods	Randomised controlled trial, multicentred study (12 centres) funded by National Cancer Institute. Recruitment period uncertain. Planned accrual: 300.
Participants	Inclusion criteria: unresectable or metastatic histologically proven pancreatic or gastric adenocarcinomas; minimum 3 weeks post major surgical procedure or 2 weeks post exploration and biopsy; ambulatory and capable of maintaining oral nutrition; ECOG status 0-3. Exclusion criteria: prior chemotherapy; active infectious process; leucopenia; (<4000); thrombocytopenia (<130); active heart disease; azotaemia or concomitant second primary cancer. Total randomised: 305. Patients with pancreatic cancer randomised: 144 (A: 50, B: 44, C: 50).
Interventions	A. 5FU alone chemotherapy (500 mg/sqm for d1-5) every 4 weeks for 3 cycles then every 5 weeks.

	B. Mallinson regimen: FA chemotherapy (5FU 400 mg/sqm for d1-4 + Adriamycin 40 mg/sqm for d1) every 4 weeks for 3 cycles then every 5 weeks. C. FAM chemotherapy (5FU 600 mg/sqm for d1,8,29,36+ doxorubicin 30 mg/sqm for d1,29+mitomycin C 10mg/sqm d1) every 8 weeks. Maximal cumulative dose adriamycin= 500mg/sqm.
Outcomes	Response rate. Median survival. Time to progression. Palliative effects (weight gain, symptoms and performance score).
Notes	Stratification within institution according to primary site, disease stage, presence of measurable disease and performance status. Survival figures obtained from survival curves. Cullinan 1985a and b are same trial. Arm C in pooled analysis
Allocation concealment	B – Unclear

Study	**Cullinan 1990a**
Methods	Randomised controlled study, multicentre study. Funding not stated. Accrual period not stated.
Participants	Inclusion criteria: histologically-proven ductal or undifferentiated adenocarcinoma of the pancreas; ambulatory; maintaining unassisted oral food intake of at least 1200 calories a day; minimum of 3 weeks recovery from any major surgical procedure involving resection or bypass or 2 weeks from exploration and biopsy only. Exclusion criteria: ECOG 4 ; prior chemotherapy; active infectious process; severe malnutrition; severe nausea or frequent vomiting; leucopenia, thrombocytopenia; elevation of serum creatinine above the upper limit of the institutional normal; active heart disease; known active second primary malignancy and prior radiotherapy within previous 4 weeks. Number randomised: 187. Eligible patients randomised: 184 (A: 64, B:61,C:59). Median age: A: 60 y (35-79 y), B: 62 y (34-79 y), C: 62 y (27-76 y) M:F ratio A: 66:33, B: 56:44, C: 64:36.
Interventions	A. 5FU 500 mg/sqm/day for d1-5 every 5 weeks. B. Mallinson regimen (5FU 270mg/sqm/day for d1-5+ cyclophosphamide 160 mg/sqm for d1, d5,+ methotrexate 11 mg/sqm for d1, d4+ vincristine 0.7 mg/sqm for d2,d5) IV induction then 5FU 350 mg/sqm+ mitomycin C 3.5 mg/sqm for d1-5 every 6 weeks. C. 5FU 300 mg/sqm/day for d1-5+ doxorubicin 40 mg/sqm for d1+cisplatin 60 mg/sq1 for d1 every 5 weeks All arms treated until progression.
Outcomes	Median survival. Survival at 6 months and 1 year. Response rate. Toxicity.
Notes	Patients stratified according to presence of measurable disease, extent of metastasis and ECOG performance status. 3 patients ineligible and not included in analysis. 6 and 12-month survival read from survival curves. Cullinan 1990a and b are same trial. Arm B comparison in pooled analysis.
Allocation concealment	B – Unclear

Characteristics of included studies (*Continued*)

Study	**Cullinan 1990b**
Methods	Randomised controlled study, multicentre study. Funding not stated. Accrual period not stated.
Participants	Inclusion criteria: histologically proven ductal or undifferentiated adenocarcinoma of the pancreas;ambulatory; maintaining unassisted oral food intake of at least 1200 calories/d; minimum of 3 weeks recovery from any major surgical procedure involving resection or bypass, or 2 weeks from exploration and biopsy only. Exclusion criteria: ECOG 4; prior chemotherapy; active infectious process; severe malnutrition; severe nausea or frequent vomiting; leucopenia; thrombocytopenia; elevation of serum creatinine above the upper limit of the institutional normal; active heart disease; known active second primary malignancy and prior radiotherapy within previous 4 weeks. Number randomised: 187. Eligible patients randomised: 184 (A: 64, B:61,C:59). Median age: A: 60 y (35-79 y), B: 62 y (34-79 y), C: 62 y (27-76 y). M:F ratio A: 66:33, B: 56:44, C: 64:36.
Interventions	A. 5FU 500 mg/sqm/day for d1-5 every 5 weeks. B. Mallinson regimen (5FU 270mg/sqm/day for d1-5+ cyclophosphamide 160 mg/sqm for d1, d5,+ methotrexate 11 mg/sqm for d1, d4+ vincristine 0.7 mg/sqm for d2,d5) IV induction then 5FU 350 mg/sqm+ mitomycin C 3.5 mg/sqm for d1-5 every 6 weeks. C. 5FU 300 mg/sqm/day for d1-5+ doxorubicin 40 mg/sqm d1+cisplatin 60 mg/sqm for d1 every 5 weeks. All arms treated until progression.
Outcomes	Median survival Survival at 6 months and 1 year. Response rate Toxicity
Notes	Patients stratified according to presence of measurable disease, extent of metastasis and ECOG performance status. 3 patients ineligible and not included in analysis. 6 and 12-month survival read from survival curves. Cullinan 1990 a and b are same trial. Arm C comparison in pooled analysis
Allocation concealment	B – Unclear

Study	**Ducreux 2002**
Methods	Randomised controlled trial, multicentre trial (18 sites), government-funded. Recruitment period: December 1992-January 1998. No patients lost to follow up.
Participants	Inclusion criteria: histologically or cytologically proven adenocarcinoma of pancreas or ampulla; locally-advanced or metastatic; life expectancy >2 months; WHO<3; age<75 y; no prior CT or RT of marker lesion; no hormonal treatment within 3 months; adequate hepatic; renal and bone marrow function. Exclusion criteria: leucopenia (<4000); thrombocytopenia (<130); raised creatinine (>110); hyperbilirubinaemia (>34); active heart disease; known previous second primary malignancy. Total randomised (pancreatic) 198 (A:99, B:99). Number with histological confirmation: 190 (A 94, B: 96).
Interventions	A. 5FU 500 mg/sqm/day bolus IV for d1-5 days every 4 weeks until progression. B. 5FU 1000mg/sqm/day infusion x 5days+cisplatin 100mg/sqm for d1 or 2 every 4 weeks until progression.
Outcomes	Median survival. 1 year survival.

	Progression-free survival. Response rate. Symptoms and performance status. QOL (Spitzer index).
Notes	Patients stratified by centre, presence of metastatic disease and by primary site. In arm B cisplatin could be ceased because of renal, neurological or otological toxicity and 5FU alone continued if stabilisation or response. Radiation therapy and surgery allowed. Second line chemotherapy given to 26 patients in arm A and 17 in arm B. Eight patients (A:5, B:3) did not have histological or cytological diagnoses. Data reported for combined group of pancreatic and ampullary cancers. Authors supplied survival figures for pancreatic cancer subgroup, but this included the patients without pathological diagnosis.
Allocation concealment	A – Adequate

Study	**Ducreux 2004**
Methods	Randomised controlled trial, multicentre trial (10 centres). Pharmaceutical company sponsored (Sanofi Synthelabo). Recruitment period: November 1997- July 1999. Planned recruitment: 84 (maximum 28 per arm).
Participants	Inclusion criteria: histologically or cytologically proven non resectable locally advanced or metastatic pancreatic carcinoma;at least one measurable lesion; no prior chemotherapy except 5FU administered with radiotherapy with disease free interval of >3 months from completion of treatment; aged 18-75 y; life expectancy >12 weeks; WHO PS 0-2; adequate bone marrow; renal and liver function. Exclusion criteria: concomitant second malignancy; symptomatic peritoneal carcinomatosis or gastric stenosis; cerebral or leptomeningeal disease; peripheral neuropathy; concurrent other experimental drugs; hypersensitivity to 5FU; pregnancy or breast feeding; pleural effusion or ascites as the only sign of disease. Number randomised: 65 (2 dropouts due to deaths after randomisation, treatment allocations not stated). Number treated 63 (A: 15, B: 17, C: 31). Median age: A: 57y (35-66 y), B: 55 y (21-74 y), C: 60 y (27-75 y). M:F ratio: A: 60:40, B: 65:35, C: 71:29. Locally advanced:metastatic: A: 0:100, B: 6:94, C: 16:84.
Interventions	A. 5 FU 1000 mg/sqm/day continuous infusion for d1-4 every 3 weeks. B. Oxaliplatin 130 mg/sqm IV over 2 hours every 3 weeks. C. Oxaliplatin 130 mg/sqm IV over 2 hours for d1+ 5 FU 1000 mg/sqm/day continuous infusion for d1-4 every 3 weeks
Outcomes	Response rate. Time to progression. Median survival. 6 and 12-month survival. Clinical benefit response.
Notes	13% of patients had prior surgery. 3% received prior radiation therapy with 5FU treatment. 3 patients (1 in each arm) found to be ineligible but analysed: 1 non measurable disease and abnormal bilirubin, 1 baseline CT > 6 weeks prior to study start and one with disease free interval <3 months after local regional chemoradiotherapy. Second line therapy given in some patients but details not given of number or type. Poor compliance with clinical benefit response assessment with only 51% evaluable. 2deaths not related to disease: 1 suicide and 1 pulmonary embolism.
Allocation concealment	A – Adequate

Characteristics of included studies (*Continued*)

Study	**Earle 1994**
Methods	Randomised trial, multicentre, funded by Public Health Service Grant. Planned accrual: 128. Recruitment period: March 1981-November 1987. No patients lost to follow-up.
Participants	Inclusion criteria: histologically confirmed adenocarcinoma of pancreas; inoperable due to local extent or regional nodes. Exclusion criteria: direct extension into liver; peritoneal seeding; unable to be included in a 20x20 cm radiation port; coexistent malignant disease; prior chemotherapy; prior radiotherapy within the field for study, coexisting infection; primary liver disease; ECOG performance status 4; bilirubin >2 x upper limit of normal or SGOT <2 x upper limit of normal; white cell count <4.1; platelets <130. Total enrolled: 87 (A: 44, B:43). Median age: A: 64 y, B: 62 y. M:F ratio: A: 28:16, B: 28:15 Surgical exploration: A 36,B 38.
Interventions	A. Radiotherapy (40-50 Gy + 5 Gy boost split course (20Gy over 10 d each with 2 week break) +5Gy boost) + 5FU 500mg/sqm/d IVI for d1-3. of each radiotherapy course. vs B. Radiotherapy (50 Gy straight course over 25 d)+ hycanthone 60mg/sqm IV for d1-5 in week 1 and 5 of radiotherapy
Outcomes	Median survival.
Notes	Study accrual slower than expected and trial closed when more than 70 deaths had been observed.
Allocation concealment	B – Unclear

Study	**Frey 1981**
Methods	Randomised controlled trial, multicentre Veterans' Hospital study. Recruitment period: January 1973- May 1977. Planned recruitment: 190.
Participants	Inclusion criteria: histologically-proven non-resectable carcinoma of pancreas; drug therapy able to commence between 10 to 60 d postoperatively. Number randomised: 152 (A: 87, B 65). Histologically confirmed adenocarcinoma: 148 (A:84, B:64). Liver metastases: A 44.8%, B 47.7%. All male. Disease extent (locally advanced:metastatic): A10:12, B 14:11.
Interventions	A. Best supportive care. B. 5FU 9mg/kg IVI for d1-5+CCNU 70 mg/sqm for d1 q 6 weekly indefinitely in absence of toxicity.
Outcomes	Median survival.
Notes	Randomisation by numbered envelopes. All had undergone initial laparotomies. 20% required reoperation. Several patients required palliative radiotherapy (number not stated). Bypass surgery control 86.2% and chemotherapy 74.5%. Survivals at 6 and 12 months obtained from survival curve.
Allocation concealment	A – Adequate

Study	**GITSG 1985b**
Methods	Randomised controlled trial, multicentred government funded study.

Characteristics of included studies (*Continued*)

	Recruitment period not stated.
Participants	Inclusion criteria: histologically proven exocrine pancreatic adenocarcinoma; surgically staged with confirmation of locally-unresectable pancreatic adenocarcinoma; pancreas and area of known malignant disease encompassable in a 400 sqcm anterior-posterior field. Exclusion criteria: islet cell, cystadenocarcinoma, carcinoid, ampullary, duodenal cancer; distant metastases; prior chemotherapy or radiotherapy; prior malignancy within 3 years; ECOG performance score 3 or 4; coexisting infection; history of active heart disease; WCC<400; platelet<150; Hb <10; bilirubin >3mg/dL. Total patients enrolled:157 Ten patients ineligible. Patients analysed 143 (A: 73, B: 78). Median age: A: 62 y, B: 62 y. M:F ratio: A: 44:29, B: 41:29. Surgical bypass: A: 48 B: 49.
Interventions	A. Radiotherapy 6000 rad (200 rad/d for 5 d for 2 weeks) x 3 split course with 2 week break+ 5FU 500mg/sqm for d1-3 with each course of radiotherapy then weekly 5FU 500 mg/sqm until tumour progression. B. Radiotherapy 4000 rad (200 r/day for 5 days for 2 weeks) x 2 split course with 2 week break+adriamycin IV 15 mg/sqm for d1, 12mg/sqm weekly for minimum 5 doses, 60 mg/sqm three weekly for 3 doses, 60 mg/sqm 4 weekly for 5 doses then 5FU 500 mg/sqm IV weekly for 2 years
Outcomes	Median survival.
Notes	
Allocation concealment	A – Adequate

Study	**GITSG 1988**
Methods	Randomised trial, multicentred study funded by a government grant. Recruitment period: August 1983-October 1985. Planned accrual: 152.
Participants	Inclusion criteria: surgically-staged pathologically-confirmed adenocarcinoma of the pancreas; locally unresectable cancer confined to pancreas and contiguous organs; nodes or peritoneum overlying the pancreas; oral intake >1500 calories/day for 3 days; ambulant for more than half the day; free of infection; white cell count >4000; platelets >150; HB>10 and bilirubin <3 mg/dL; creatinine clearance >70 ml/min. Total enrolled 48 (A: 24, B: 24). Number of patients eligible: 43 (A:22, B:21). Median age: A: 61 y B: 60 y. M/F ratio: A:14:8 B:13:8. Biliary bypass A: 13, B: 15.
Interventions	A. SMF chemotherapy (5FU 600mg/sqm IV on day 1,8,29,26; streptozotocin 1/g/sqm every 8 weeks, mitomycin 10 mg/sqm IV every 8 weeks) for 2 years or until progression. B. Radiotherapy (5400 rad (180 rad x 5 days every week for 6 weeks) with 5FU 350 mg/sqm IV daily on first last 3 d of radiotherapy,followed by SMF chemotherapy beginning on day 64 every 8 weeks for 2 years or until progression.
Outcomes	Median survival. Survival at 6, 12, 18 and 24 months.
Notes	Stratified by performance status and presence of surgical clips. Study terminated early due to lack of funding.
Allocation concealment	D – Not used

Study	**Gansauge 2002**
Methods	Randomised trial, single centre study (Ulm). Gemcitabine supplied by Lilly and NSC 631570 supplied by Nowicky Pharma.

