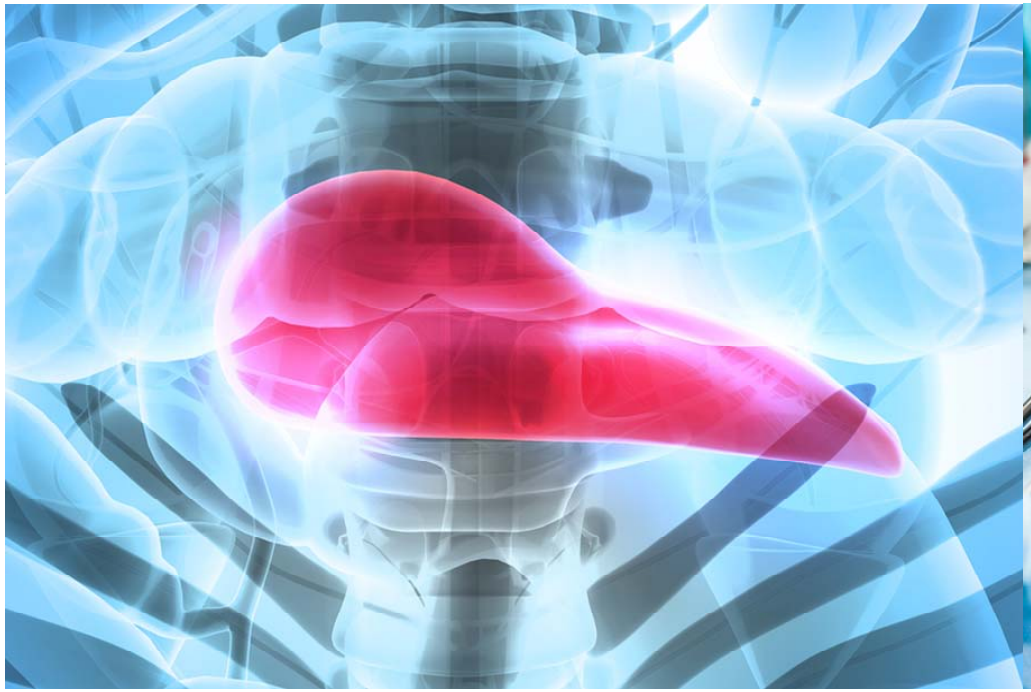
KCE REPORT 286

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

MANAGEMENT OF PANCREATIC CANCER – PART 4: RECURRENT AND METASTATIC CANCER



KCE REPORT 286
GOOD CLINICAL PRACTICE

Federaal Kenniscentrum voor de Gezondheidszorg
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MANAGEMENT OF PANCREATIC CANCER – PART 4: RECURRENT AND METASTATIC CANCER

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
BSC	Best supportive care
CAP	Cyclophosphamide, adriamycin, cisplatin
CI	Confidence interval
CCNU	Chloroethylcyclohexylnitrosurea
CRT	Chemoradiotherapy
DSS	Disease specific survival
EPA	Eicosapentaenoic acid
FOLFIRINOX	Folinic acid (leucovirin), fluorouracil (5-FU), irinotecan, oxaliplatin
FU	Fluorouracil
GDG	Guideline development group
GEMOXEL	Gemcitabine/oxaliplatin/capecitabine
HR	Hazard ratios
KCE	Belgian health care knowledge centre
LAPC	Locally advanced pancreatic cancer
LASA	Linear-analogue self-assessment
MMC	Mitomycin C
MPC	Metastatic pancreatic cancer
OS	Overall survival
PC	Pancreatic cancer
P.I.C.O.	Population-intervention-comparator-outcome
QUALY	Quality-adjusted life-year
QoL	Quality of life
RCT	Randomised controlled trial
RQ	Research question
S-1	Tegafur/gimeracil/oteracil

SEER	Surveillance, Epidemiology and End Results
SR	Systematic review
UFT	Tegafur-uracil
yrs	Years

SCIENTIFIC REPORT

1 INTRODUCTION

Recurrent and metastatic PC (MPC) carry a grim prognosis. The five year relative survival for PC is estimated at 7.7% by the Surveillance, Epidemiology and End Results (SEER) database for the period 2006-2012. Relative survival by cancer stage was 29.3% for localised cancer, 11.1% for regional, 2.6% for distant and 4.9% for unstaged cancers.[1]

The Belgian Cancer Registry reported survival by TMN stage for men and women for the period 2004-2008. Five-year relative survival was highest for stage I (males: 39.5%, females: 30.3%) and lowest for stage IV (males: 2.9%, females: 2.6%). The Registry mentions that most of the patients 54.2% of known stages in males and 49.6% in females are diagnosed in stage IV. Age influences survival: which is better in the age group 15-59 (males: 16.5%, females: 22.5%), than for other age groups (60-74 years age group: males: 9.2%, females: 7.0%; 75+ years age group: males: 4.0%, females: 4.6%).[2]

This section focusses on the evidence regarding various current therapeutic attempts in case of recurrent pancreatic cancer (PC) or the occurrence of metastases. Treatment after failure of first line therapy was not part of the research question (RQ). The RQ was formulated as follows: What is the optimal treatment strategy in patients with recurrent/metastatic pancreatic cancer? The population-intervention-comparator-outcome (P.I.C.O.) design is described in Table 1.

Table 1 – P.I.C.O.

What is the optimal treatment strategy in patients with recurrent/metastatic pancreatic cancer?	
P	Patients presenting with recurrent/metastatic pancreas cancer?
I	Chemotherapy Radiotherapy Chemoradiotherapy (crt) Re - resection
C	Best supportive care (BSC) , including palliative care
O	Overall survival (OS), Quality of Life (QoL)

2 SELECTING STUDIES AND QUALITY APPRAISAL

2.1 Selection of systematic reviews

On May 9, 2016 a search was performed in MEDLINE, Embase and The Cochrane Library (from 2008 onwards) to identify systematic reviews (SR) regarding the effect of chemotherapy, radiotherapy, CRT or re-resection in patients with recurrent or MPC. In total, 500 studies were identified. After deduplication, 349 potentially relevant references remained (Figure 6). Based on title and abstract 330 references were excluded. Of the remaining 19 articles four were suitable for inclusion and 15 were excluded with reason (Table 2).

Table 2 – Initially included SRs (n = 4)

Reference	Search date	In- and exclusion criteria	Interventions
Chin 2017[3] (Protocol published as Nagrial 2013[4])	September 2015 – Updated June 30, 2016	Studies that analysed patients with pancreatic ductal adenocarcinoma, who were of locally advanced or metastatic stage with a randomised trial design, in which OS was an endpoint	Chemotherapy, biological agents, immunotherapy, radiotherapy, alone or in combination compared with best supportive care or with each other
Li 2014[5]	January 2014	RCTs in patients with LA/MPC, histologically or cytologically confirmed pancreatic adenocarcinoma. Studies that included patients with major comorbidities or second tumours, and studies that included adjuvant chemotherapy within six months or concomitant interventions such as radiotherapy that differed systematically between the investigated arms, were excluded.	Gemcitabine plus 5- Fluorouracil (FU) / cyclophosphamide, adriamycin, cisplatin (CAP)/ tegafur/gimeracil/oteracil (S-1) vs gemcitabine alone
Li 2015[6]	July 2014	Randomised controlled trials (RCT) including patients with locally advanced (LAPC) or metastatic disease treated with GS or GEM alone. Histologic or confirmation of PC was required. Trials with concomitant interventions such as radiotherapy or radioisotope treatment that differed systematically between the study arms, and trials in patients with coronary artery disease,	Gemcitabine plus S-1 vs gemcitabine alone

		unstable diabetes mellitus or concomitant malignancy were excluded.	
Sun 2012[7]	November 2011	(1) prospective, randomized, controlled open or blinded trial; (2) patients with histologically confirmed locally advanced or metastatic pancreatic ductal adenocarcinoma; (3) assessment of the efficacy of gemcitabine combination therapy vs gemcitabine alone. Non-randomized trials and quasi-randomized trials, studies of curatively aimed resection, and studies where patients had multiple cancers, were excluded to avoid clinical heterogeneities between different studies.	Gemcitabine combination therapy vs gemcitabine alone

From the four initially selected SRs regarding chemotherapy, radiotherapy or both, it was decided to select for further processing only the most comprehensive and recent systematic one was selected.[3, 4] No SR regarding re-resection was identified. We had access to the evidence retrieved by Chin prior to the publication of the manuscript.[3]

2.2 Selection of primary studies

On June 29, 2016 a search was performed in MEDLINE, Embase and CENTRAL to identify RCTs and/or comparative observational studies regarding the effect of CRT or re-resection in patients with recurrent PC. In total, 1095 studies were identified. After deduplication, 965 potentially relevant references remained (Figure 7). Based on title and abstract 951 references were excluded. Of the remaining 14 articles no RCT or comparative observational study was included and all studies were excluded with reason (Table 4 in Appendix).