	Other funding not stated. Accrual period: August 1999-July 2001. No patients lost to followup.
Participants	Inclusion criteria: histologically-proven unresectable adenocarcinoma of pancreas. Exclusion criteria:< 18 y;pregnancy;lack of contraception, other cancer diseases; viral hepatitis B/C or HIV;immunosuppressive therapy;disease of CNS. Number randomised: 90 (A:30, B:30, C:30). Mean age: A: 63.8 y (53-79 y), B: 60.6 y (40-80 y), C: 58.2 y (22-74 y). Male:female ratio: A: 22:8, B: 16:14, C: 19:11. Locally advanced: metastatic: A: 1:29, B: 0:30, C: 1:29.
Interventions	A. Gemcitabine 1000 mg/sqm IV weekly for 7 weeks then 1 week off then weekly for 3 out of 4 weeks. B. NSC 631570 (Ukrain) 20 mg IV weekly for 7 weeks followed by 1 week off and then weekly for 3 out of 4 weeks for 12 cycles. C. Gemcitabine 1000mg/sqm IV weekly +NSC 631570 20 mg IV for 7 weeks then one week off followed by weekly for 3 out of 4 weeks for 12 cycles. NSC 631570 given for d1-5 in the first week in arms B and C.
Outcomes	Response rate. Survival at 6, 9 and 12 months. Median survival. Tumour marker response. QOL (EORTC QLC C30).
Notes	Most patients received supplementary vitamins, especially vitamin C.
Allocation concealment	B – Unclear

Study	**Glimelius 1996**
Methods	Randomised controlled trial, multicentred study. Recruitment period: January 1991 to February 1995 Planned recruitment: at least 60 patients.
Participants	Inclusion criteria: pancreatic and biliary adenocarcinoma with histological or cytological confirmation; non curable by surgery; less than 76 years of age. Exclusion criteria: creatinine >125, bilirubin>60 and KPS <50. Total enrolled: 90 , 53 pancreatic (A: 24, B: 29). No patients lost to follow up.
Interventions	A. Best supportive care. B. FLv (5FU bolus 500 mg/sqm IV+leucovorin 60 mg/sqm on d1, and d2 every fortnight) if > 60 years old with KPS<70. or FELv (5FU bolus 500mg/sqm+leucovorin 60 mg/sqm+etoposide 120 mg/sqm on d1-d3 three weekly) otherwise. Treatment until tumour progression or discontinuation if stable disease for 4 months or treatment to 6 months if no symptoms at randomisation.
Outcomes	Median survival. QOL (EORTC QLQ C30 scale). Average quality adjusted survival.
Notes	Radiation therapy allowed in both arms of trial. 1-year survival obtained by personal communication wiht author. Survival curve for combined biliary and pancreatic patients in paper. Survival figures for pancreas subgroup obtained by personal communication with first author.
Allocation concealment	A – Adequate

Characteristics of included studies (*Continued*)

Study	**Hazel 1981**
Methods	Randomised trial, single centre study. Source of funding not stated.
Participants	Inclusion criteria: biopsy proven adenocarcinoma of the pancreas; advanced disease; "non curative surgery" undertaken. Total number randomised: (pancreas only): 30 (A: 15; B 15). Mean age: 62 y. M:F ratio: 2.4:1.
Interventions	A. Chemotherapy 5FU 500mg/sqm IV weekly+ methyl CCNU PO 100mg/sqm 6 weekly for 2 years or until disease progression. B. Radiotherapy (4600 rad over 4.5 weeks) with weekly 5FU 500mg/sqm IV and methyl CCNU 100mg/sqm added 6 weekly after completion of radiotherapy for 2 y or until disease progression.
Outcomes	Median survival. 2-year survival.
Notes	Gastric and pancreas patients enrolled. Data available separately for pancreatic cancer.
Allocation concealment	B – Unclear

Study	**Heinemann 2003**
Methods	Randomised study, multicentre study (34 centres). Recruitment period: December 1997-January 2002. Funding not stated.
Participants	Inclusion criteria: histologically confirmed advanced pancreatic carcinoma. Number randomised: 198 (A: 100, B:98). Median age: A: 66 (43-85) B:64 (37-82). Locally-advanced: A: 20.9% B: 19.7%. Metastatic: 79.2% B: 80.2%.
Interventions	A. Gemcitabine 1000mg/sqm on d1,8,15 IV of 28 day cycle B. Gemcitabine 1000mg/sqm + cisplatin 50 mg/sqm on d1,d15 IV of 28 day cycle
Outcomes	Median survival Time to progression Tumour response Toxicity QOL
Notes	Three patients lost to follow up in each arm. Second-line chemotherapy used in 16.5% of arm A and 15.8% of arm B Non-adenocarcinoma histology in 7.1% of arm A and 3.2% of arm B
Allocation concealment	A – Adequate

Study	**Herrmann 2005**
Methods	Randomised study, multicentred study (8 countries (Europe and Isreal) 30 centres). Recruitment period: June 2001-June 2004. Planned recruitment: not stated.
Participants	Inclusion criteria: histological proof of primary inoperable pancreatic adenocarcinoma; KPS>60;adequate organ function; no prior chemotherapy; adjuvant 5FU/radiotherapy allowed if more than 2 months prior. Number randomised: 319 (A: 159, B: 160). Median age: A: 62 y (36-84 y), B: 62 y (27-83 y). M: F: ratio: A: 53:47, B: 54:46. Locally-advanced:metastatic:A 21:79, B: 20:80.

Characteristics of included studies (*Continued*)

Interventions	A. Gemcitabine 1000 mg/sqm IV weekly for 7 weeks then 1 week off and weekly for 3 out of 4 weeks. B. Gemcitabine 1000 mg/sqm IV for d1,d8+ capecitabine 650 mg/sqm PO bd for d1-14 every 3 weeks.
Outcomes	Median survival. Response rate. Progression free survival. Clinical benefit response.
Notes	Patients stratified on basis of KPS, disease extent and presence or absence of pain.
Allocation concealment	A – Adequate

Study	**Horton 1981**
Methods	Randomised controlled trial.multicentred study (31 institutions), government-funded. Recruitment period not stated.
Participants	Inclusion criteria: histologically proven carcinoma of the pancreas; residual recurrent or metastatic disease. Exclusion criteria: major surgery within 2 weeks; exploratory procedures within 2 weeks; prior chemotherapy or radiotherapy within the previous month; prior VP-16-213 or melphalan chemotherapy; active infectious disease process; severe malnutrition; leucopenia >4500; thrombocytopenia <150; evidence of renal or liver function impairment. Total enrolled: 140 (chemonaive). Dropouts: 15 patients cancelled or not eligible. Number of eligible randomised: 127 (A:43, B:41, C:43).
Interventions	A. Melphalan 6mg/sqm PO for d1-5 every 6 weeks. B. 5FU 350 mg/sqm IV d1-5, 5FU 400mg/sqm IV d36-40, Me CCNU 150 mg/sqm/day PO d1 every 10 weeks. C. 5FU 350 mg/sqm IV d1-5, 5FU 400mg/sqm IV d 36-40, MeCCNU 150 mg/sqm PO d1, streptozocin 400 mg/sqm D1-5 IVI every 10 weeks.. Treatment crossover of arm A to arm B on progression. Salvage treatment of arms B and C to VP-16-213 on progression.
Outcomes	Median survival.
Notes	
Allocation concealment	B – Unclear

Study	**Huguier 2001**
Methods	Randomised controlled trial, multicentre study (8 sites in France). Funding source not stated. Recruitment period: June 1992-December 1996. Planned enrollment: 120.
Participants	Inclusion criteria: histologically proven pancreatic adenocarcinoma not resectable for cure. Exclusion criteria: other histology: neuroendocrine, mucinous, cholangiocarcinoma, ampullary; active heart disease; abnormal creatinine clearance; WHO PS >2; prior chemotherapy or radiation therapy. Number randomised: 45 (A:23; B:22). Mean age: A: 62.2 y (36-77y), B: 64.7 y (67-75 y). M:F: A: 6:17, B: 18:4. Locally-advanced:metastatic: A: 13:10, B:11:11.
Interventions	A: Best supportive care. B. Leucovorin 200 mg/day IV+ 5FU 365 mg/sqm/day+cisplatin 15 mg/sqm/day for d1-5 q 21 days.
Outcomes	Median survival.
Notes	2 patients in arm B did not receive chemotherapy but were included in intention to treat analysis. Unplanned interim safety analysis. Study ceased early as suggested that endpoints could not be reached.

	Overall survivals estimated from survival curves.
Allocation concealment	A – Adequate

Study	**Kelsen 1991**
Methods	Randomised trial, multicentre government funded. Planned enrolment: 80. Recruitment period: September 1987-November 1989.
Participants	Histologically confirmed adenocarcinoma of the pancreas Inclusion: KPS>60%; life expectancy >8 weeks; no symptomatic or labile cardiac disease; WCC>3.5; platelets >150; bilirubin <2.0; normal auditory function; adequate renal function Exclusion: Prior chemotherapy or external beam radiotherapy Number enrolled: 82 (A: 42, B: 40) Median age: A: 58 (32-74), B: 60 (28-74) Male: Female ratio: A: (26:16), B(26:14) Locally advanced /metastatic: A 17/25. B: 14/26
Interventions	A. SMF chemotherapy (streptozotocin 1g/sqm for d1,8,29,36, mitomycin C 10 mg/sqm for d1, 5FU 600 mg/sqm for d1,8,29,36) every 8 weeks. B. CAC chemotherapy (cisplatin 100mg/sqm d1, Ara C 2g/sqm 2 doses 12 hours apart on d1, caffeine 400 mg/sqm 2 doses at end of each Ara C) every 4 weeks for 3 cycles then 6 weekly in responding patients.
Outcomes	Median survival. Response rate. Time to progression.
Notes	Anticipated non-prespecified safety analysis after 45 patients. Study ceased early as suggested that endpoints could not be reached.
Allocation concealment	B – Unclear

Study	**Klaassen 1985**
Methods	Randomised trial, multicentred government funded. Enrollment period: 1974- not stated. 11 patients lost to follow up.
Participants	Inclusion criteria: histologically confirmed; non-resectable; less than 75 years; no simultaneous; heterochromic multiple or recurrent carcinoma; performance status 0-3; no severe complications; white cell count >4000; platelets >100; GPT<100 and urinary protein negative. Total enrolled (pancreatic): 52 (A: 24 B: 28) Mean age: A: 61.5 (43-74) B: (46-74) Male/female ratio: A: 15/9 B: 22/6 Surgical treatment (laparotomy or palliative bypass): A 20, B:22 Metastatic disease; A: 24 B: 27
Interventions	A. 5FU 600 mg/sqm IV once weekly until disease progression. B. Radiotherapy (4000 rad over four weeks in 25 fractions) + 5FU 600mg/sqm d1-3 then maintenance 5FU 600mg/sqm weekly beginning on day of completion of radiotherapy continuing until disease progression.
Outcomes	Median survival Locoregional progression.
Notes	Patients stratified by grade of anaplasia and randomised within strata by permuted block design. Dynamic method of Zelen used to ensure treatment balance within institutions. Outcome data for pancreatic cancer available separately in this study.
Allocation concealment	A – Adequate

Characteristics of included studies (*Continued*)

Study	**Kovach 1974**
Methods	Randomised trial, multicentred study, government funded.
Participants	Inclusion criteria: histologically proven unresectable adenocarcinoma of the pancreas and stomach; measurable disease; ambulatory outpatients; reasonable nutritional status. Exclusion criteria: moribund state; leucopenia; thrombocytopenia; major surgery or radiotherapy within 3 d; extensive pelvic radiotherapy; previous chemotherapy with 5FU; 5-fluoro2 deoxyuridine; other chemotherapy or radiotherapy in last month. Total patients enrolled: 167. Number pancreatic cancer patients randomised: 82 (A: 31, B: 21 C: 30). Mean age: A 59.2 y, B 60.0 y, C:59.2 y. M:F ratio: A 1.4:1, B: 1.7:1, C 1.7:1.
Interventions	A: 5FU 13.5 mg/kg IV for d1-5 IV every 5 weeks. B. BCNU 50 mg/sqm for d1-5 IV every 8 weeks. C. 5FU 10mg/kg + BCNU 40 mg/sqm IV for d1-5 every 8 weeks.
Outcomes	Response. Overall survival.
Notes	Trial enrolled pancreatic and gastric cancer patients. Data for pancreatic cancer available separately. Stratification for site of origin, grade and site of primary indicator lesion 33 patients presumed to have pancreatic carcinoma on the basis of histology of metastatic lesion, negative barium exam and convincing clinical presentation. At interim analysis after 130 patients BCNU found to have significantly worse response rate so enrolment continued on the two other arms only.
Allocation concealment	B – Unclear

Study	**Levi 2004**
Methods	Randomised trial, multicentred (15 European centres). Funding: EORTC trial with NCI, ARC, ARTBG. Planned accrual not stated.
Participants	Inclusion criteria: histologically-proven locally advanced or metastatic cancer of the pancreas. Number randomised: 107 (A: 55, B:52). Chronotherapy: constant rate: 54:53. Median age: 63 y. Locally-advanced:metastatic: 25:82.
Interventions	2 by 2 factorial design. A. 5 FU constant rate or chronomodulated IV infusion,over 5 days every 3 weeks cycle 1 5g/sqm, cycle 2 6g/sqm, cycle 3 6.5g/sqm. B. 5 FU constant rate or chronomodulated IV infusion cycle 1 5g/sqm, cycle 2 6g/sqm, cycle 3 6.5g/sqm + cisplatin 100mg/sqm IV day 1
Outcomes	Progression free survival. Median overall survival. Toxicity.
Notes	Chronomodulation infusion: 5FU 10pm-10am, peak at 4am, cisplatin 10am-10pm peak at 4pm. Escalation of 5FU dose on successive cycles.
Allocation concealment	A – Adequate

Study	**Li 2003**
Methods	Randomised trial; single centre study (Taiwan), government funded. Planned accrual: 34 patients.