2.3 Assessment of risk of bias

2.3.1 Systematic reviews

One SR was selected for further processing.[3] The review scored positively on all AMSTAR items. Overall, the SR was considered as having a low risk of bias (Table 5 in Appendix).

2.3.2 Primary studies

No primary studies regarding the treatment of recurrent disease were identified.

3 EVIDENCE DESCRIPTION

3.1 What is the optimal treatment strategy in patients with recurrent/metastatic pancreatic cancer?

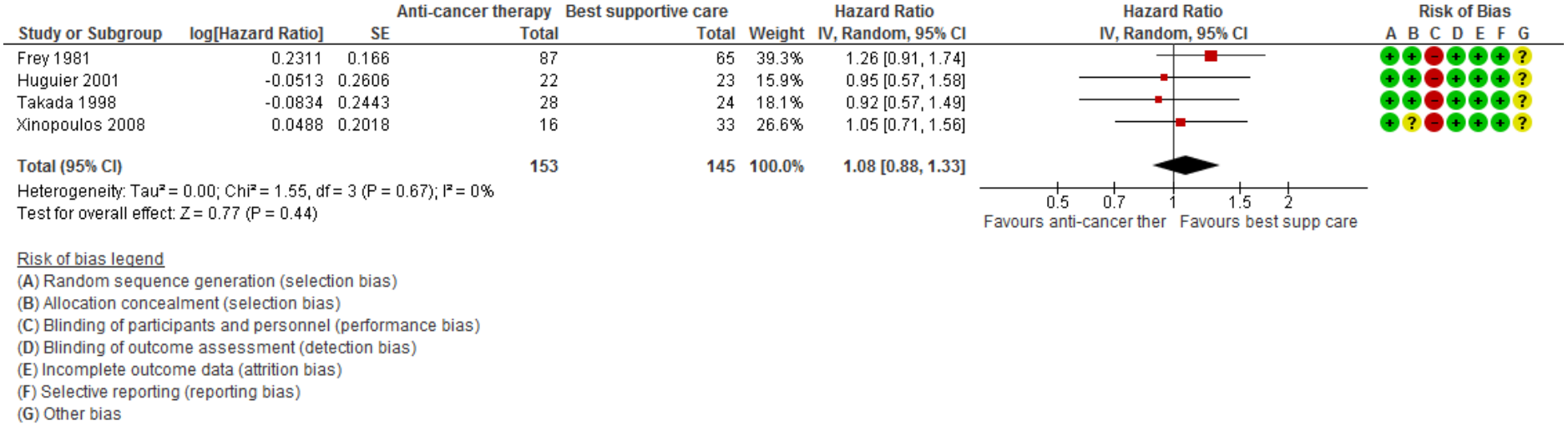
A high-quality Cochrane SR[3] was identified and shared by the authors before publication. It was decided to use this review as a basis. The search date of Chin's review was June 30, 2016. The review addressed 94 studies that compared pharmacologic and radiotherapeutic interventions in patients with advanced pancreatic adenocarcinoma, including LAPC, unresectable or recurrent disease (confirmed by histological or cytological findings). OS was the primary outcome. Secondary outcomes were disease-specific survival (DSS), progression-free survival (PFS), QoL and adverse effects. The review was considered to have low risk of bias. The detailed evidence table can be found in Table 6. The Grade evidence profiles are to be found under section 0.

3.1.1 Anticancer therapy vs best supportive care

Overall survival

Four studies (298 patients) addressed this outcome.[8-11] Three studies applied to unresectable PC and one to LAPC.[9] Treatments were 5-FU + chloroethylcyclohexylnitrosurea (CCNU),[8] cisplatin + 5-FU + leucovorin,[9] 5-FU + doxorubicin + mitomycin C (MMC),[10] and gemcitabine in monotherapy.[11] The HR was 1.08 (95% CI 0.88 to 1.33) ( ). When removing the study including patients with LAPC the HR was 1.10 (95% confidence interval (CI) 0.86 to 1.39).

Figure 1 – Forest plot and risk of bias plot for OS of anti-cancer therapy vs BSC



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Quality of life

Three studies addressed QoL.[11-13] One study applied to patients with inoperable PC, one to patients with non-curable pancreatic or biliary tract cancer and one to LAPC. Treatments were 5-FU + CCNU + vincristine, 5-FU/leucovorin with or without etoposide, and gemcitabine. No significant differences between the groups were found in one study with respect to the Karnofsky Performance Status. The EORTC-QLQ-C30 scores, a measure for QoL, favoured the anticancer treatment group in one study (with a high rate of drop outs)[11] and the third study (in LAPC patients) reported significantly higher EORTC-QLQ-C30 scores after 1 month in favour of gemcitabine (P= 0.028), no significant differences between the groups after 2-4 months (P> 0.05) and significantly higher scores in favour of BSC for the physical and role functioning (P=0.010) and global health scales (P=0.0003) after 5-6 months.

3.1.2 Various types of chemotherapy vs gemcitabine

Overall survival

Five studies in 1200 patients addressed this outcome (.[14-18] One study applied to patients with advanced, symptomatic PC with stabilised pain, three studies to MPC and one to both LAPC and MPC. Treatments were 5-FU (1 study in advanced PC),[14] Folinic acid (leucovirin), 5-FU, irinotecan, oxaliplatin (FOLFIRINOX) (2 studies),[14-16] CO-101 (1 study)[17] and ZD9331 (1 study).[18] The test for subgroup differences was significant (P< 0.0001). Therefore, the results are presented by subgroup.

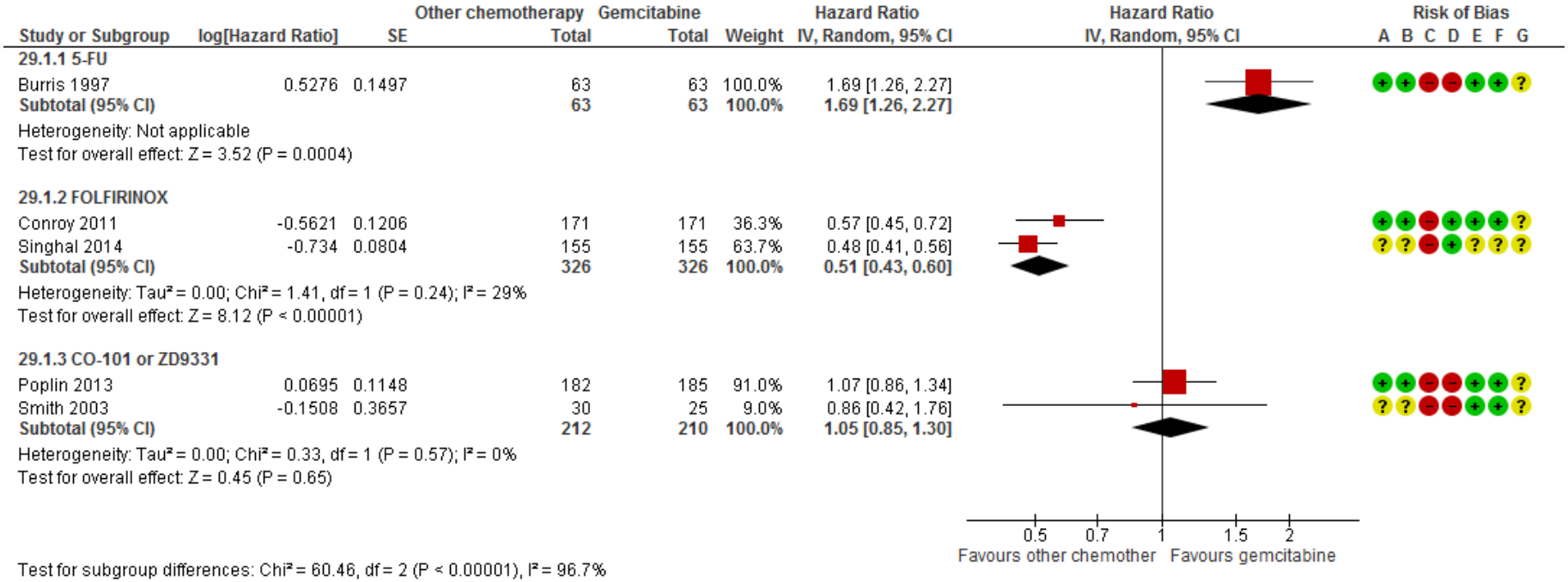
The HR for 5-FU was 1.69 (95% CI 1.26 to 2.27) in favour of gemcitabine (1 study; 126 patients). Clinical benefit response was experienced by 23.8% of emcitabine-treated patients compared with 4.8% of 5-FU-treated patients (P = 0.0022). The median survival durations were 5.65 and 4.41 months for gemcitabine-treated and 5-FU-treated patients, respectively (P = 0.0025). The survival rate at 12 months was 18% for gemcitabine patients and 2% for 5-FU patients. Treatment was well tolerated.

The HR for FOLFIRINOX vs gemcitabine (2 studies; 652 patients) was 0.51 (95% CI 0.43 to 0.60) in favour of FOLFIRINOX.

- Conroy et al.[15] (metastatic cancer) The median OS was 11.1 months in the FOLFIRINOX group as compared with 6.8 months in the gemcitabine group (hazard ratio for death, 0.57; 95% confidence interval [CI], 0.45 to 0.73; P<0.001). More adverse events were noted in the FOLFIRINOX group. At 6 months, 31% of the patients in the FOLFIRINOX group had a definitive degradation of the QoL versus 66% in the gemcitabine group (hazard ratio, 0.47; 95% CI, 0.30 to 0.70; P<0.001). Authors' conclusions: As compared with gemcitabine, FOLFIRINOX was associated with a survival advantage and had increased toxicity. FOLFIRINOX is an option for the treatment of patients with metastatic pancreatic cancer and good performance status.
- Singhal et al.[16] (metastatic cancer): conference proceeding.

The HR for the other treatments vs gemcitabine (2 studies; 422 patients) was 1.05 (95% CI 0.85 to 1.30) (Figure 2).

Figure 2 – Forest plot and risk of bias plot for OS of various types of chemotherapy vs gemcitabine



Test for subgroup differences: Chi² = 60.46, df = 2 (P < 0.00001), I² = 96.7%

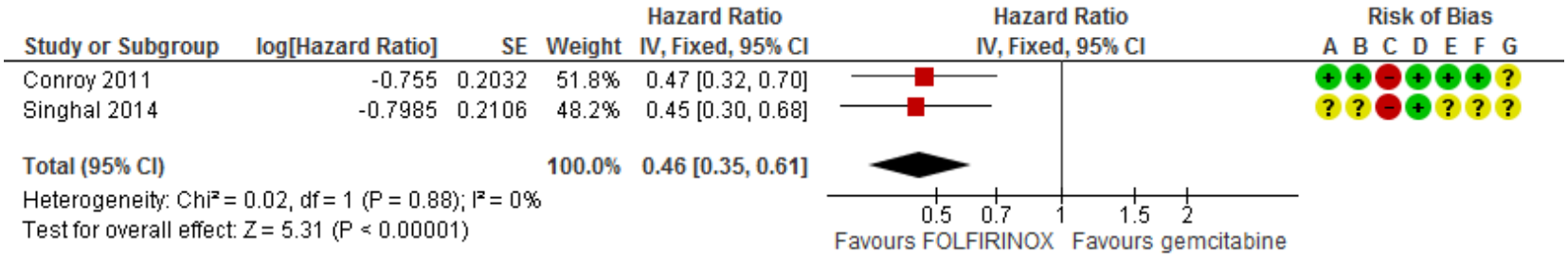
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Quality of life

Two studies (both comparing FOLFIRINOX with gemcitabine) addressed this outcome.[15, 16] In one study 31% of the patients in the FOLFIRINOX group had a definitive decrease in the Global Health Status score and QoL scale (EORTC-QLQ-C30) after six months compared to 66% in the gemcitabine group (HR=0.47; 95% CI 0.30 to 0.70). The other study (presented as a conference abstract) showed that at 6 months 29% of the FOLFIRINOX group had degradation of QoL (type of QoL instrument not mentioned) compared to 59% in the gemcitabine group (hazard ratio, 0.45; 95% CI, 0.29 to 0.68). The pooled HR for definitive degradation of QoL at six months was 0.46 (95% CI 0.35 to 0.61), favouring FOLFIRINOX (Figure 3).

Figure 3 – Forest plot and risk of bias plot for degradation of QoL of FOLFIRINOX vs gemcitabine



Risk of bias legend
(A) Random sequence generation (selection bias)
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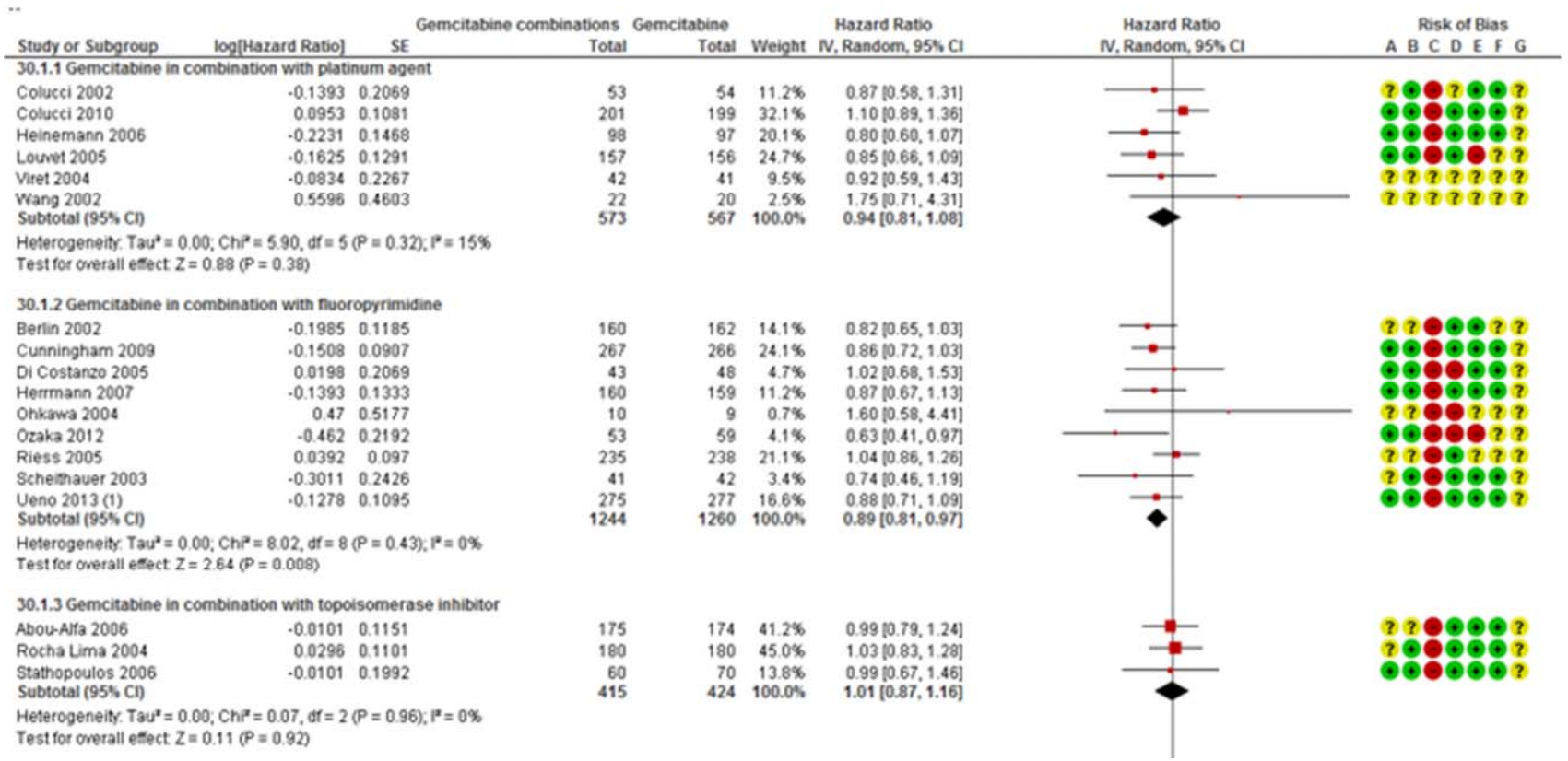
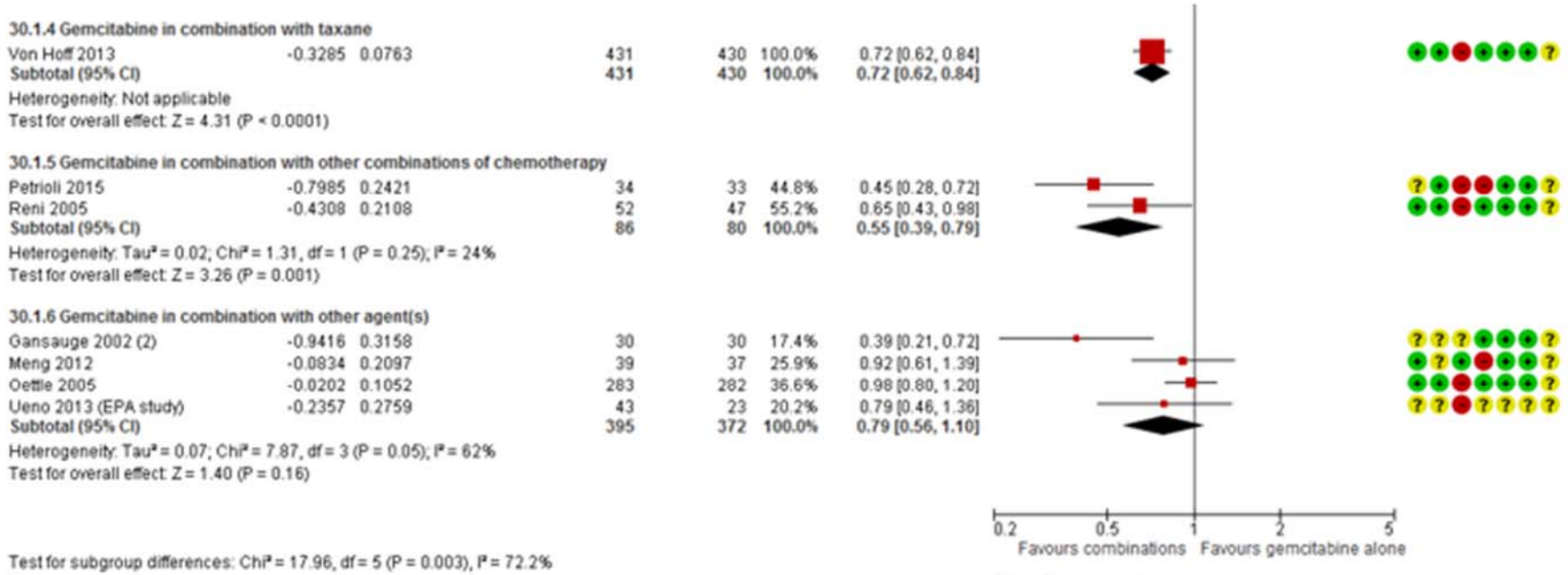
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