	Recruitment period: January 1998- December 2001. .
Participants	Inclusion criteria: histologically proven locally advanced pancreatic carcinoma; AJCC Stage IVA; Karnofsky performance status >50; neutrophil count >1500; platelets >100; AST/ALT < 5 x upper limit of normal; no prior chemotherapy or radiotherapy; no other malignancy; no serious medical or psychological problems that would prevent informed consent. Total patients enrolled: 34 (A: 16, B:18). Median age: A: 69 (range 31-77) B: 68.5 (range 45-83). M:F ratio: A 12:4 B 13:5. No patients had surgery. No patients lost to follow-up.
Interventions	A. Radiotherapy (50.4- 61.2 Gy in 1.8 Gy fractions) + 5FU 500mg/sqm IV over 30 min for d1-3 fortnightly x3 concurrent with radiotherapy. B. Radiotherapy (50.4-61.2 Gy in 1.8 Gy fractions)+ Gemcitabine 600 mg/sqm IV weekly x6 over 30 min concurrent with radiotherapy. All patients then received maintenance gemcitabine 1000 mg/sqm IV weekly for 3 out of 4 weeks indefinitely after chemoradiotherapy.
Outcomes	Median survival. 1 and 2-year survival. Time to progression. Time to local progression. Time to metastasis. Response rate. Quality of survival. Quality adjusted life months.
Notes	This study employed 3D conformal radiotherapy.
Allocation concealment	B – Unclear

Study	**Li 2004**
Methods	Randomised controlled trial, single centre study (Taiwan). Funding source not stated. Recruitment period: Jan 1998-June 2002.
Participants	Inclusion criteria: metastatic pancreatic carcinoma; KPS>50. Total patients enrolled: 46 (A: 25, B:21). Mean age: A: 66 y, B: 69 y. M:F ratio: A: 17:8, B: 19:2.
Interventions	A: Gemcitabine 1000 mg/sqm IV weekly for 3 out of 4 weeks. B: Gemcitabine 1000 mg/sqm IV +cisplatin 25 mg/sqm IV weekly for 3 out of 4 weeks.
Outcomes	Median survival. Survival at 6, 12 and 24 months. Time to progression. Clinical benefit. Response rate. Quality adjusted life months.
Notes	Survivals read off Kaplan Meier survival curves.
Allocation concealment	B – Unclear

Study	**Louvet 2005**
Methods	Randomised study,multicentre (France and Italy).

Characteristics of included studies (*Continued*)

	Pharmaceutical company sponsorship (Sanofi-Synthelabo). Enrolment period: March 2001-February 2003. Planned recruitment: 300.
Participants	Inclusion criteria: pathologically proven adenocarcinoma of the pancreas; locally advanced or metastatic; measurable disease; no prior radiation or chemotherapy; WHO performance status 0-2; adequate biological parameters; pain and jaundice controlled; written informed consent. Number enrolled: 326. Number randomised: 313 (A: 156,B:157). Mean age: A :60.1 y (22-75 y). B: 61.3 (35-77 y). M:F ratio: A: 53:47, B: 60:40. Locally advanced:metastatic: A 30:70, B: 32:68.
Interventions	A: Gemcitabine 1 g/sqm IV weekly for 7 weeks, 1 week break then 3 out of 4 weeks. B. GEMOX (Gemcitabine 1 g/sqm IV d1+ oxaliplatin 100 mg/sqm d2 every 2 weeks) Gemcitabine in arm A was administered over 30 minutes and in arm B as a 100 minute fixed dose rate infusion.
Outcomes	Survival Progression free survival. Response rate. Clinical benefit. Tolerability. QOL.
Notes	Stratification on centre, performance status and disease extent. 13 patients ineligible, 2 neuroendocrine, 8 high bilirubin level, 2 died before randomisation, 1 withdrawal of consent. Second-line chemotherapy received by 53.4% in A and 52.3% in B. Chemoradiation recommended in both arms in locally-advanced disease after 3 months if stable disease or response but left to investigator discretion. Chemoradiation received by 11/33 in arm A and 16/40 in arm B.
Allocation concealment	A – Adequate

Study	**Maisey 2002**
Methods	Randomised controlled trial, unfunded Multicentred (5 sites). Enrolment period: July 1994-October 2000. Planned recruitment: 208.
Participants	Inclusion criteria:histologically confirmed locally advanced or metastatic pancreatic cancer; not amenable to radiotherapy or surgery; adequate marrow reserve; renal and hepatic function Exclusion criteria: intracerebral metastases; ethanol or drug abuse; prior malignancy; uncontrolled angina; psychological condition preventing informed consent. Number randomised: 209 (A 107, B:102). Median age: A: 62 (29-80), B: 61 (28-86). M:F ratio: A: 64:36, B: 61:39. Metastatic: A: 64%, B: 56%
Interventions	A: Epirubicin 100 mg/sqm IV every 28 days until progression B: FEM (5FU 600 mg/sqm (max 1g), epirubicin 50 mg/sqm, mitomycin 6mg/sqm (max 10mg)) IV every 28 days until progression
Outcomes	Median survival. Response rate. Toxicity.

	QOL (EORTC QLQ C30).
Notes	Second-line chemotherapy given in 43 patients (A: 20 and B: 23) Crossover in A: 13, and B: 5.
Allocation concealment	A – Adequate

Study	**Mallinson 1980**
Methods	Randomised controlled trial,multicentred study. Accrual commenced 1975. Funding not stated. Planned recruitment not stated.
Participants	Inclusion criteria: unresectable pancreas cancer diagnosed at laparotomy; age between 35 and 75 y. Exclusion criteria: unable to attend outpatients department regularly; unrelievable gastrointestinal obstruction; reduced renal function; WCC <3.5, platelets<80; prior radiotherapy or chemotherapy. Total enrolled: 40 (A: 19, B: 21). Histology confirmed: A: 11, B: 7. Median age: A: 66.9 y, B: 63.4 y. M:F ratio: A: 10:9, B: 12:9. Disease extent: locally-advanced: metastatic A: 11:8, B: 14:7.
Interventions	A. Best supportive care. B. Cyclophosphamide 300 mg for d1 and d5 (4.5mg/kg if weight <60kg or >80 kg)+5FU 500mg d1-5 (7.5 mg/kg if weight <60 kg or >80kg)+ vincristine 1mg for d2 and d5 (0.02 mg/kg if weight <60kg or >80kg)+ methotrexate 20 mg for d1 and d4 (0.3 mg/kg if weight <60kg or >80kg) induction then 5FU 10mg/kg d1-d5+mitomycin C 100 ug/kg d1-d5 a month post induction and q6 weekly until death or for 2 y.
Outcomes	Median survival.
Notes	All patients had laparotomy. Method of randomisation not assessable. Survival obtained from survival curves that included histologically confirmed and unconfirmed patients.. Statement in manuscript that "relatives and family doctors of the patients were informed of the diagnosis but the patients themselves were not necessarily aware of the finding of a malignant tumour". This would suggest that informed consent was not always obtained.
Allocation concealment	B – Unclear

Study	**Moertel 1969**
Methods	Randomised double blind controlled trial, single institution. Recruitment period not stated.
Participants	Inclusion criteria: histologically confirmed locally-advanced adenocarcinoma of the stomach, pancreas or bowel. Total enrolled (pancreatic only): 64 (A:32, B:32).
Interventions	A. Radiotherapy (3500-4000 rad 6 d per week, 900-1200 rad /week) + saline. B. Radiotherapy (3500-4000 rad 6 d per week, 900-1200 rad /week) + 5FU (Divided doses on first 3 days of radiation with 45 mg/kg total dose).
Outcomes	Mean survival.
Notes	Randomisation stratified on basis of primary site and histologic grade. Ideal or actual body weight was used whichever was less. Survival curves available for pancreatic patients. This trial is likely to be an expanded and update of the series reported by Childs 1965
Allocation concealment	B – Unclear

Characteristics of included studies (*Continued*)

Study	**Moertel 1981**
Methods	Randomised controlled trial, multicentre study (7 centres). Government funded. Recruitment period: January 1974- not stated. No patients lost to follow up.
Participants	Inclusion criteria: locally-unresectable histologically confirmed adenocarcinoma of the pancreas; tumour confined to pancreas; regional lymph nodes; regional lymph nodes and regional peritoneum or peripancreatic organs provided entire area of involvement could be encompassed within a 400 sq cm area. Exclusion criteria: Coexistent malignant disease; prior radiotherapy or chemotherapy; islet cell carcinoma or cystadenocarcinoma. Total enrolled: 227. Number completing trial 194 (14 cancelled due to disease complications or rapid deterioration, 19 ineligible). Number in each group: A: 25 B: 86 C:83. Median age: A: 54, B 60, C:61. Patients undergoing biliary bypass: A 32%, B 44%, C 34%.
Interventions	A. Radiation therapy alone (6000 rads) split course B. Radiation therapy (6000 rads) split course+ 5FU chemotherapy (500mg/sqm/day IV) for first 3 d of each course+ weekly maintenance 5FU (500mg/sqm/week IV) indefinitely C. Radiation therapy (4000 rads) split course+ 5FU chemotherapy (500 mg/sqm/day IV) for first 3 d of each course+ weekly maintenance 5FU (500mg/sqm/week IV) indefinitely
Outcomes	Median survival. Time to progression.
Notes	Split course treatment consisted of 2000 rad courses given over 2 weeks with a 2 week break in between. Enrolment into radiation alone arm terminated after 106 patients enrolled as preliminary analysis indicated a significantly inferior survival compared to combined-modality therapy. Stratification of assigned treatment by research institution.
Allocation concealment	B – Unclear

Study	**O'Reilly 2004**
Methods	Randomised trial,multicentred study, sponsored by pharmaceutical company (Daiichi). Recruitment period: August 2001-January 2003. Planned recruitment: 340 patients.
Participants	Inclusion criteria:histological or cytological proof of locally-advanced or metastatic pancreatic cancer; KPS>60; no prior chemotherapy; prior radiation therapy allowed for locally advanced disease; good major organ function. Patients randomised: 349 (A: 174, B: 175). Median age:A. 62 y (30-84 y) B: 64 y (36-85y). M:F ratio: A: 57:43 B: 53:47. Locally advanced: metastatic: A: 22:78 B: 21:79.
Interventions	A. Gemcitabine 1g/sqm IV weekly for 7 weeks, one week break then weekly for 3 out of 4 weeks. B. Exatecan mesylate (DX-8951f) 2.0 mg/sqm IV+gemcitabine 1g/sqm IV for d1,d8 every 3 weeks
Outcomes	Median survival. 1 year survival. Time to progression. Time to marker progression. Tumour response. Toxicity. Clinical benefit response.
Notes	Patients stratified according to KPS, disease stage and prior radiation therapy.

	Intent to treat analysis. 27 patients randomised but did not receive treatment (A: 17, B: 7). Reasons for no treatment: patient request (A: 10, B:3), progressive disease (A: 3, B:1), non compliance (A: 1,B: 1) and other (A:3,B:2).
Allocation concealment	A – Adequate

Study	**Oettle 2005b**
Methods	Randomised study, multicentred (USA and Europe). Pharmaceutical company sponsored (Eli Lilly). Planned recruitment: 520. Recruitment period: not stated.
Participants	Inclusion criteria: histologically or cytologically confirmed adenocarcinoma of the pancreas; locally advanced or metastatic; ECOG 0-2; measurable disease; no prior chemotherapy; adequate haematological; renal and liver function; informed consent. Number randomised: 565 (A: 282, B: 283). Number completing trial: 546. Median age: A: 63 y (28-82 y), B: 63 (27-82 y). M:F ratio: A: 54:47, B: 60:40. Losses to follow-up: A:9, B: 10.
Interventions	A. Gemcitabine 1g/sqm IV d1,d8,d15 every 4 weeks. B. Gemcitabine 1.25 g/sqm Iv d1,d8+ pemetrexed 500 mg/sqm IV d8 every 3 weeks.
Outcomes	Median survival. Median progression free survival. Overall survival at 12 months. Median time to progression. Response rate. Duration of response. QOL (EORTC QLQ C30).
Notes	Patients receiving pemetrexed received vitamin B12 and folic acid supplementation. Patients stratified for performance status, disease stage, centre and baseline homocysteine level. 3 treatment deaths reported in the combination therapy arm.
Allocation concealment	A – Adequate

Study	**Ohkawa 2004**
Methods	Randomised trial, two centred study (Japan). Funding source not stated. Recruitment period: July 2001-March 2003. Planned recruitment not stated.
Participants	Inclusion criteria locally-advanced or metastatic pancreatic cancer; no pretreatment (radiotherapy or chemotherapy); KPS 50-100; <75 years old. Number randomised: 19 (A: 9, B:10) M:F ratio: A. 7:2, B: 7:3. Median age: A: 58 y.4, B: 60.5 y. Locally-advanced:metastatic: A 2:7, B: 3:7.
Interventions	A. Gemcitabine 1g/sqm IV for d1,d8,d15 every 4 weeks. B. Gemcitabine 1g/ sqm IV for d1,d8,d15 +UFT 300 mg/day PO continuous every 4 weeks.
Outcomes	Mean survival. Response rate. Time to progression. Clinical benefit response.