3.1.3 Gemcitabine combinations versus gemcitabine alone

Twenty-five studies in 6277 patients addressed OS (Figure 4). The test for subgroup differences was significant (P= 0.003) Therefore, the results are presented by subgroup. For QoL, a meta-analysis was not possible due to the variation in the presentation of the results.

Figure 4 – Forest plot and risk of bias plot for OS of gemcitabine in combination with another agent vs gemcitabine alone





Test for subgroup differences: Chi² = 17.96, df = 5 (P = 0.003), I² = 72.2%

Footnotes

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

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

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

3.1.3.1 Gemcitabine with platinum agent

Overall survival

Six studies (1140 patients) addressed OS.[19-24] Four included patients with LAPC or MPC and two included patients with stage III/IV PC. Cisplatin was the additional treatment in all studies except one, which used oxaliplatin. The HR was 0.94 (95% CI 0.81 to 1.08).

Quality of life

Three studies addressed QoL.[20, 21, 23] Two included patients with LAPC or MPC and one included patients with stage III/IV PC. Cisplatin was the additional treatment in all studies. No significant differences were found in global QoL scores (0.09 vs 6.20; P= 0.07; 1 study), the Spitzer index or pain intensity score (1 study) and the EORTC-QLQ C30 scores (1 study).

3.1.3.2 Gemcitabine with fluoropyrimidine

Overall survival

Nine studies (2504 patients) addressed OS.[25-33] Five included patients with LAPC or MPC, one MPC, one advanced PC, one inoperable or MPC and one unresectable PC. The additional treatments were 5-FU (3 studies), capecitabine (3 studies), oral tegafur (S1) (2 studies), tegafur-uracil (UFT) (1 study). The HR was 0.89 (95% CI 0.81 to 0.97).

Quality of life

Five studies addressed QoL.[26, 27, 32-34] No significant differences in QoL were found in two studies addressing capecitabine and 5-FU, respectively, in patients with LAPC or MPC. There was improvement in pain response and Karnofsky performance status, but not in weight gain in patients with MPC in the capecitabine arm (1 study; no statistical results presented) and there was statistically significant more improvement in QALYs in a study that addressed S1 in patients with LAPC or MPC (0.525 vs 0.401; P< 0.001). In the fifth study that addressed capecitabine in patients with inoperable or MPC, no statistically significant differences between the groups in QoL (linear-analogue self-assessment (LASA) indicators) were found over the whole observation period or at any of the assessment periods (1 study).

3.1.3.3 Gemcitabine with topoisomerase inhibitor

Overall survival

Three studies (839 patients) addressed OS.[35-37] These included patients with LAPC or MPC. Additional treatments were irinotecan (2) and exatecan. The HR was 1.01 (95% CI 0.87 to 1.16).

Quality of life

One study addressed QoL (FACT-Hep questionnaires) in patients with LAPC or MPC.[36] The additional treatment was irinotecan. No significant differences were observed.

3.1.3.4 Gemcitabine with taxane

Overall survival

One study (862 patients) addressed patients with MPC.[38] The additional treatment was nab-paclitaxel. The HR was 0.72 (95% CI 0.62 to 0.84).

Quality of life

No study assessed QoL.

3.1.3.5 Gemcitabine with other chemotherapy combinations

Overall survival

Two studies (166 patients) addressed this outcome.[39, 40] One study included patients with only MPC and one included patients with LAPC or MPC. The additional treatments were gemcitabine/oxaliplatin/capecitabine (GEMOXEL) and cisplatin/epirubicin/gemcitabine and 5-FU, respectively. The HR was 0.55 (95% CI 0.39 to 0.79).

Quality of life

The same two studies addressed also QoL.[39, 40] Global QoL was more improved in the GEMOXEL group at 2 and 4 months (1 study in patients with MPC). In the other study LAPC or MPC patients in the combination treatment group (cisplatin/epirubicin/gemcitabine and 5-FU) were more likely to have improved emotional functioning, overall QoL, cognitive measures, pain, fatigue, indigestion, dyspnoea, appetite loss and flatulence, but sexual function and body image were better in the gemcitabine alone group.

3.1.3.6 Gemcitabine with other agents

Overall survival

Four studies (767 patients) addressed various other combinations of gemcitabine with additional treatments.[41-44] This applied to the following patients and additional treatments:

- unresectable PC and ukrain (herbal medicine).[41]
- unresectable PC and huachansu (Chinese herbal medicine).[42]
- LAPC or MPC and pemetrexed (chemotherapy).[43]
- advanced PC and eicosapentaenoic acid (EPA) supplement.[44]

The overall HR was 0.79 (95% CI 0.56 to 1.10).

Quality of life

Two studies addressed QoL of various other combinations of gemcitabine and additional therapies.[42, 43] No significant differences in the FACT-G and MD Anderson Symptom Inventory questionnaire were found at eight weeks in a study that addressed huachansu as additional treatment in patients with unresectable PC. In another study advanced PC patients in the pemetrexed combination arm had lower pain scores, but patients in the gemcitabine alone group had lower financial difficulties and better physical and cognitive functioning.