	Toxicity.
Notes	Study stopped early due to inferiority of combination arm with respect to time to progression.
Allocation concealment	B – Unclear

Study	**Oster 1986**
Methods	Randomised trial,single centred, government-funded. Recruitment period: August 1979-November 1981 12 patients ineligible or not evaluable.
Participants	Inclusion criteria: histologically confirmed adenocarcinoma of the pancreas;not suitable for surgery and/or radiotherapy; no prior chemotherapy. Total number enrolled: 196. Number evaluable: 184 (A: 94 B:90). M:F ratio: A: 61:39, B: 52:48. Bypass surgery: A: 41%, B: 39%.
Interventions	A. FSM chemotherapy (fluorouracil 600 mg/sqm for d1,8,29,36, streptomycin 1g/sqm for d1,8,29,36, mitomycin C 10mg/sqm d1) every 8 weeks until progression or relapse. B. FAM chemotherapy (fluorouracil 600mg/sqm for d1,8,29,36), Adriamycin 30 mg/sqm for d1,29, mitomycin C 10 mg/sqm d1) every 8 weeks until progression or relapse.
Outcomes	Median survival. Response rate.
Notes	Stratified by measurable versus non-measurable disease. Adriamycin discontinued after a total dose of 480 mg/sqm.
Allocation concealment	B – Unclear

Study	**Palmer 1994**
Methods	Randomised controlled trial, two-centred study. Recruitment period: April 1989-September 1991. Planned recruitment: not stated.
Participants	Irresectable advanced pancreatic cancer Exclusion: Previous malignancy;significant renal or cardiovascular disease; thrombocytopenia or leucopenia; gross psychiatric disease; WHO PS>3 . Patients randomised: 43 (Control 20,Treatment 23) Median age: Control 62 (range 41-81) and Treatment 61 (45-76). M:F ratio: A: 15:5 B: 16:7. 31 patients had histological confirmation.
Interventions	A. Best supportive care. B. 5FU 600mg/sqm IV d1 and 29, oral 5FU d8 and 36, adriamycin 30mg/sqm d1 and 29. Mitomycin 10mg/sqm d1 and 29 on an 8 week cycle until disease progression or unacceptable toxicity.
Outcomes	Median survival. 1 year survival. Quality of survival.
Notes	Survivals at 6 and 12 months obtained from survival curve. Randomised using permuted block technique. Author contacted: no separate survival figures for patients with histological diagnosis.
Allocation concealment	A – Adequate

Study	**Reni 2005**
Methods	Randomised controlled trial, multicentred (5 centres Italy)

Characteristics of included studies (*Continued*)

	Unfunded study. Recruitment period: April 2000-March 2003. Planned recruitment: 100.
Participants	Inclusion criteria: Stage IVa or IV b adenocarcinoma of the pancreas confirmed histologically; measurable disease; age18-70 years; KPS >40; adequate bone marrow; renal and hepatic function; no prior radiotherapy or chemotherapy. Number randomised: 104. Number treated: 99 (M:F: 48:51). Median age: A: 59 y (25-69 y) B: 62 y (37-69 y). M:F ratio: A: 24:23, B: 24:28. Locally advanced: metastatic A: 30%: 70%, B:29%: 71%.
Interventions	A: Gemcitabine 1g/sqm weekly for 7 weeks then 1 week off and weekly for 3 out of 4 weeks until progression. B:PEFG (Cisplatin 40 mg/sqm IV d1+epirubicin 40mg/sqm IV for d1+5FU continuous infusion 200 mg/sqm/day+ gemcitabine 600 mg/sqm IV for d1, d8 every 28 days).
Outcomes	4 month progression free survival. Response rate. Clinical benefit. QOL (EORTC QLQ C30 and PAN26). Overall survival.
Notes	Five patients not eligible (A:3, B:2). Reasons: 4 had liver dysfunction and 1 had biliary tract cancer. Crossover from gemcitabine to PEFG was allowed in protocol after disease progression.
Allocation concealment	A – Adequate

Study	**Riess 2005**
Methods	Randomised study, multicentred (98 centres). Funding: German Cancer Society and Eli Lilly. Recruitment period: August 2000-November 2003. Planned recruitment: 472.
Participants	Inclusion criteria: histological or cytological proven locally advanced or metastatic pancreatic cancer; measurable disease; KPS 60% or better; no prior chemotherapy or radiation therapy; adequate haematological, renal and hepatic function; written and informed consent. Number randomised: 473. Number eligible: 466 (A: 230, B: 236). Mean age: A: 63.7 y, B: 62.7 y. Locally advanced:metastatic: A: 23:77 B: 23:77.
Interventions	A. Gemcitabine 1g/sqm weekly for 7 weeks then one week off and weekly for three weeks out of four until progression. B. Gemcitabine 1000 mg/sqm +5FU 750 mg/sqm continuous infusion over 24 h+folinic acid 200 mg/sqm fir d1,d8,d15,d22 every 6 weeks until progression.
Outcomes	Median survival. 1 year survival. Time to progression Overall response rate. Toxicity. QOL.
Notes	Seven patients ineligible (3 had other tumours, 2 were resectable, 1 had concomitant methotrexate and 1 was without histological diagnosis). Secondline chemotherapy given in 37.4% of arm A and 32.8% of arm B. A variety of different salvage regimens were used but notably 21% of arm B received paclitaxel compared to none in arm A.

Characteristics of included studies (*Continued*)

Allocation concealment	A – Adequate

Study	**Rocha Lima 2004**
Methods	Randomised trial, multicentred (USA, Canada, NZ, Australia). Pharmaceutical company funded (Pfizer). Recruitment period: February 2000-December 2001. Planned recruitment: 350.
Participants	Inclusion criteria: histologically or cytologically confirmed locally advanced or metastatic pancreatic carcinoma; measurable disease; ECOG 0-2; no prior systemic chemotherapy except 5FU as a radiosensitizer; adequate haematogical; renal and hepatic function. Total enrolled: 360. Treated patients: 342 (A: 173, B: 169). Median age: A: 60 (32-83) B 63(39-81). M:F ratio: A: 57:43, B: 58:42. Locally advanced:metastatic: A: 14%: 86%, B: 16%:84%.
Interventions	A: Gemcitabine 1000mg/sqm IV weekly for 7 weeks then one week break and weekly for 3 out of 4 weeks. B: Gemcitabine 1000mg/sqm IV followed by irinotecan 100 mg/sqm IV on d1 and d8 every 21 days.
Outcomes	Tumour response. Median survival. 1 year survival. Time to progression. QOL.
Notes	18 patients randomised but not treated. (A:11, B:7) Reasons withdrawal of consent 10, protocol violation 4, disease progression 3, adverse event 1. Second-line therapy given in 46% of A and 39% of B.
Allocation concealment	A – Adequate

Study	**Scheithauer 2003**
Methods	Randomised controlled trial, multicentred (4 Austrian sites). Government funded. Recruitment period: June 1999-May 2001. Planned recruitment: 41.
Participants	Inclusion criteria: histologically or cytologically ascertained metastatic adenocarcinoma of the exocrine pancreas;bidimensionally measurable; age 19-75; life expectancy > 3 months; KPS >50; informed consent. Exclusion criteria: operable patients or locally-advanced disease; serious medical illness; CNS metastases. Number randomised: 83 (A: 42,B:41). Median age: A 66 y (39-75 y), B: 64 y (40-75 y). M:F ratio: A:55:45, B: 27:14. Prior palliative surgery: A 26%, B: 12%. All patients had metastatic disease.
Interventions	A: Gemcitabine 2200 mg/sqm IV over 30 minutes d1 fortnightly. B. Gemcitabine 2200 mg/sqm IV over 30 minutes fortnightly d1+ capecitabine 1250 mg/sqm PO bd for d1-7 fortnightly.
Outcomes	Response rate. Median duration of response. Median progression-free survival. Median survival. Clinical benefit response. Toxicity.

Characteristics of included studies (*Continued*)

Notes	7 patients ineligible (3 had other tumours, 2 were resectable, 1 had concomitant methotrexate and one without histological diagnosis) Second-line chemotherapy given in 37.4% of arm A and 32.8% of arm B. A variety of difference salvage regimens were used but notably 21% of arm B received paclitaxel compared to none in arm A.
Allocation concealment	A – Adequate

Study	**Shinchi 2002**
Methods	Randomised controlled trial. Single-site study. Recruitment period: January 1997-June 2000. Planned recruitment not stated.
Participants	Inclusion criteria: histologically or cytologically confirmed pancreatic adenocarcinoma; locally advanced disease at laparotomy or inoperable on CT scan; adequate biliary drainage; Karnofsky score >60; normal renal function. Total enrolled: 31 (A:15, B: 16). Mean age: A: 64.6 y, 62.0 y. M:F ratio: A. 68:32, B: 63: 37 Obstructive jaundice in 15 patients treated with biliary bypass (9)and endoprosthesis (6). No patients lost to follow up.
Interventions	A. Best supportive care. B. Radiotherapy (50.8 Gy 1.8Gy daily 5 days a week)+ 5FU continuous infusion 200 mg/sqm/day during radiation therapy then maintenance weekly 5FU 500 mg/sqm IVI until progression or toxicity.
Outcomes	Median survival One year survival Quality of survival.
Notes	4-field radiotherapy technique. Best supportive care patients did not receive any chemotherapy or radiotherapy.
Allocation concealment	B – Unclear

Study	**Stathopoulos 2005**
Methods	Randomised trial. Funding source not stated. Recruitment period not stated. Planned recruitment not stated.
Participants	Inclusion criteria: chemotherapy naive patients with histologically or cytologically confirmed pancreatic cancer and documented extrapancreatic disease. Number randomised: 92 (A: 50, B: 42). Patients balanced in respect of age, gender,stage, performance status and organ involvement.
Interventions	A. Gemcitabine 1000 mg/sqm IV for d1,d8,d15 every 4 weeks. B. Gemcitabine 1000 mg/sqm IV d1,d8+ irinotecan 300 mg/sqm on d8 every 3 weeks.
Outcomes	Objective response rate. Median time to progression. 1-year survival.
Notes	G-CSF support was given in the study.
Allocation concealment	B – Unclear

Study	**Takada 1998**
Methods	Randomised controlled trial, multicentre (32 centres).

Characteristics of included studies (*Continued*)

	Recruitment period: August 1981-July 1991.
Participants	Inclusion criteria: histologically confirmed; non-resectable, < 75 y; no simultaneous, heterochromic multiple or recurrent carcinoma; performance status 0-3 (Japanese Cancer Therapy Efficacy Evaluation Criteria); no severe complications; white cell count >4000; platelets >100; GPT<100 and urinary protein negative. Total enrolled (pancreatic): 52 (A: 24 B: 28). Mean age: A: 61.5 y (43-74 y), B: 62.8 y (46-74 y). M:F ratio: A: 15:9, B: 22:6. Surgical treatment (laparotomy or palliative bypass): A 20, B:22. Metastatic disease: A: 24, B: 27.
Interventions	A. Best supportive care B. Modified FAM (5FU 200 mg/sqm+doxorubicin 15mg/sqm)+mitomycin C 5mg/sqm) IV on day of surgery 4-weekly until severe adverse reaction or disease progression.
Outcomes	Median survival. Response rate. Clinical effects (performance status improvement, body weight improvement).
Notes	Study enrolled patients with pancreatic, gallbladder and bile duct cancer. Data available for pancreatic subgroup. Survivals from Kaplan Meier survival curves. Envelope method of randomisation.
Allocation concealment	A – Adequate

Study	**Topham 1991**
Methods	Randomised trial, multicentred study. Funding source not stated. Planned enrolment: not stated.
Participants	Inclusion criteria: locally advanced or metastatic pancreatic carcinoma;cytological or histopathological diagnosis; no prior chemotherapy or radiotherapy. Total patients randomised: 69 (4 ineligible in arm A). Number assessable: 65(A:31, B: 34). Metastatic: A: 12, B:14.
Interventions	A. FEM chemotherapy (5FU 1 g IV d1 and 28, epirubicin 60 mg/sqm d1 and 28, mitomycin C 10mg) d1 every 8 weeks. B. Epirubicin 100 mg/sqm IV d1 4 weekly. Treatment for 3 months, if response then treatment for 4 further cycles.
Outcomes	1 year survival. Response rate. Toxicity.
Notes	Survivals obtained from intention to treat survival curve. Dropouts: A: 3 refused treatment after randomisation (A:1, B: 2). Probable final publication of Topham 1993 but unable to confirm with authors. Note slight variation in the chemotherapy doses between two publications.
Allocation concealment	B – Unclear

Study	**Topham 1993**
Methods	Randomised controlled study, multicentred trial (3 centres). Funding source not stated.

Participants	Inclusion criteria: histologically confirmed advanced local and/or metastatic adenocarcinoma of the pancreas;previously untreated with chemotherapy or radiotherapy; no concomitant psychiatric or uncontrolled cardiovascular disorders; no prior malignancy; WBC count >3.0; platelets >100 and serum creatinine <150. Total patients enrolled: 60. Number evaluable for toxicity and survival: 47 (A: 25, B: 22). Mean age: A 62 y (42-78 y), B: 64 y (39-80 y). M: F ratio: A: 15:10, B: 11:11. Liver metastases in 9 patients on each arm.
Interventions	A: Epirubicin 100 mg/sqm IV every 28 days until progression. B: FEM (5FU 600 mg/sqm (max 1g), epirubicin 50 mg/sqm, mitomycin 6mg/sqm (max 10mg)) IV every 28 days until progression.
Outcomes	Median survival. Toxicity.
Notes	Stratification on basis of presence or absence of liver metastases. Patients excluded on basis of following: 1 died prior to treatment, data for 3 not available for analysis, 3 had incorrect histology, previous chemotherapy and refusal of informed consent. Preliminary results of ongoing study. See notes from Topham 1991.
Allocation concealment	B – Unclear

Study	**Wang 2002**
Methods	Randomised controlled trial, multicentred study. Funding not stated. Recruitment period: July 2000-May 2001. Planned recruitment: not stated.
Participants	Inclusion criteria: cytologically and pathologically proven locally advanced or metastatic pancreatic carcinoma; KPS 60-80; age 18-75; adequate haematological; renal and liver function; measurable disease and controllable pain. Number randomised: 42
Interventions	A. Gemcitabine 1g/sqm/wk x 7, 1 week of rest for the first cycle then gemcitabine 1g/sqm/wk 3 out of 4 weeks for subsequent cycles. B. Gemcitabine 1g/sqm/wk x 3+cisplatin 60mg/sqm on day 15 (after gemcitabine) for 3 cycles 4 weekly. Regimens given for maximum of 8 cycles
Outcomes	Survival at 3, 6 and 12 months. Median survival. Time to disease progression. Objective response. Clinical benefit response. Toxicity.
Notes	Abstract presented at American Society of Clinical Oncology Annual Scientific meeting 2002. Extra information obtained from poster.
Allocation concealment	B – Unclear

Characteristics of excluded studies

Study	**Reason for exclusion**
Aigner 1998	Regional coeliac axis chemotherapy with starch microembolisation versus systemic chemotherapy