3.1.4 Fluoropyrimidine combinations versus fluoropyrimidine alone

Overall survival

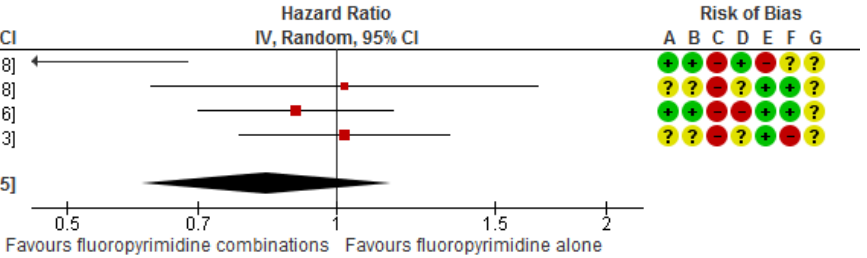
Four studies (491 patients) addressed this outcome.[45-48] One study applied to MPC, two to both LAPC and MPC and one to unresectable PC and measurable disease. Treatments (all vs 5-FU alone) were 5-FU plus oxaliplatin, bis-chloroethylnitrosurea, MMC and streptozocin. The HR was 0.84 (95% CI 0.61 to 1.15) (

Figure 5).

Figure 5 – Forest plot and risk of bias plot for OS of fluoropyrimidine in combination with another agent vs fluoropyrimidine alone

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

Heterogeneity: Tau² = 0.07; Chi² = 8.83, df = 3 (P = 0.03); I² = 66%
Test for overall effect: Z = 1.10 (P = 0.27)



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

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Quality of life

One study comparing infusional 5FU with MMC with 5-FU alone in patients with LAPC or MPC did not demonstrate a difference between the two groups in the EORTC-QLQ C30 questionnaire at baseline, 12 or 24 weeks.[47]

3.1.5 Radiation therapy or chemoradiation therapy

CRT was also part of the inclusion criteria of the included Cochrane review.[3] However, no studies were identified that addressed those interventions.

3.1.6 Re-resection vs best supportive care, including palliative care

Re-resection was not part of the Cochrane review. An extensive search did not yield any SR, RCT or comparative observational study that addressed re-resection in patients with recurrent or MPC. Many publications of uncontrolled series of patients were identified (seeTable 4). However, due to their high risk of bias (especially confounding by indication and selective publication) and the inability of comparing the results thereof directly with those of other interventions or no intervention, these types of studies were not part of this SR.

4 CONCLUSIONS, OTHER CONSIDERATIONS AND RECOMMENDATIONS

4.1 Conclusions

- In patients with unresectable or advanced PC a difference in OS or QoL between various types of anti-cancer therapy and BSC could neither be demonstrated nor refuted (low to very low level of evidence).
- There is evidence of moderate quality that compared to 5-FU, gemcitabine leads to better OS in patients with symptomatic advanced PC (moderate level of evidence). QoL was not assessed.
- There is evidence of high quality that compared to gemcitabine, FOLFIRINOX leads to better OS in patients with MPC (high level of evidence).
- There is evidence of moderate quality that compared to gemcitabine, FOLFIRINOX leads to better QoL in patients with MPC (moderate level of evidence).
- In patients with LAPC or MPC a difference in OS between various types of chemotherapy (CO-101 or ZD9331) and gemcitabine could neither be demonstrated nor refuted (low level of evidence). QoL was not assessed.
- There is evidence that compared to gemcitabine alone gemcitabine in combination with fluoropyrimidine (low level of evidence), oxaliplatin/capecitabine (GEMOXEL) or cisplatin/epirubicin/5-FU (low level of evidence) leads to better survival in patients with advanced PC.
- For patients with MPC gemcitabine in combination with taxane leads to better survival than gemcitabine alone (high level of evidence).
- In patients with advanced PC a difference in OS between gemcitabine in combination with platinum agent (low level of evidence), topoisomerase inhibitor (low level of evidence) or various types of other additional interventions (very low level of evidence) and gemcitabine alone could neither be demonstrated nor refuted.
- In patients with advanced PC a difference in QoL between gemcitabine combinations versus gemcitabine alone could neither be demonstrated nor refuted (very low level of evidence).
- In patients with unresectable PC, LAPC or MPC a difference in OS between fluoropyrimidine combinations versus fluoropyrimidine alone could neither be demonstrated nor refuted (very low level of evidence).In patients with LAPC or MPC a difference in QoL between fluoropyrimidine combinations versus fluoropyrimidine alone could neither be demonstrated nor refuted (very low level of evidence).
- No RCT or comparative observational study could be identified that adressed the effect CRT in patients with recurrent or MPC.
- No RCT or comparative observational study could be identified that adressed the effect of re-resection in patients with recurrent or MPC.

4.2 Other considerations

Factor	Comment
Balance between clinical benefits and harms	Based on the conclusions a statement was proposed that no difference in OS or QoL between various types of anti-cancer therapy and BSC could be expected. The GDG did not support such a recommendation because the chemotherapy regimens that were compared to BSC (5-FU + chloroethylcyclohexylnitrosurea (CCNU), cisplatin + 5-FU/leucovorin, 5-FU + doxorubicin + 5FU/doxorubicin and MMC and gemcitabine) were considered outdated. The selected publications did not show an advantage for OS. The Guideline Development Group (GDG) stated that since gemcitabine is more effective than 5-FU, OS with gemcitabine should be compared to BSC. Regarding QoL one study [11] showed significantly higher EORTC-QLQ-C30 scores after 1 month in favour of gemcitabine but not after 2-4 months and was in favour of BSC after 5-6 months. Therefore, the physician should inform patient with unresectable and advanced PC that no difference in OS or QoL between various types of anti-cancer therapy and BSC may be expected. The recommendation to treat patients with advanced PC with gemcitabine is based on the study by Burris.[14] The term 'fit patients' indicates patients with adequate performance status (ECOG 0-1 or WHO 0-1). In patients with poor performance status gemcitabine alone is mostly used. The GDG indicated that resection of metastasis can be considered in very selected cases and stressed that the term 'surgery' indicates curative resection, not partial ablation.
Quality of evidence	Moderate for recommendation1 , high for recommendation 2, and none available for recommendation 3
Costs (resource allocation)	Cost was not considered in this study
Patient preferences	Patient organisations were consulted in a Stakeholder meeting (see section 0) They underlined the importance of open communication and information on benefits and harms in adapted language. The GDG also stressed that in decision making regarding recurrent PC each patient needs to be discussed individually and potential benefits and risks need to be balanced carefully. Kom op tegen Kanker pointed out that better outcomes can be expected in more experienced centers. Patient organisations further underline the need to be allowed to seek a second opinion. Given the poor prognosis of PC the need for research need to be brought to public attention.

4.3 Recommendations

Recommendation	Level of Evidence	Strength of recommendation
1. If patients with advanced PC (LAPC or metastatic) are treated with chemotherapy, gemcitabine in monotherapy is to be preferred over 5-FU in monotherapy.	moderate	strong
2. If fit patients with MPC are treated with chemotherapy, combination therapy with gemcitabine and taxane, or the FOLFIRINOX combination are to be preferred over gemcitabine in monotherapy.	high	strong
3. Do not recommend re-resection in patients with recurrent or MPC.	NA	strong

5 APPENDIX

5.1 STUDY SELECTION

Figure 6 – Study flow of selection of SRs

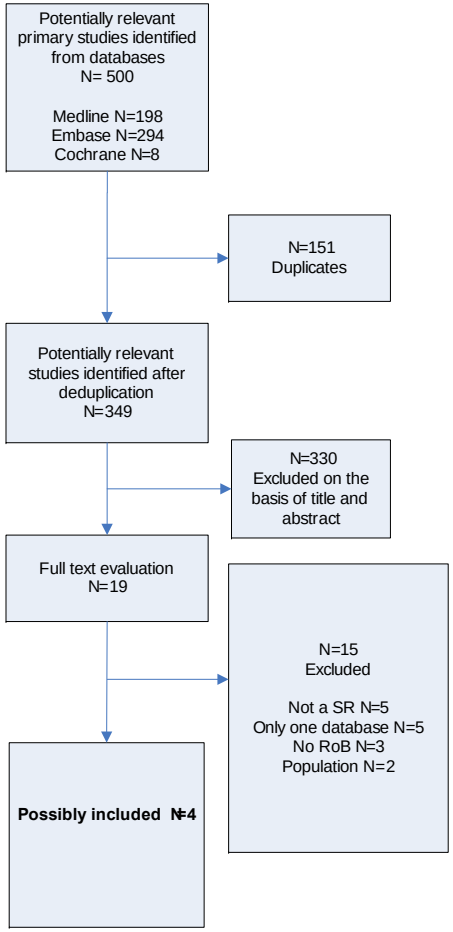


Figure 7 – Study flow of selection of primary studies regarding recurrent disease