Alberts 2004	Randomised phase II study of a biological agent PS-341(proteosome inhibitor) versus PS-341+ gemcitabine.
Asbury 1994	Randomised phase II three-armed trial with no defined control arm.
Auerbach 1997	Phase II trial.
Bramhall 2001	Randomised study of gemcitabine versus a biological agent marimastat (matrix metalloproteinase inhibitor).
Bramhall 2002	Gemcitabine compared to gemcitabine plus marimastat, (matrix metalloproteinase inhibitor) a biological agent.
Bukowski 1993	Sequential randomised phase II studies with crossovers at treatment failure.
Cascinu 1995	Biological agent (octreotide) versus best supportive care
Chau 2003	Two randomised trials: gastrazole (CCK/gastrin receptor antagonist) a biological agent versus protracted infusional placebo and gastrazole versus protracted venous 5FU.
Chen 2006	Randomised study of gemcitabine versus imatinib mesylate (tyrosine kinase inhibitor), a biological agent.
Colucci 1999	Preliminary report of randomised phase II study with no survival endpoints listed. Final publication in 2002 does have survival data.
Ebert 2004	Randomised study of imatinib mesylate (tyrosine kinase inhibitor), a biological agent in combination with gemcitabine.
GITSG 1985a	Randomised phase II study of maytansin and two dose levels of chlorozotocin.
Gilliam 2004	G17DT a biological agent versus best supportive care.
Heinemann 2004	Survival data not available yet.
Jacobs 2004	Randomised phase III study of rubitecan versus best supportive care in patients with refractory pancreatic cancer. Second-line study.
Johnson 2001	Dose-finding study of oral or intravenous lithium gamolenate
Jones 1987	Non-randomised retrospective study
Klapdor 1982	Survival endpoints not stated.
Klein 2000	Non-randomised retrospective study.
Kojima 1983	Randomised trial of three chemotherapy regimens in hepatic,biliary and pancreatic cancer patients. No separate data available for pancreatic cancer patients.
Lersch 2001	Randomised phase II study of gemcitabine in combination with SCH 66336 (lonafanib) a farnesyl transferase inhibitor a biological agent.
Lokich 1974	Non-randomised study.
Lygidakis 1995	Randomised trial of palliative bypass (gastric or biliary) versus palliative bypass with locoregional immunostimulation (with IL2, interferon) and regional intra-arterial chemotherapy (mitomycin C, carboplatin, epirubicin, 5FU, leucovorin and interferon) i.e. biological and regional therapy.
McCracken 1980	Randomised trial of chemoradiation (using methyl CCNU and 5FU) with or without testolactone a hormonal agent.
Moore 2003	Randomised trial of gemcitabine versus BAY 12-9566 (matrix metalloproteinase inhibitor), a biological agent.
Moore 2005	Randomised trial of gemcitabine with or without erlotinib (tyrosine kinase inhibitor) a biological agent.
Oettle 2005a	Randomised trial of oxaliplatin/5FU and folinic acid versus best supportive care in gemcitabine refractory pancreatic cancer.
Pancreatic Soc 1989	British randomised trial of 5FU and epirubicin versus best supportive care. Study terminated early due to poor accrual. Never published. Original data now lost.
Richards 2002	Placebo controlled trial of gemcitabine in combination with histone deacetylase inhibitor C1-994, a biological agent. No survival data in abstract.
Schein 1978	Randomised phase II trial with no defined control arm.
Shapiro 2005	Randomised phase III trial of gemcitabine with or without G17DT immunogen, a biological agent.

Characteristics of excluded studies (*Continued*)

Stephens 1978	Randomised trial of carmustine and fluorouracil with or without spironolactone, a diuretic.
Stolinsky 1975	Comparison of oral and intravenous 5FU
Sunamura 2004	Comparison of intraoperative radiotherapy for locally advanced pancreatic carcinoma with or without use of an hypoxic cell radiosensitizer PR-350, not a cytotoxic.
Takada 1994	Final publication of expanded 1992 series included pancreatic and biliary-tract cancers and combined results. Authors have stated that source data for 5 of pancreatic patients lost.
Tempero 2003	Comparison of gemcitabine given in two different dosing schedules.
Ulrich-Pur 2003	Raltitrexed plus irinotecan versus irinotecan in gemcitabine pretreated pancreatic cancer. Second-line study
Van Cutsem 2004	Randomised study of gemcitabine with or without tipifarnib (R115777) a biological agent.
Wagener 2002	Comparison of cisplatin-5FU with cisplatin-5FU and alfa interferon, a biological agent.
Zemskov 2000	Randomised trial of high dose vitamin C versus high dose vitamin C plus NSC-631570.

Characteristics of ongoing studies

Study	**CALGB 80303**
Trial name or title	Randomized phase III trial of gemcitabine plus bevacizumab vs. gemcitabine plus placebo in patients with advanced pancreatic cancer
Participants	Locally advanced or metastatic pancreatic carcinoma.
Interventions	A.Gemcitabine+placebo vs B.Gemcitabine+bevacizumab
Outcomes	Survival. Response rate. Duration of response. Toxicity. Resource utilization. Marginal cost.
Starting date	
Contact information	Hedy Kindler, MD, Protocol chair.Ph+1773-702-0360;
Notes	Planned accrual 528 patients

Study	**CALGB-89904**
Trial name or title	Phase II randomised study of gemcitabine alone vs gemcitabine with cisplatin vs gemcitabine with Docetaxel vs gemcitabine with irinotecan in patients With metastatic pancreatic cancer
Participants	Histologically-confirmed adenocarcinoma of the pancreas. Metastatic disease by CT scan.
Interventions	A: Gemcitabine IV over 30 minutes on d 1, 8, and 15 followed by cisplatin IV over 30 minutes on d 1 and 15. Treatment repeats every 28 d for at least 2 courses in the absence of disease progression or unacceptable toxicity. vs B: Gemcitabine IV over 150 minutes on d 1, 8, and 15. Treatment repeats every 28 d for at least 2 courses in the absence of disease progression or unacceptable toxicity. vs C: Gemcitabine IV over 30 minutes followed by docetaxel IV over 60 minutes on d1 and 8. Treatment repeats every 21 d for at least 3 courses in the absence of disease progression or unacceptable toxicity.

Characteristics of ongoing studies (*Continued*)

	vs D: Gemcitabine IV over 30 minutes followed by irinotecan IV over 90 minutes on d1 and 8. Treatment repeats every 21 d for at least 3 courses in the absence of disease progression or unacceptable toxicity. Patients are followed 3 monthly for 1 y and then every 6 months for 3 y.
Outcomes	Overall survival. Time to disease progression. CA19.9 biomarker response. Toxicity. Response rate.
Starting date	
Contact information	Matthew Kulke, MD, Study Chair, Dana-Farber/Harvard Cancer Center.
Notes	Planned accrual: 240 patients (study closed).

Study	**ECOG-4201**
Trial name or title	Phase III randomised study of gemcitabine with or without radiotherapy in patients with locally advanced, unresectable pancreatic cancer
Participants	Locally-advanced unresectable adenocarcinoma and adenosquamous carcinoma of the pancreas.
Interventions	A: Gemcitabine vs B:Gemcitabine+concurrent radiotherapy
Outcomes	Overall survival. Progression-free survival. Toxicity. Quality of life.
Starting date	03/2003
Contact information	ECOG Patrick Loehrer Tel: +1 317278 7418
Notes	Planned accrual: 332 patients (study closed)

Study	**ECOG-6201**
Trial name or title	Phase III randomised study of standard infusion gemcitabine vs prolonged infusion gemcitabine with or without oxaliplatin patients with locally advanced or metastatic pancreatic cancer.
Participants	Locally advanced or metastatic pancreatic adenocarcinoma or poorly differentiated carcinoma.
Interventions	A: Gemcitabine standard infusion vs B. Gemcitabine prolonged infusion vs C.Gemcitabine prolonged infusion+oxaliplatin
Outcomes	Survival. Toxicity. Response rate. Patterns of failure. Progression free survival. Frequency of thromboembolism.

Characteristics of ongoing studies (*Continued*)

	Quality of life.
Starting date	03/2003
Contact information	ECOG Elizabeth Poplin Tel:+1 732 235 677
Notes	Planned accrual: 666 patients

Study	**ECOG-E8200**
Trial name or title	Phase II randomised study of irinotecan and docetaxel with or without cetuximab in patients with metastatic adenocarcinoma of the pancreas.
Participants	Histologically-confirmed metastatic adenocarcinoma of the pancreas. Core or open-biopsy material available for epidermal growth factor receptor testing.
Interventions	A:Docetaxel+irinotecan vs B:Docetaxel+irinotecan+cetuximab
Outcomes	Overall response rate. Time to progression. Overall survival.
Starting date	
Contact information	Barbara A. Burtness, MD, Study Chair, Yale Cancer Center
Notes	Planned accrual: 92 patients

Study	**EORTC 40033**
Trial name or title	Phase III trial of docetaxel/gemcitabine vs gemcitabine in advanced pancreatic cancer.
Participants	
Interventions	A: Gemcitabine vs B: Gemcitabine/docetaxel
Outcomes	
Starting date	
Contact information	M.Lutz
Notes	

Study	**EORTC-05962**
Trial name or title	Phase III randomised multicentre trial of infusional fluorouracil with or without cisplatin and with or without chronomodulation against locally advanced or metastatic pancreatic cancer.
Participants	Locally-advanced or metastatic adenocarcinoma of the exocrine pancreas.
Interventions	A: Chronomodulated 5FU vs B. Chronomodulated 5FU+cisplatin vs C: 5FU flat infusion vs D: Cisplatin flat infusion
Outcomes	Survival

Characteristics of ongoing studies (*Continued*)

Starting date	
Contact information	EORTC Chronotherapy Group Francis Levi Tel:+33 1 45 583 855
Notes	Planned accrual: 200 patients (Trial now closed)

Study	**FRE-GERCOR-GEM-GEMOX**
Trial name or title	Phase III randomised study of gemcitabine with or without oxaliplatin in patients with locally or advanced or metastatic unresectable pancreatic cancer.
Participants	Locally-advanced or metastatic unresectable pancreatic adenocarcinoma.
Interventions	A: Gemcitabine vs B: Gemcitabine fixed dose rate+oxaliplatin
Outcomes	Overall survival. Time of response. Clinical benefit. QOL. Progression free survival.
Starting date	
Contact information	Christophe Louvet: Tel:+33 1 49 282343
Notes	Planned accrual 230

Study	**Heinemann 2005**
Trial name or title	Randomised phase II trial of capecitabine plus oxaliplatin (CapOx) vs capecitabine plus gemcitabine (CapGem) versus gemcitabine plus oxaliplatin (GemOx)
Participants	Locally advanced and metastatic pancreatic cancer.
Interventions	A: Capecitabine+oxaliplatin vs B: Capecitabine+gemcitabine vs C: Gemcitabine+oxaliplatin
Outcomes	Response rate. Progression free survival. Overall survival. Toxicity.
Starting date	07/2002
Contact information	
Notes	Planned accrual: 190 (study closed).

Study	**LORUS-LOR-VIR-PO3-00**
Trial name or title	Phase III randomised study of gemcitabine with or without virulizin followed by optional secondline therapy with virulizin or placebo with or without fluorouracil in patients with chemotherapy-naive locally-advanced or metastatic pancreatic cancer.

Characteristics of ongoing studies (*Continued*)

Participants	Locally-advanced or metastatic pancreatic adenocarcinoma.
Interventions	A:Gemcitabine+placebo vs B:Gemcitabine+virulizin
Outcomes	Overall survival. Time to progression. Pharmacokinetics and pharmacodynamics. Safety.
Starting date	09/2002
Contact information	Lorus Therapeutics Suzanne Cadden Tel:+1 416 798 1200
Notes	Planned accrual: 400 patients

Study	**MEYER-AIT-PAN-201**
Trial name or title	Phase II randomised study of gemcitabine vs immunotherapy with CYTOIMPLANT as first line therapy in patients with unresectable, locally advanced or metastatic pancreatic cancer.
Participants	Histologically-proven stage II, III, or IV pancreatic cancer that is unresectable No symptomatic third-space fluid collection (e.g., ascites, pleural effusion).
Interventions	A:Gemcitabine vs. B: Endoscopic implanation of patient lymphocytes admixed with donor lymphocytes into tumour.
Outcomes	Overall survival. Progression free survival. Response rate. QOL. Safety and toxicity.
Starting date	12/1998
Contact information	Meyer Pharmaceuticals, LLC, Irvine, California, 92614, United States
Notes	Planned accrual: 150 patients (study closed).

Study	**MRC PANRAD**
Trial name or title	A randomised trial of CF (Infusional 5-Fluorouracil and Cisplatin) alone versus CF plus concurrent radiotherapy in patients with locally advanced pancreatic carcinoma
Participants	Histological evidence of locally-advanced or unresectable pancreatic adenocarcinoma. Patients evaluable for response must have bidmensionally measurable disease as assessed by Computed Tomography (CT) scans. No prior chemotherapy or radiotherapy. Life expectancy of >3 months. Adequate bone marrow and renal function. World Health Organisation (WHO) performance status 0-2 at randomisation. No medical contraindications to treatment protocols.
Interventions	A: 5-fluorouracil, continuous infusion for 18 weeks, plus cisplatin repeated every 3 weeks for 6 cycles. vs B: Cisplatin repeated every 3 weeks for 4 cycles plus 5-fluorouracil, continuous infusion for 12 weeks followed by continuous infusion for a further 6 weeks at a reduced dose. Radiotherapy 50 Gy in twenty-five fractions given over 5 weeks. Radiotherapy to commence on week 13 of chemotherapy.

Characteristics of ongoing studies (*Continued*)

Outcomes	
Starting date	
Contact information	Royal Marsden Hospital, London, UK
Notes	Study closed due to poor accrual

Study	**NCCTG-N014C**
Trial name or title	Phase II randomized study of bortezomib with or without gemcitabine in patients with metastatic pancreatic adenocarcinoma
Participants	Histologically-confirmed metastatic ductal or undifferentiated adenocarcinoma consistent with a pancreatic primary for which no standard curative measures exist No participants with locally-advanced disease only.
Interventions	A:Bortezomib vs B:Bortezomib+gemcitabine
Outcomes	Response rate. Progression-free survival. Overall survival. QOL.
Starting date	Study closed
Contact information	Steven R. Alberts, MD, Study Chair, Mayo Clinic Cancer Center
Notes	Planned accrual: 88

Study	**NCI-6580**
Trial name or title	Phase II randomised study of bevacizumab and gemcitabine with either cetuximab or erlotinib in patients with advanced adenocarcinoma of the pancreas.
Participants	Histologically or cytologically confirmed adenocarcinoma of the pancreas. Patients with locally-advanced disease must have disease that extends outside the boundaries of a standard radiation port.
Interventions	A:Bevacizumab+gemcitabine+cetuximab vs B:Bevacizumab+gemcitabine+erlotinib
Outcomes	Response rate. Progression free survival. Overall survival.
Starting date	
Contact information	University of Chicago Cancer Research Center
Notes	Planned accrual: 54-126 patients

Study	**NCT00051467**
Trial name or title	A randomised, phase II, study of TNFerade™ biologic with 5-FU and radiation therapy for first-line treatment of unresectable locally advanced pancreatic cancer
Participants	Participants with biopsy proven locally advanced adenocarcinoma of the pancreas assessed to be unresectable, who have not received previous treatment for pancreatic cancer
Interventions	A:Chemoradiation + 5FU vs

Characteristics of ongoing studies (*Continued*)

	B: Chemoradiation + 5FU + intratumoural injection of TNFerade
Outcomes	
Starting date	
Contact information	Joel Randolph Hecht, MD, Principal Investigator, Jonsson Comprehensive Cancer Center
Notes	TNFerade™ is a replication deficient (E1, E3 and E4 deleted) adenovirus vector containing the gene for TNF-alpha controlled by a radiation inducible promoter.

Study	**RTOG-PA-0020**
Trial name or title	Randomised phase II trial to compare the effectiveness of gemcitabine, paclitaxel, and radiation therapy with or without tipifarnib in treating patients who have locally-advanced pancreatic cancer.
Participants	Histologically confirmed unresectable, locally advanced adenocarcinoma of the pancreas Residual disease after resection (R1 or R2, microscopic or macroscopic) allowed
Interventions	A: Patients receive radiotherapy once daily, 5 d a week, for 5.5 weeks, beginning on d 1. Patients also receive paclitaxel IV over 1 hour and gemcitabine IV over 30 minutes on days 1, 8, 15, 22, 29, and 36. vs B: Patients receive chemoradiotherapy as in arm I. Within 3-8 weeks after completion of chemoradiotherapy, patients without disease progression receive oral tipifarnib twice daily for 21 days. Treatment continues every 28 days in the absence of disease progression or unacceptable toxicity. Patients are followed-up every 3 months for 2 y, every 6 months for 3 y, and then annually thereafter.
Outcomes	One year survival Toxicity Determine the feasibility and toxicity of prolonged administration of tipifarnib after chemoradiotherapy in these patients. Effect of
Starting date	
Contact information	Tyvin Andrew Rich, MD, Study Chair, University of Virginia, Health Sciences Center Cancer Center
Notes	Planned accrual:154 patients Study closed

Study	**SWOG S0205**
Trial name or title	Phase III randomised open label study comparing gemcitabine with cetuximab vs gemcitabine as first line therapy of patients with advanced pancreatic carcinoma.
Participants	Locally-advanced or metastatic pancreatic carcinoma.
Interventions	A:Gemcitabine vs B:Gemcitabine+cetuximab
Outcomes	Survival. Time to treatment failure. Response rate. Self assessed pain. QOL .
Starting date	
Contact information	Dr Philip Philip Wayne State University philipp@karmanos.org
Notes	Planned accrual

Characteristics of ongoing studies (*Continued*)

	613 patients

Study	**TBC-PAN-003**
Trial name or title	Phase III randomised controlled study to evaluate the safety and efficacy of PANVAC-VF in combination with GM-CSF vs best supportive care or palliative chemotherapy in patients with metastatic adenocarcinoma of the pancreas who have failed a gemcitabine containing chemotherapy regimen.
Participants	Metastatic adenocarcinoma of pancreas. Vaccinated against smallpox
Interventions	A:Best supportive care vs B:PANVAC-VF+GM CSF vs C.Palliative chemotherapy
Outcomes	
Starting date	06/2004
Contact information	Therion Biologics Corporation
Notes	Planned accrual: 250

Study	**TC-CR-302**
Trial name or title	Study of efficacy and safety of glufosfamide compared with best supportive care in metastatic pancreatic cancer
Participants	Metastatic pancreatic adenocarcinoma
Interventions	A:Best supportive care vs B:Glufosfamide
Outcomes	Survival. Tumour response. Duration of response. Progression-free survival. 6-and 12-month survival. Pain intensity. Performance status.
Starting date	09/2004
Contact information	www.thresholdpharm.com
Notes	Planned accrual: 300 patients Second line study

Study	**WELLSTAT-401.00.0012**
Trial name or title	Phase III randomised study of triacetyleluridine and high dose fluorouracil versus gemcitabine in patients with unresectable locally-advanced or metastatic pancreatic cancer.
Participants	Unresectable locally-advanced or metastatic pancreatic adenocarcinoma.
Interventions	A.Gemcitabine vs B.High Dose 5FU+oral triacetyluridine
Outcomes	Survival. Time to progression Response rate

Characteristics of ongoing studies (*Continued*)

	Response duration Safety
Starting date	09/01
Contact information	Wellstat Therapeutics Lenny Smith Tel:+1 240 6312500
Notes	Planned accrual: 260 patients

ADDITIONAL TABLES

Table 01. Best supportive care versus chemotherapy trials for advanced pancreatic cancer

Study ID	No. participants	Treatment arms	Clinical benefit/QOL	12 month survival	Median survival
Mallinson (1980)	26	Best supportive care vs cyclophosphamide/ 5FU/vincristine/ methotrexate		5% vs 48%	1.6 mo vs 7.1 mo (P= 0.006)
Andersen (1981)	40	Best supportive care vs 5FU/BCNU	QOL(number of hospital days,. need for analgesics,rate of weight loss) : no significant difference	10% vs 10%	3.2 mo vs 3.0 mo (P= 0.8)
Andren-Sandberg (1983)	47	Best supportive care vs 5FU/ vincristine/CCNU			4 mo (1-20) vs 5 mo (1-17)
Frey (1981)	46	Best supportive care vs 5FU/CCNU		8% vs 12%	3.9 vs 3.0 mo (P= 0.17)
Palmer (1994)	46	Best supportive care vs 5FU/adriamycin/ mitomycin C	HADS:significantly less depression but not anxiety in treated group	5% vs 26%	3.5 mo vs 7.6 mo (P<0.002)
Glimelius (1996)	53	Best supportive care vs 5FU/leucovorin	EORTC QLQ C30: improved or prolonged high quality life 10% vs 36% (p<0.01).	12.5% vs 20.7%	2.5 mo vs 6 mo (P= 0.05)
Takada (1998)	52	Best supportive care vs 5FU/mitomycin C and doxorubicin	Clinical effects: improvement in performance status (8% vs 14%), improvement in body weight (4% vs 14%)	4.2% vs 7.1%	4.8 mo vs 4.9 mo (P=0.39)
Hugier (2001)	45	Best supportive care vs 5FU/leucovorin/		18.4% vs 12.6%	7.0 mo vs 8.6 mo (P=0.33)

Table 01. Best supportive care versus chemotherapy trials for advanced pancreatic cancer (*Continued*)

Study ID	No. participants	Treatment arms	Clinical benefit/QOL	12 month survival	Median survival
		cisplatin			

Table 02. 5FU versus 5FU combination chemotherapy regimens

Study ID	No. participants	Treatment arms	Tumour response rate	12 month survival	Median survival	QOL/Clinical benefit
Kovach 1974	82	5FU vs BCNU vs 5FU/BCNU	16% vs 0% vs 33.3%	23% vs 10% vs 21%	5.4 mo vs 5.1 vs 7.5 mo	
Cullinan 1985	144	5FU vs 5FU/ adriamycin vs 5FU/ adriamycin/ mitomycin C	30% vs 30% vs 7.6%	12% vs 16% vs 12%	22 wk vs 22 wk vs 18 wk (P=ns)	
Cullinan 1990	187	5FU vs Mallinson regimen vs 5FU/ adriamycin/ cisplatin	7% vs 21% vs 15%	17% vs 9% vs 13.5%	3.5 mo vs 4.5 m vs 3.5 mo	
Ducreux 2002	190	5FU vs 5FU+ cisplatin	0% vs 12% (P<0.01)	8% vs 15%		Spitzer index: significant treatment effect in favour of combination arm (P=0.03)
Maisey 2002	209	5FU vs 5FU+ mitomycin C	8.4% vs 17.6% (P=0.04)	23.5% vs 26.2%	5.1mo vs 6.5 mo (P=0.34)	EORTC QLQ C30: No difference between groups during treatment.
Ducreux 2004	63	5FU vs oxaliplatin vs oxaliplatin 5FU	0% vs 0% vs 10%	6% vs 6% vs 23%	2.4 mo vs 3.4 mo vs 9.0 mo	Clinical benefit response: 0% vs 14% vs 21%
Levi 2004	107	5FU vs 5FU+ cisplatin (constant rate vs chronomodu-lated infusion)	Not stated	Not stated	5.4 mo vs 8.3 mo (P=0.26)	

Table 03. Gemcitabine versus gemcitabine combination chemotherapy regimens

Study ID	No. participants	Treatment arms	Tumour Response rate	Clinical benefit QOL	12 month survival	Median PFS	Median survival
Berlin (2002)	322	Gemcitabine vs gemcitabine+ 5FU	5.6% vs 6.9%		20% vs 20% (P=ns)	2.2 vs 3.4 mo (P=0.022)	7.1 vs 9.0 mo (P=0.09)
Wang (2002)	42	Gemcitabine vs gemcitabine+ cisplatin	6.3% vs 11%	Clinical benefit response: 87.5% vs 70%	31% vs 11%		9.0 vs 7.1 mo
Collucci (2002)	107	Gemcitabine vs gemcitabine+ cisplatin	9.2% vs 24.4% (P= 0.02)	Clinical benefit response: 49% vs 52.6%	11% vs 11.3%	2.0 vs 5.0 mo (P=0.048)	5.0 vs 6.0 (P= 0.43)
Heineman (2003)	198	Gemcitabine vs gemcitabine+ cisplatin	8.0% vs 10.2% (P=ns)		22% vs 26%	2.8 vs 5.4 mo (P<0.01)	6.0 vs 7.6 mo (P=ns)
Li (2004)	46	Gemcitabine vs gemcitabine+ cisplatin	12% vs 10% (P=ns)	Clinical benefit response: 36% vs 29% (P>0.05). Quality adjusted life months 5.6 vs 3.8 (p<0.001).	6.3% vs 13.6%	2.8 vs 2.8 mo (P=0.9)	4.6 vs 5.6 mo (P=0.75)
Louvet (2005)	313	Gemcitabine vs gemcitabine+ oxaliplatin	17.3% vs 26.8% (P= 0.04)	Clinical benefit response: 26.9% vs 38.2% (P= 0.03)	27.8 vs 34.5%	3.7 vs 5.8 mo (P=0.04)	7.1 vs 9.0 (P= 0.13)
O'Reilly (2004)	349	Gemcitabine vs gemcitabine+ exetecan	7.1% vs 8.2%	No difference in clinical benefit response. Improvement in time to deterioration of analgesic consumption and	21% vs 23%	3.8 vs 3.7 mo (P=0.22)	6.2 vs 6.7 mo (P=0.52)

Table 03. Gemcitabine versus gemcitabine combination chemotherapy regimens (*Continued*)

Study ID	No. participants	Treatment arms	Tumour Response rate	Clinical benefit QOL	12 month survival	Median PFS	Median survival
				performance score with combination.			
Oettle (2002)	565	Gemcitabine vs gemcitabine+ pemetrexed	7.1% vs 14.8% (P= 0.004)	EORTC QLQ C30: well preserved in both arms	20% vs 21%	3.3 vs 3.9 mo (P=0.11)	6.3 vs 6.2 mo (P=0.08)
Reni (2005)	104	Gemcitabine vs cisplatin, epirubicin, gemcitabine and 5FU	8.5% vs 38.5% (P= 0.0008)	Clinical benefit response: 25% vs 65% (P=0.0139). EORTC QLQ C30 and PAN26 suggested no worsening in QOL with combination regimen.	21.3% vs 38.5% (P= 0.1119)	3.3 vs 5.4 mo (P=0.0033)	9.0 vs 9.0 mo
Ohkawa (2004)	19	Gemcitabine vs gemcitabine+ UFT	33% vs 0%	Clinical benefit: 33% vs 25%		5.0 vs 1.9 mo (P=0.04)	7.6 vs 5.0 (P= ns)
Rocha Lima (2004)	360	Gemcitabine vs gemcitabine+ irinotecan	4.4% vs 16.1% (P<0.001)	FACT-Hep: no significant difference	22% vs 21%	3.0 vs 3.5 mo (P=0.352)	6.6 vs 6.3 mo (P=0.79)
Scheithauer (2003)	83	Gemcitabine vs gemcitabine+ capecitabine	14.3% vs 17.1%	Clinical benefit response :33% vs 48.2%	38% vs 32%	4.0 vs 5.1 mo	8.2 vs 9.5 mo (P=ns)
Gansauge (2002)	90	Gemcitabine vs gemcitabine+ NSC-631570	3.6% vs 21.4%	Significant improvement in self assessed QOL in both arms.	13% vs 32%		5.2 vs 10.4 mo (P<0.01)
Herrmann (2005)	319	Gemcitabine vs gemcitabine+ capecitabine	7.9% vs 10.1%	Clinical benefit response: 20% vs 18%.	27% vs 27%	4.0 vs 4.8 mo (P=0.207)	7.3 vs 8.4 mo (P=0.314)
Reiss (2005)	466	Gemcitabine	7.2% vs 4.8%		22% vs 21%	3.5 vs 3.5 mo	6.2 vs 5.85

Table 03. Gemcitabine versus gemcitabine combination chemotherapy regimens (*Continued*)

Study ID	No. participants	Treatment arms	Tumour Response rate	Clinical benefit QOL	12 month survival	Median PFS	Median survival
		vs gemcitabine+ 5FU/folinic acid			(P=0.68)	(P=0.44)	mo (P=0.68)
Stathopoulos (2005)	92	Gemcitabine vs gemcitabine+ irinotecan	8.2% vs 12.8% (P= 0.474)		24% vs 19.6% (P=ns)	Similar	

Table 04. Miscellaneous chemotherapy versus chemotherapy trials for pancreatic cancer

Study ID	No. participants	Study arms	Overall response	Median survival
Buroker 1979	140	5FU/mitomycin C vs 5FU/CCNU	22% vs 5%	19 wk vs 17 wk (P=ns)
Bukowski 1983	181	5FU mitomycin C vs 5FU/ mitomycin C/ streptozotocin	Not stated	17 wk vs 18 wk (measurable) & 18 wk vs 21 wk (non measurable)
Horton 1981	127	Melphalan vs 5FU/CCNU vs 5FU/CCNU/streptozocin	2% vs 10% vs 7%	8 wk vs 14 wk vs 12 wk (P=ns)
Oster 1984	184	5FU/streptozocin/mitomycin C vs 5FU/adriamycin/mitomycin	4% vs 14%	18.3 wk vs 26.4 wk (P=0.21)
Kelsen 1991	28	5FU streptozotocin/mitomycin C vs cisplatin/AraC/caffeine	10.2% vs 5.5%	40 wk vs 20 wk (P=0.008)
Topham 1991	69	Epirubicin vs 5FU/epirubicin/ mitomycin C	4% vs 11%	22 wk vs 18 wk (P=0.55)