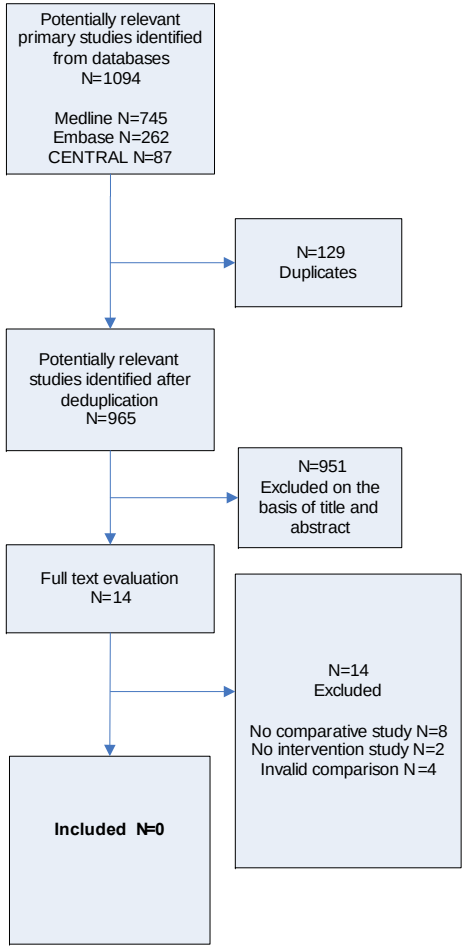


Table 3 – Excluded SRs (n= 15)

Reference	Reasons
Cannistra 2015[49]	Not a SR
Cao 2015[50]	Searched only PubMed
Collins 2015[51]	Not a SR
Gangl 2010[52]	Searched only PubMed. No RCTs or comparative observational studies identified
Gennatas 2009[53]	Not a SR
Gounaris 2010[54]	Not a SR
Heinemann 2008[55]	Searched only PubMed. Quality assessment not reported on study level
Hu 2011[56]	Searched only PubMed. No quality assessment
Michalsky 2009[57]	No quality assessment. No RCTs or comparative observational studies identified
Mössner 2010[58]	Not a SR; search PubMed only
Ruano-Ravina 2008[59]	Included only patients with LAPC
Sultana 2008[60]	Quality assessment not reported on study level
Tu 2015[61]	No quality assessment
Zhou 2014[62]	Treatment of cutaneous metastases
Zygogianni 2011[63]	Searched only PubMed. No quality assessment

Table 4 – Excluded primary studies: recurrent disease (n=14)

Reference	Reasons
Boone 2014[64]	Not a comparative study
Habermehl 2013[65]	Patients who were considered to be resectable were compared with those not judged to be resectable (not a fair comparison)
Hashimoto 2009[66]	Not an intervention study
Hashimoto 2014[67]	Not a comparative study
Lavu 2011[68]	Not a comparative study
Miyazaki 2014[69]	67 patients with isolated local recurrence; comparison re-resection of isolated local recurrence (n=11) vs 56 isolated local recurrences considered unresectable (not a fair comparison)
Nakamura 2014[70]	Not a comparative study
Shima 2015[71]	Not a comparative study
Strobel 2013[72]	Re-resection (n=41) vs unresectable (n=16) (not a fair comparison)
Suzuki 2015[73]	Re-resection (n=12) vs chemotherapy (n=6, of whom four refused surgery and two were considered not resectable) vs BSC (n=5: two were considered not resectable and three refused surgery). No fair comparisons.
Thomas 2012[74]	Re-resection (n=21) vs not reoperated (n=405). Of the re-resected patients, 7 had an isolated local recurrence. Those who were not operated, had liver metastases (amongst others) (not a fair comparison)
Wilkowski 2006[75]	Not a comparative study
Xue 2014[76]	Not an intervention study
Zhang 2012[77]	Not a comparative study

5.2 CRITICAL APPRAISAL

Table 5 – Methodological quality of the included SR (AMSTAR)

Systematic review	A priori study design	Duplicate study selection and data extraction	Compre-hensive literature search	Publica-tion status not used as inclusion	List of in- and excluded studies	Charac-teristics of included studies provided	Study quality assess-ed and docu-mented	Quality assess-ment used in conclus-ions	Appro-p-riate methods to combine findings	Likelihood of publica-tion bias assessed	Conflict of interest stated
Chin 2016[3]	+	+	+	+	+	+	+	+	+	+	+

5.3 EVIDENCE TABLES

Table 6 – Evidence table of the included SR regarding interventions for recurrent or MPC

Pharmacologic and radiotherapeutic interventions for advanced pancreatic cancer; Chin 2017[3]	
Methods	
• **Design**	Cochrane SR
• **Source of funding and competing interest**	The Garvan Institute of Medical Research, The Royal Australasian College of Physicians, National Health and Medical Research Council, Pancare Australia and Sydney Catalyst, Australia: PhD stipends top up for Venessa Chin (first author). Declaration of interest: none.
• **Search date**	September 2015 – Updated June 30, 2016
• **Searched databases**	MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), CANCERLIT (up to 2002), Cochrane Upper Gastrointestinal and Pancreatic Diseases Group Trials Register. Prospective trial registers: Australian and New Zealand Clinical Trials Registry; National Research Register; Medical Research Council; Clinicaltrials.gov; Current Controlled Trials; Trialscentral; Center Watch. Other resources: National Cancer Institute Physician Data Query; UK Co-ordinating Committee on Cancer Research. Reference lists from trials and review articles selected by electronic searching and published abstracts from pertinent conference proceedings were handsearched to identify further relevant trials.
• **Included study designs**	RCTs (both published and unpublished) in which one of the interventions was compared with either placebo, another intervention or BSC.
• **Number of included studies**	Before search update (June 30, 2016): 94 RCTs regarding 18,870 patients (applying to all interventions that were addressed). The search update did not result in any new studies regarding RQ3; one study was retrieved that addressed QoL results of an already included study.
• **Statistical analysis**	Inverse-variance weighting for survival outcomes (HRs) and continuous outcomes. Mantel-Haenszel method for dichotomous outcomes.

Pharmacologic and radiotherapeutic interventions for advanced pancreatic cancer; Chin 2017[3]	
Patient characteristics	
• **Eligibility criteria**	Advanced, LAPC, unresectable or recurrent pancreatic adenocarcinoma (confirmed by histological or cytological findings).
• **Exclusion criteria**	None.
• **Patient & disease characteristics**	*I. Anticancer therapy vs BSC (BSC)* Of four studies that addressed OS, three applied to unresectable PC and one to LAPC. Treatments: 5-FU + chloroethylcyclohexylnitrosurea (CCNU), cisplatin + 5-FU/leucovorin, 5-FU/doxorubicin and MMC and gemcitabine. Of three studies that addressed QoL, one applied to patients with inoperable PC, one to patients with non-curable pancreatic or biliary tract cancer and one to LAPC. Treatments: 5-FU + CCNU + vincristine, 5-FU + leucovorin with or without etoposide and gemcitabine. *II. Various types of chemotherapy vs gemcitabine* One study applied to patients with advanced, symptomatic PC with stabilised pain, three studies to MPC and one to both LAPC and MPC. Treatments: 5-FU (one study), FOLFIRINOX (2 studies), CO-101 (a lipid drug conjugate of gemcitabine; 1 study) and ZD9331 (a non-polyglutamatable thymidylate synthase inhibitor; 1 study). *III. Gemcitabine combinations vs gemcitabine alone* **Gemcitabine with platinum agent** Of the six studies that addressed OS, four included patients with LAPC or MPC and two included patients with stage III/IV PC. Cisplatin was the additional treatment in all studies except one, which used oxaliplatin. Of the three studies that addressed QoL, two included patients with LAPC or MPC and one included patients with stage III/IV PC. Cisplatin was the additional treatment in all studies. **Gemcitabine with fluoropyrimidine** Of the nine studies that addressed OS, five included patients with LAPC or MPC, one MPC, one advanced PC, one inoperable or MPC and one unresectable PC. Additional treatments: 5-FU (3 studies), capecitabine (3 studies), oral tegafur (S1) (2 studies), tegafur-uracil (UFT) (1 study). Of the five studies that addressed QoL, three included patients with LAPC or MPC, one MPC and one inoperable or MPC. Additional treatments: 5-FU (1 study), capecitabine (3 studies) and S1 (1 study). **Gemcitabine with topoisomerase inhibitor** All three studies that addressed OS included patients with LAPC or MPC. Additional treatments: irinotecan (2 studies) and exatecan. One study addressed QoL in patients with LAPC or MPC. Additional treatment: irinotecan. **Gemcitabine with taxane** One study addressed OS in patients with MPC. Additional treatment: nab-paclitaxel. No study assessed QoL.

Pharmacologic and radiotherapeutic interventions for advanced pancreatic cancer; Chin 2017[3]	
	Gemcitabine with other types of chemotherapy combinations Two studies addressed both OS and QoL in patients with MPC and in patients with LAPC or MPC. Additional treatments were gemcitabine/oxaliplatin/capecitabine (GEMOXEL) and cisplatin/epirubicin/gemcitabine and 5-FU, respectively. **Gemcitabine with other agents** Four studies addressed OS. Additional treatments: ukrain (herbal medicine) in patients with unresectable PC huachansu (Chinese herbal medicine) in patients with unresectable PC pemetrexed in patients with LAPC or MPC eicosapentaenoic acid (EPA) supplement in patients with advanced PC Two studies addressed QOL huachansu (Chinese herbal medicine) in patients with unresectable PC eicosapentaenoic acid (EPA) supplement in patients with advanced PC *IV. Fluoropyrimidine combinations vs fluoropyrimidine alone* One study applied to MPC, two to both LAPC and MPC and one to unresectable PC and measurable disease. Treatments (vs 5-FU alone): 5-FU plus oxaliplatin, bis-chloroethylnitrosurea, MMC and streptozocin.
Interventions	
• **Intervention groups**	Chemotherapy (any cytotoxic or anti-neoplastic drug treatment), radiotherapy (cobalt source, megavoltage external beam radiotherapy, stereotactic body radiation therapy or brachytherapy), combined CRT In addition: biological therapies (antibodies, signal transduction inhibitors, growth factors and vaccines).
• **Control groups**	BSC (any treatment other than chemotherapy that may include symptom control by radiotherapy, palliative surgery, biliary stent insertion, analgesia, blood transfusion or psychological or social support), chemotherapy, radiotherapy or CRT.
Results	
• **Overall survival**	*I. Anticancer therapy vs BSC (4 studies; 298 patients)* HR= 1.08 (95% CI 0.88 to 1.33) Analysis without study in LAPC patients only (gemcitabine): HR 1.10 (95% CI 0.86 to 1.39) *II. Various types of chemotherapy vs gemcitabine (5 studies; 1200 patients)* Test for subgroup differences: P < 0.0001 *Subgroup analyses* 5-FU vs gemcitabine (1 study; 126 patients) : HR= 1.69 (95% CI 1.26 to 2.27) FOLFIRINOX vs gemcitabine (2 studies; 652 patients): HR= 0.51 (95% CI 0.43 to 0.60) CO-101 or ZD9331 vs gemcitabine (2 studies; 422 patients): HR= 1.05 (95% CI 0.85 to 1.30)

Pharmacologic and radiotherapeutic interventions for advanced pancreatic cancer; Chin 2017[3]

	III. Gemcitabine combinations versus gemcitabine alone (25 studies; 6277 patients) Test for subgroup differences: P= 0.01 *Subgroup analyses* Gemcitabine with platinum agent (6 studies; 1140 patients): HR= 0.94 (95% CI 0.81 to 1.08) Gemcitabine with fluoropyrimidine (9 studies; 2504 patients): HR= 0.89 (95% CI 0.81 to 0.97) Gemcitabine with topoisomerase inhibitor (3 studies; 839 patients): HR= 1.01 (95% CI 0.87 to 1.16) Gemcitabine with taxane (1 study; 862 patients): HR= 0.72 (95% CI 0.62 to 0.84) Gemcitabine with other chemotherapy combinations (2 studies; 166 patients): HR= 0.55 (95% CI 0.39 to 0.79) Gemcitabine with other agents (4 studies; 767 patients): HR= 0.79 (95% CI 0.56 to 1.10). *IV. Fluoropyrimidine combinations versus fluoropyrimidine alone (4 studies; 491 patients)* HR= 0.84 (95% CI 0.61 to 1.15)
• **Quality of life**	*I. Anticancer therapy vs BSC (2 studies)* 1. No significant differences in Karnofsky Performance Status (1 study) 2. EORTC-QLQ-C30 scores favoured anticancer treatment group in one study (high rate of drop outs) 3. After 1 month: EORTC-QLQ-C30 score significantly higher after gemcitabine than in BSC group (1 study; P= 0.028) After 2-4 months: no significant differences in EORTC-QLQ-C30 (1 study; P> 0.05) After 5-6 months: significantly higher EORTC-QLQ-C30 scores after BSC compared with gemcitabine (physical and role functioning and global health; P= 0.010 and 0.0003) *II. FOLFIRINOX vs gemcitabine (2 studies*) *Study 1* EORTC-QLQ-C30: decrease in Global health Status and QOL scale at 3 months: 17% vs 31% EORTC-QLQ-C30: decrease in Global health Status and QoL scale at 6 months: 31% vs 66% (HR= 0.47; 95% CI 0.30 to 0.70) Median time to definitive deterioration: not reached vs 5.7 months *Study 2 (conference abstract)* The other study showed that at 6 months 29% of the FOLFIRINOX group had degradation of QOL compared to 59% in the gemcitabine group. *Pooled HR for definitive degradation of QoL at six months*: 0.46 (95% CI 0.35 to 0.61) *III. Gemcitabine combinations versus gemcitabine alone* *Gemcitabine with platinum (3 studies)* No significant differences in global QOL scores (0.09 vs 6.20; P= 0.07; 1 study) No difference in the Spitzer index or pain intensity score (1 study) No difference in the EORTC-QLQ-C30 scores (1 study)

Pharmacologic and radiotherapeutic interventions for advanced pancreatic cancer; Chin 2017[3]	
	Gemcitabine with 5-FU (5 studies) No statistically significant differences in QOL (2 studies) Improvement in pain response and Karnofsky performance status, but not weight gain in the combination arm (1 study) Statistically significant improvement in QALYs (0.525 vs 0.401; P< 0.001; 1 study) No statistically significant differences in QOL (linear-analogue self-assessment (LASA) indicators) over the whole observation period or at any of the assessment periods (1 study). *Gemcitabine with topoisomerase inhibitor (1 study)* No significant differences (FACT-Hep questionnaires) *Gemcitabine with taxane* No study assessed QoL. *Gemcitabine with other chemotherapy combinations (2 studies)* Global QOL was more improved in the GEMOXEL group at 2 and 4 months (1 study) Patients in the combination treatment group (cisplatin/epirubicin/gemcitabine and 5-FU) more likely to have improved emotional functioning, overall QOL, cognitive measures, pain, fatigue, indigestion, dyspnoea, appetite loss and flatulence; sexual function and body image were better in the gemcitabine alone group (1 study) *Gemcitabine with other agents (2 studies)* No significant differences (FACT-G and MD Anderson Symptom Inventory questionnaire) at 8 weeks (1 study – huachansu) Patients in the pemetrexed combination arm had lower pain scores; patients in the gemcitabine alone group had lower financial difficulties, better physical and cognitive functioning (1 study) *IV. Fluoropyrimidine combinations versus fluoropyrimidine alone (1 study)* No statistical differences between the groups for the EORTC-QLQ-C30 scores.
Limitations and other comments	
• **Limitations**	The review fulfilled all AMSTAR items (low risk of bias).

5.4 GRADE evidence profiles

Question: Anti-cancer therapy compared to BSC for advanced PC

Bibliography: Chin V, Nagrial A, Sjoquist K, O'Connor CA, Chantrill L, Biankin A, Yip D. Pharmacologic and radiotherapeutic interventions for advanced pancreatic cancer. Cochrane Database of SRs 2017 *(under review)*[3].