Table 05. Chemoradiotherapy trials in locally advanced pancreatic cancer

Study ID	No. participants	Study arms	Median survival	One year survival
Childs 1964	25	RT 35-40 Gy + saline vs RT 35-40 Gy+5FU	5.4 vs 7.0 mo	11.6% vs 30.8% (P= ns)
Moertel 1969	64	RT 35- 40 Gy vs RT 35-40 Gy+5FU	6.3 vs 10.4 mo (P< 0.05)	5% vs 25%
Moertel 1981	194	RT 40Gy split + 5FU vs60 Gy split+5FU vs 60Gy split	9.6 vs 9.2 vs 5.2 mo (P< 0.01)	40% vs 40% vs 12% (P < 0.01)
Hazel 1981	30	5FU+CCNU vs RT 46 Gy+ 5FU+CCNU	7.8 mo vs 7.8 mo (P = ns)	
Klaassen 1985	91	5FU vs RT 40 Gy+5FU	8.2 vs 8.3 mo (P= ns)	28% vs 30%
GITSG 1985b	157	RT 60Gy split + 5FU vs 60Gy split +adriamycin	8.4 mo vs 7.5 mo (P>0.8)	
GITSG 1988	42	SMF + RT 54 Gy vs SMF	10.5 mo vs 8.0 mo	19% vs 41% (P <0.05)
Earle 1994	87	RT 40-60 Gy split + 5FU vs RT 40-60 Gy split+ hycanthone	7.8 vs 7.8 mo (P=0.82)	35% vs 28%

Shinchi 2002	31	RT 50.8Gy + inf 5FU followed by 5FU maintenance vs best supportive care	13.2 mo vs 6.4 mo (P= 0.001)	53% vs 0%
Li 2003	34	RT 50.4-61.2 Gy conformal + inf 5FU vs RT 50.4-61.2 Gy conformal + gemcitabine concurrent and after	6.7 mo vs 14.5 mo (P= 0.019)	31% vs 56%

ANALYSES

Comparison 01. Chemotherapy versus best supportive care for advanced pancreatic cancer

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Mortality at 6 months	7	425	Odds Ratio (Fixed) 95% CI	0.37 [0.25, 0.57]
02 Mortality at 12 months	7	425	Odds Ratio (Fixed) 95% CI	0.46 [0.25, 0.84]

Comparison 02. 5FU alone versus another chemotherapy agent

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Mortality at 6 months	4	312	Odds Ratio (Fixed) 95% CI	0.58 [0.37, 0.92]
02 Mortality at 12 months	4	312	Odds Ratio (Fixed) 95% CI	0.67 [0.34, 1.31]

Comparison 03. 5FU alone versus 5FU chemotherapy combinations

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Mortality at 6 months	8	842	Odds Ratio (Fixed) 95% CI	0.79 [0.59, 1.05]
02 Mortality at 12 months	8	842	Odds Ratio (Fixed) 95% CI	0.90 [0.62, 1.30]

Comparison 04. Gemcitabine versus another chemotherapy agent

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Mortality at 6 months	4	627	Odds Ratio (Fixed) 95% CI	1.10 [0.80, 1.51]
02 Mortality at 12 months	4	627	Odds Ratio (Fixed) 95% CI	1.34 [0.88, 2.02]

Comparison 05. Gemcitabine versus gemcitabine chemotherapy combinations

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Mortality at 6 months	14	3298	Odds Ratio (Fixed) 95% CI	0.88 [0.77, 1.02]
02 Mortality at 12 months	15	3390	Odds Ratio (Fixed) 95% CI	0.89 [0.76, 1.05]

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Agents [therapeutic use]; Combined Modality Therapy [methods]; Deoxycytidine [analogs & derivatives; therapeutic use]; Fluorouracil [therapeutic use]; Pancreatic Neoplasms [*drug therapy; mortality; *radiotherapy]; Quality of Life; Randomized Controlled Trials

MeSH check words

Humans

COVER SHEET

Title	Chemotherapy and radiotherapy for inoperable advanced pancreatic cancer
Authors	Yip D, Karapetis C, Strickland A, Steer CB, Goldstein D
Contribution of author(s)	All reviewers were involved in the design of the protocol and in assessing the studies identified. Desmond Yip performed data entry and analysis. Desmond Yip and David Goldstein drafted the review manuscript and contributions were made to this by the other reviewers. All reviewers approved the final document.
Issue protocol first published	2000/1
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What's New	Information not supplied by author
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	01 December 2005
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GRAPHS AND OTHER TABLES

Figure 01. Funnel plot of chemotherapy versus best supportive care one year mortality

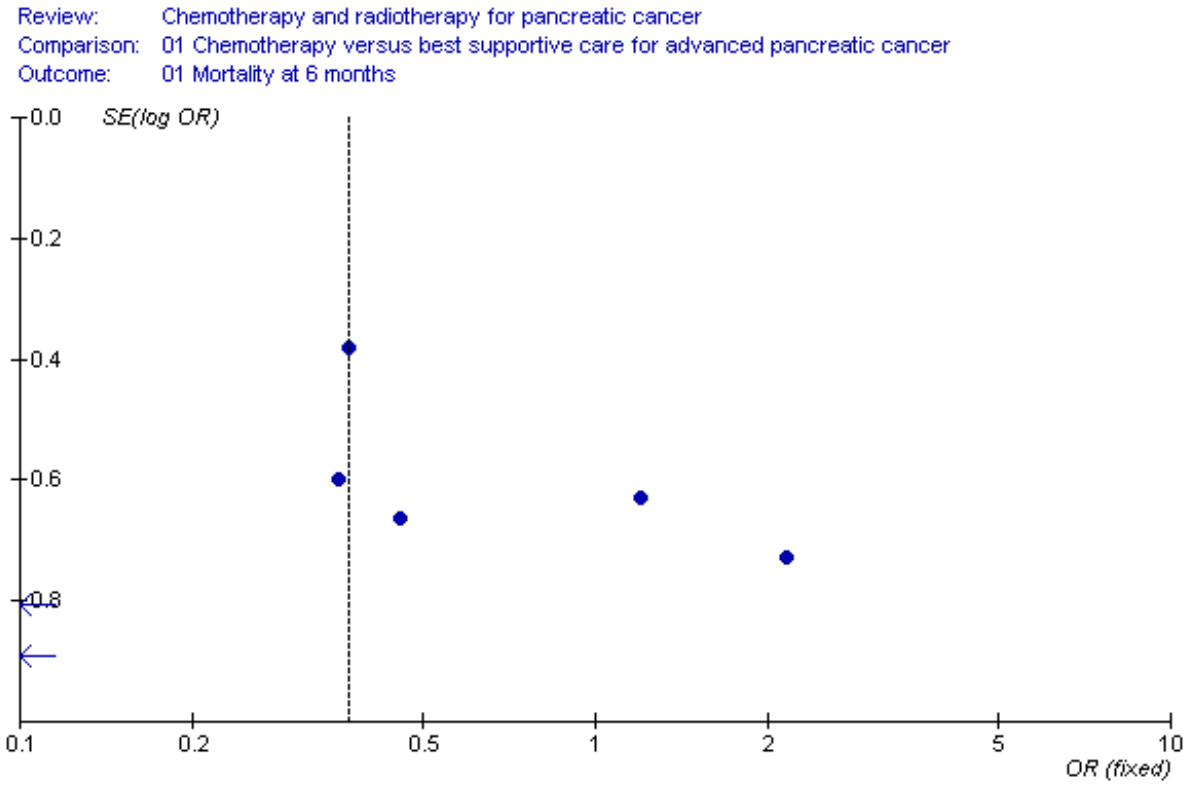
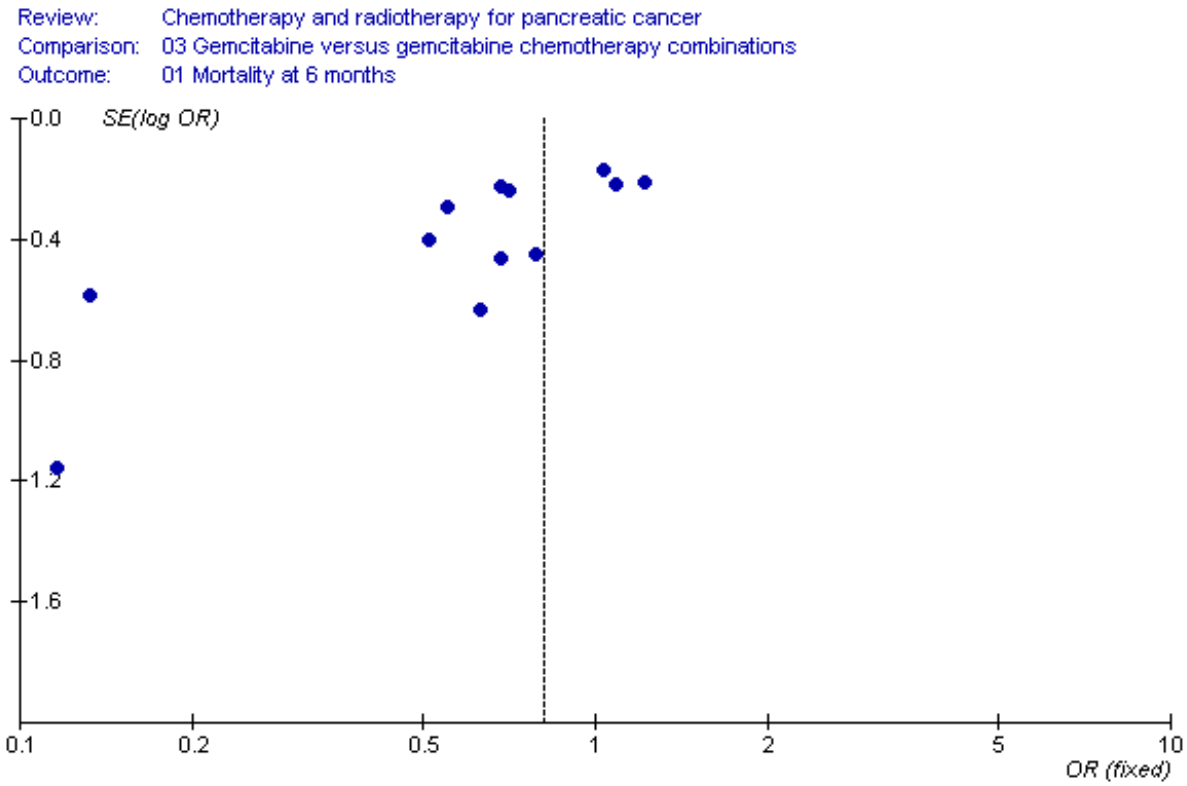


Figure 02. Funnel plot of six-month mortality in gemcitabine versus gemcitabine combination studies.



Analysis 01.01. Comparison 01 Chemotherapy versus best supportive care for advanced pancreatic cancer, Outcome 01 Mortality at 6 months

Review: Chemotherapy and radiotherapy for inoperable advanced pancreatic cancer

Comparison: 01 Chemotherapy versus best supportive care for advanced pancreatic cancer

Outcome: 01 Mortality at 6 months

Study	Chemotherapy n/N	Best supportive care n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
Glimelius 1996	15/29	18/24		12.8	0.36 [0.11, 1.16]
Frey 1981	13/65	35/87		32.2	0.37 [0.18, 0.78]
Mallinson 1980	6/21	17/19		17.1	0.05 [0.01, 0.27]
Andersen 1981	16/20	13/20		3.5	2.15 [0.52, 9.00]
Palmer 1994	5/23	17/20		19.1	0.05 [0.01, 0.24]
Takada 1998	8/28	6/24		6.2	1.20 [0.35, 4.13]
Huguier 2001	5/22	9/23		9.1	0.46 [0.12, 1.68]
Total (95% CI)	208	217		100.0	0.37 [0.25, 0.57]

Total events: 68 (Chemotherapy), 115 (Best supportive care)

Test for heterogeneity chi-square=21.08 df=6 p=0.002 I^2 =71.5%

Test for overall effect z=4.64 p<0.00001

Analysis 01.02. Comparison 01 Chemotherapy versus best supportive care for advanced pancreatic cancer, Outcome 02 Mortality at 12 months

Review: Chemotherapy and radiotherapy for inoperable advanced pancreatic cancer

Comparison: 01 Chemotherapy versus best supportive care for advanced pancreatic cancer

Outcome: 02 Mortality at 12 months

Study	Chemotherapy n/N	Best supportive care n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
Glimelius 1996	23/29	21/24		14.4	0.55 [0.12, 2.47]
Frey 1981	5/65	10/87		23.9	0.64 [0.21, 1.98]
Mallinson 1980	11/21	18/19		27.2	0.06 [0.01, 0.55]
Andersen 1981	18/20	18/20		5.4	1.00 [0.13, 7.89]
Palmer 1994	17/23	19/20		16.0	0.15 [0.02, 1.37]
Takada 1998	26/28	23/24		5.4	0.57 [0.05, 6.65]
Huguier 2001	19/22	19/23		7.7	1.33 [0.26, 6.78]
Total (95% CI)	208	217		100.0	0.46 [0.25, 0.84]

(*Continued . . .*)

(. . . *Continued*)

Study	Chemotherapy n/N	Best supportive care n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
Total events: 119 (Chemotherapy), 128 (Best supportive care)					
Test for heterogeneity chi-square=6.87 df=6 p=0.33 I^2 =12.6%					
Test for overall effect z=2.53 p=0.01					

Analysis 02.01. Comparison 02 5FU alone versus another chemotherapy agent, Outcome 01 Mortality at 6 months

Review: Chemotherapy and radiotherapy for inoperable advanced pancreatic cancer

Comparison: 02 5FU alone versus another chemotherapy agent

Outcome: 01 Mortality at 6 months

Study	Other agent n/N	5FU n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
Burris 1997	34/63	44/63		42.9	0.51 [0.24, 1.05]
Kovach 1974	5/21	19/31		24.8	0.20 [0.06, 0.68]
Ducreux 2004	10/17	12/15		11.1	0.36 [0.07, 1.75]
Cantore 2004	35/67	16/35		21.3	1.30 [0.57, 2.95]
Total (95% CI)	168	144		100.0	0.58 [0.37, 0.92]
Total events: 84 (Other agent), 91 (5FU)					
Test for heterogeneity chi-square=7.12 df=3 p=0.07 I^2 =57.9%					
Test for overall effect z=2.29 p=0.02					

Analysis 02.02. Comparison 02 5FU alone versus another chemotherapy agent, Outcome 02 Mortality at 12 months

Review: Chemotherapy and radiotherapy for inoperable advanced pancreatic cancer

Comparison: 02 5FU alone versus another chemotherapy agent

Outcome: 02 Mortality at 12 months

Study	Other agent n/N	5FU n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
Burris 1997	52/63	62/63		51.0	0.08 [0.01, 0.61]
Kovach 1974	19/21	24/31		8.7	2.77 [0.51, 14.91]
Ducreux 2004	16/17	14/15		4.1	1.14 [0.07, 20.02]
Cantore 2004	53/67	28/35		36.2	0.95 [0.34, 2.61]
Total (95% CI)	168	144		100.0	0.67 [0.34, 1.31]

Total events: 140 (Other agent), 128 (5FU)

Test for heterogeneity chi-square=7.51 df=3 p=0.06 I^2 =60.0%

Test for overall effect z=1.17 p=0.2

Analysis 03.01. Comparison 03 5FU alone versus 5FU chemotherapy combinations, Outcome 01 Mortality at 6 months

Review: Chemotherapy and radiotherapy for inoperable advanced pancreatic cancer

Comparison: 03 5FU alone versus 5FU chemotherapy combinations

Outcome: 01 Mortality at 6 months

Study	5FU combinations n/N	5FU alone n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
Ducreux 2002	73/99	72/99		17.6	1.05 [0.56, 1.98]
Maisey 2002	48/102	59/107		28.4	0.72 [0.42, 1.25]
Cullinan 1990a	36/61	18/32		9.0	1.12 [0.47, 2.66]
Cullinan 1990b	38/59	19/32		8.2	1.24 [0.51, 3.00]
Kovach 1974	11/30	19/31		11.0	0.37 [0.13, 1.03]
Ducreux 2004	8/31	12/15		11.2	0.09 [0.02, 0.39]
Cullinan 1985a	27/44	15/25		6.9	1.06 [0.39, 2.89]
Cullinan 1985b	31/50	16/25		7.6	0.92 [0.34, 2.49]
Total (95% CI)	476	366		100.0	0.79 [0.59, 1.05]

Total events: 272 (5FU combinations), 230 (5FU alone)

Test for heterogeneity chi-square=13.39 df=7 p=0.06 I^2 =47.7%

Test for overall effect z=1.65 p=0.1

Analysis 03.02. Comparison 03 5FU alone versus 5FU chemotherapy combinations, Outcome 02 Mortality at 12 months

Review: Chemotherapy and radiotherapy for inoperable advanced pancreatic cancer

Comparison: 03 5FU alone versus 5FU chemotherapy combinations

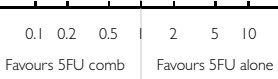
Outcome: 02 Mortality at 12 months

Study	5FU combination n/N	5FU alone n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
Ducreux 2002	84/99	91/99		23.3	0.49 [0.20, 1.22]
Maisey 2002	75/102	82/107		35.8	0.85 [0.45, 1.59]
Cullinan 1990a	58/61	26/32		2.8	4.46 [1.04, 19.23]
Cullinan 1990b	51/59	27/32		8.0	1.18 [0.35, 3.96]
Kovach 1974	24/30	24/31		8.0	1.17 [0.34, 3.99]
Ducreux 2004	24/31	14/15		7.2	0.24 [0.03, 2.20]
Cullinan 1985a	37/44	21/25		7.2	1.01 [0.26, 3.85]
Cullinan 1985b	42/50	21/25		7.6	1.00 [0.27, 3.70]
Total (95% CI)	476	366		100.0	0.90 [0.62, 1.30]

Total events: 395 (5FU combination), 306 (5FU alone)

Test for heterogeneity chi-square=8.11 df=7 p=0.32 I^2 =13.7%

Test for overall effect z=0.56 p=0.6



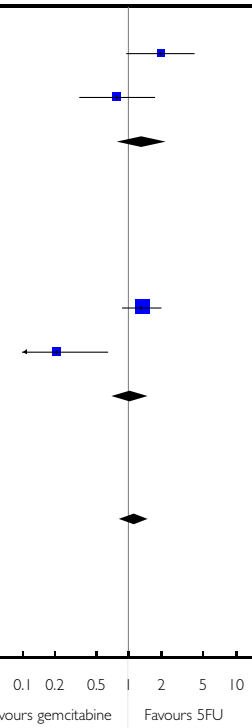
Analysis 04.01. Comparison 04 Gemcitabine versus another chemotherapy agent, Outcome 01 Mortality at 6 months

Review: Chemotherapy and radiotherapy for inoperable advanced pancreatic cancer

Comparison: 04 Gemcitabine versus another chemotherapy agent

Outcome: 01 Mortality at 6 months

Study	Other agent n/N	Gemcitabine n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
01 Gemcitabine versus fluorouracil					
Burris 1997	44/63	34/63		13.9	1.98 [0.95, 4.10]
Cantore 2004	16/35	35/67		17.6	0.77 [0.34, 1.75]
Subtotal (95% CI)	98	130		31.5	1.30 [0.76, 2.23]
Total events: 60 (Other agent), 69 (Gemcitabine)					
Test for heterogeneity chi-square=2.83 df=1 p=0.09 I^2 =64.6%					
Test for overall effect z=0.96 p=0.3					
02 Gemcitabine versus other agents					
Cheverton 2004	94/169	83/170		49.7	1.31 [0.86, 2.01]
Gansauge 2002	11/30	22/30		18.8	0.21 [0.07, 0.63]
Subtotal (95% CI)	199	200		68.5	1.01 [0.69, 1.49]
Total events: 105 (Other agent), 105 (Gemcitabine)					
Test for heterogeneity chi-square=9.29 df=1 p=0.002 I^2 =89.2%					
Test for overall effect z=0.05 p=1					
Total (95% CI)	297	330		100.0	1.10 [0.80, 1.51]
Total events: 165 (Other agent), 174 (Gemcitabine)					
Test for heterogeneity chi-square=12.56 df=3 p=0.006 I^2 =76.1%					
Test for overall effect z=0.60 p=0.5					

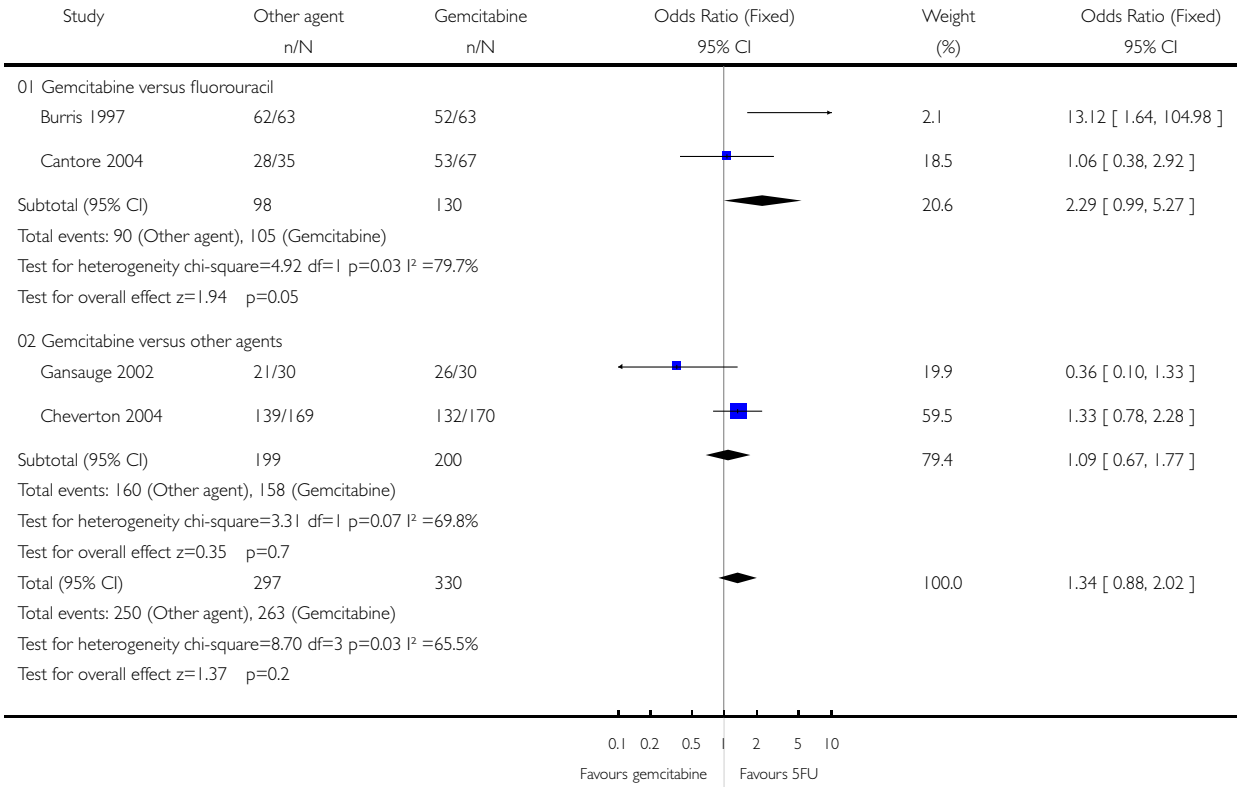


Analysis 04.02. Comparison 04 Gemcitabine versus another chemotherapy agent, Outcome 02 Mortality at 12 months

Review: Chemotherapy and radiotherapy for inoperable advanced pancreatic cancer

Comparison: 04 Gemcitabine versus another chemotherapy agent

Outcome: 02 Mortality at 12 months



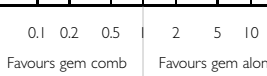
Analysis 05.01. Comparison 05 Gemcitabine versus gemcitabine chemotherapy combinations, Outcome 01 Mortality at 6 months

Review: Chemotherapy and radiotherapy for inoperable advanced pancreatic cancer

Comparison: 05 Gemcitabine versus gemcitabine chemotherapy combinations

Outcome: 01 Mortality at 6 months

Study	Gemcitabine combined n/N	Gemcitabine n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
01 Gemcitabine vs gemcitabine-fluoropyrimidine combinations					
Scheithauer 2003	13/41	17/42		2.7	0.68 [0.28, 1.68]
O'Reilly 2004	84/175	80/174		9.7	1.08 [0.71, 1.65]
Herrmann 2005	68/160	61/159		8.2	1.19 [0.76, 1.86]
Riess 2005	118/236	109/230		12.9	1.11 [0.77, 1.60]
Berlin 2002	70/160	86/162		11.2	0.69 [0.44, 1.07]
Subtotal (95% CI)	772	767		44.7	0.99 [0.81, 1.21]
Total events: 353 (Gemcitabine combined), 353 (Gemcitabine)					
Test for heterogeneity chi-square=4.50 df=4 p=0.34 I^2 =11.1%					
Test for overall effect z=0.13 p=0.9					
02 Gemcitabine vs gemcitabine-Irinotecan combination					
Rocha Lima 2004	90/180	81/180		9.4	1.22 [0.81, 1.85]
Subtotal (95% CI)	180	180		9.4	1.22 [0.81, 1.85]
Total events: 90 (Gemcitabine combined), 81 (Gemcitabine)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.95 p=0.3					
03 Gemcitabine vs gemcitabine-platinum combinations					
Wang 2002	1/20	5/16		1.2	0.12 [0.01, 1.12]
Heinemann 2003	37/95	52/97		7.3	0.55 [0.31, 0.98]
Colucci 2002	28/53	37/54		4.0	0.51 [0.23, 1.13]
Li 2004	13/21	18/25		1.5	0.63 [0.18, 2.18]
Louvet 2005	50/157	62/156		9.9	0.71 [0.45, 1.13]
Subtotal (95% CI)	346	348		23.9	0.59 [0.43, 0.81]
Total events: 129 (Gemcitabine combined), 174 (Gemcitabine)					
Test for heterogeneity chi-square=2.74 df=4 p=0.60 I^2 =0.0%					
Test for overall effect z=3.28 p=0.001					
04 Gemcitabine vs other gemcitabine combinations					
Gansauge 2002	8/30	22/30		3.8	0.13 [0.04, 0.42]
Oettle 2005b	139/273	137/273		15.7	1.03 [0.74, 1.44]
Reni 2005	13/52	14/47		2.6	0.79 [0.32, 1.91]



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Study	Gemcitabine combined n/N	Gemcitabine n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
Subtotal (95% CI)	355	350		22.0	0.85 [0.63, 1.14]
Total events: 160 (Gemcitabine combined), 173 (Gemcitabine)					
Test for heterogeneity chi-square=11.45 df=2 p=0.003 I^2 =82.5%					
Test for overall effect z=1.09 p=0.3					
Total (95% CI)	1653	1645		100.0	0.88 [0.77, 1.02]
Total events: 732 (Gemcitabine combined), 781 (Gemcitabine)					
Test for heterogeneity chi-square=28.09 df=13 p=0.009 I^2 =53.7%					
Test for overall effect z=1.75 p=0.08					

Analysis 05.02. Comparison 05 Gemcitabine versus gemcitabine chemotherapy combinations, Outcome 02 Mortality at 12 months

Review: Chemotherapy and radiotherapy for inoperable advanced pancreatic cancer

Comparison: 05 Gemcitabine versus gemcitabine chemotherapy combinations

Outcome: 02 Mortality at 12 months

Study	Gemcitabine combined n/N	Gemcitabine n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
01 Gemcitabine vs gemcitabine-fluropyrimidine combinations					
Scheithauer 2003	28/41	26/42		2.6	1.33 [0.54, 3.28]
O'Reilly 2004	135/175	137/174		10.1	0.91 [0.55, 1.51]
Berlin 2002	128/160	139/162		8.9	0.66 [0.37, 1.19]
Herrmann 2005	117/160	116/159		10.1	1.01 [0.62, 1.65]
Riess 2005	186/236	179/230		12.4	1.06 [0.68, 1.65]
Subtotal (95% CI)	772	767		44.1	0.95 [0.75, 1.21]
Total events: 594 (Gemcitabine combined), 597 (Gemcitabine)					
Test for heterogeneity chi-square=2.29 df=4 p=0.68 I^2 =0.0%					
Test for overall effect z=0.42 p=0.7					
02 Gemcitabine vs gemcitabine-irinotecan combinations					
Rocha Lima 2004	142/180	140/180		9.5	1.07 [0.65, 1.76]
Stathopoulos 2005	34/42	38/50		2.1	1.34 [0.49, 3.67]
Subtotal (95% CI)	222	230		11.7	1.12 [0.71, 1.75]
Total events: 176 (Gemcitabine combined), 178 (Gemcitabine)					
Test for heterogeneity chi-square=0.16 df=1 p=0.69 I^2 =0.0%					
Test for overall effect z=0.49 p=0.6					

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