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**anti-cancer therapy**	**best supportive care**	**Relative (95% CI)**	**Absolute (95% CI)**		
Overall survival												
4	randomised trials	not serious	not serious	serious [1]	serious [2]	none	-/153	-/145	**HR 1.08** (0.88 to 1.33)		⊕⊕◯◯ LOW	CRITICAL
Quality of life (assessed with: various instruments)												
3	randomised trials	serious [3]	serious [4]	serious [1]	serious [5]	none	No significant differences between the groups with respect to the Karnofsky Performance Status in one study. The EORTC-QLQ-C30 scores favoured the anticancer treatment group in one study (with a high rate of drop outs). One study (in LAPC patients) reported significantly higher EORTC-QLQ-C30 scores after 1 month in favour of gemcitabine (P= 0.028), no significant differences between the groups after 2-4 months (P> 0.05) and significantly higher scores in favour of BSC for the physical and role functioning (P= 0.010) and global health scales (P= 0.0003) after 5-6 months.				⊕◯◯◯ VERY LOW	CRITICAL

***CI:** Confidence interval; **HR:** Hazard Ratio*

1. Different interventions
2. Confidence interval includes both benefit and harm
3. No blinding of participants (blinding not possible)
4. Results in opposite directions
5. Pooling not possible

Question: Various types of chemotherapy compared to gemcitabine for advanced PC

Bibliography: Chin V, Nagrial A, Sjoquist K, O'Connor CA, Chantrill L, Biankin A, Yip D. Pharmacologic and radiotherapeutic interventions for advanced pancreatic cancer. Cochrane Database of SRs 2017 *(under review)*[3].

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**various types of chemotherapy**	**gemcitabine**	**Relative (95% CI)**	**Absolute (95% CI)**		
Overall survival - 5-FU												
1	randomised trials	not serious	not serious	not serious	serious [1]	none	-/63	-/63	**HR 1.69** (1.26 to 2.27)		⊕⊕⊕◯ MODERATE	CRITICAL
Overall survival - FOLFIRINOX												
2	randomised trials	not serious	not serious	not serious	not serious	none	-/326	-/326	**HR 0.51** (0.43 to 0.60)		⊕⊕⊕⊕ HIGH	CRITICAL
Overall survival - CO-101 or ZD9331												
2	randomised trials	not serious	not serious	serious [2]	serious [3]	none	-/212	-/210	**HR 1.05** (0.85 to 1.30)		⊕⊕◯◯ LOW	CRITICAL
Degradation of QoL at six months (FOLFIRINOX)												
2	randomised trials	serious [4]	not serious	not serious	not serious	none			**HR 0.46** (0.35 to 0.61)		⊕⊕⊕◯ MODERATE	CRITICAL

***CI:** Confidence interval; **HR:** Hazard Ratio*
OIS not reached

1. LAPC included in one study; different interventions
2. Confidence interval includes both benefit and harm
3. No blinding of participants

Question: Gemcitabine combinations compared to gemcitabine alone for advanced PC

Bibliography: Chin V, Nagrial A, Sjoquist K, O'Connor CA, Chantrill L, Biankin A, Yip D. Pharmacologic and radiotherapeutic interventions for advanced pancreatic cancer. Cochrane Database of SRs 2017 *(under review)*[3].

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**gemcitabine combinations**	**gemcitabine alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Overall survival - Gemcitabine in combination with platinum agent												
6	randomised trials	not serious [1]	not serious	serious [2]	serious [3]	none	-/573	-/567	**HR 0.94** (0.81 to 1.08)		⊕⊕◯◯ LOW	CRITICAL
Quality of life - Gemcitabine in combination with platinum agent												
3	randomised trials	serious [4]	not serious	serious [2]	serious [5]	none	No significant differences in global QoL scores (0.09 vs 6.20; P= 0.07; 1 study), the Spitzer index or pain intensity score (1 study) and the EORTC-QLQ C30 scores (1 study)				⊕◯◯◯ VERY LOW	CRITICAL
Overall survival - Gemcitabine in combination with fluoropyrimidine												
9	randomised trials	not serious [1]	not serious	serious [2]	serious [6]	none	-/1244	-/1260	**HR 0.89** (0.81 to 0.97)		⊕⊕◯◯ LOW	CRITICAL
Quality of life - Gemcitabine in combination with fluoropyrimidine												

5	randomised trials	serious [4]	not serious	serious [2]	serious [5]	none	No significant differences in QOL in two studies. Improvement in pain response and Karnofsky performance status, but not weight gain in the combination arm (1 study; no statistical results presented). Statistically significant more improvement in QALYs in one study (0.525 vs 0.401; P< 0.001). No statistically significant differences between the groups in QOL (linear-analogue self-assessment (LASA) indicators) over the whole observation period or at any of the assessment periods (1 study).				⊕◯◯◯ VERY LOW	CRITICAL
Overall survival - Gemcitabine in combination with topoisomerase inhibitor												
3	randomised trials	not serious	not serious	serious [7]	serious [3]	none	-/415	-/424	**HR 1.01** (0.87 to 1.16)		⊕⊕◯◯ LOW	CRITICAL
Quality of life - Gemcitabine in combination with topoisomerase inhibitor												
1	randomised trials	serious [4]	not serious	serious [8]	serious [9]	none	No significant differences were observed for QoL (FACT-Hep questionnaires)				⊕◯◯◯ VERY LOW	CRITICAL
Overall survival - Gemcitabine in combination with taxane												
1	randomised trials	not serious	not serious	not serious	not serious	none	-/431	-/430	**HR 0.72** (0.62 to 0.84)		⊕⊕⊕⊕ HIGH	CRITICAL
Quality of life - Gemcitabine in combination with taxane - not measured												
-	-	-	-	-	-	-					-	CRITICAL
Overall survival - Gemcitabine in combination with other chemotherapeutic agent(s)												
2	randomised trials	not serious	not serious	serious [10]	serious [11]	none	-/86	-/80	**HR 0.55** (0.39 to 0.79)		⊕⊕◯◯ LOW	CRITICAL

Quality of life - Gemcitabine in combination with other chemotherapeutic agent(s)												
2	randomised trials	serious [4]	serious [12]	serious [10]	serious [5]	none	Improved global QOL in the GEMOXEL group at 2 and 4 months (1 study). Patients in the combination treatment group (cisplatin/epirubicin/gemcitabine and 5-FU) more likely to have improved emotional functioning, overall QOL, cognitive measures, pain, fatigue, indigestion, dyspnoea, appetite loss and flatulence; sexual function and body image better in the gemcitabine alone group (1 study).				⊕◯◯◯ VERY LOW	CRITICAL
Overall survival - Gemcitabine in combination with other agent(s)												
4	randomised trials	not serious	serious [13]	serious [14]	serious [3]	none	-/395	-/372	**HR 0.79** (0.56 to 1.10)		⊕◯◯◯ VERY LOW	CRITICAL
Quality of life - Gemcitabine in combination with other agent(s)												
2	randomised trials	serious [4]	serious [12]	serious [14]	serious [5]	none	No significant differences in the FACT-G and MD Anderson Symptom Inventory questionnaire at 8 weeks (1 study; huachansu as additional treatment). Lower pain scores in the pemetrexed combination arm; lower financial difficulties and better physical and cognitive functioning in the gemcitabine alone group (1 study).				⊕◯◯◯ VERY LOW	CRITICAL

***CI:** Confidence interval; **HR:** Hazard Ratio*

1. Unclear risk of bias for many items. No downgrading.
2. Majority of studies also included patients with LAPC
3. Confidence interval includes both benefit and harm
4. High risk of performance and detection bias
5. Pooling not possible
6. Confidence interval includes clinically irrelevant benefit
7. All studies included also patients with LAPC
8. Study included also patients with LAPC
9. No significant differences (includes both beneficial and harmful effect)
10. One study also included patients with LAPC
11. OIS not reached
12. No clear trend in QoL scores
13. Significant heterogeneity
14. Different interventions

Question: Fluoropyrimidine combinations compared to fluoropyrimidine alone for advanced PC

Bibliography: Chin V, Nagrial A, Sjoquist K, O'Connor CA, Chantrill L, Biankin A, Yip D. Pharmacologic and radiotherapeutic interventions for advanced pancreatic cancer. Cochrane Database of SRs 2017 *(under review)*[3].

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**fluoropyrimidine combinations**	**fluoropyrimidine alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Overall survival												
4	randomised trials	serious [1]	serious [2]	serious [3]	serious [4]	none	-/250	-/241	**HR 0.84** (0.61 to 1.15)		⊕◯◯◯ VERY LOW	CRITICAL
Quality of life												
1	randomised trials	serious [5]	not serious	serious [6]	serious [7]	none	No significant differences for EORTC-QLQ C30 scores at 12 and 24 weeks.				⊕◯◯◯ VERY LOW	CRITICAL

CI: *Confidence interval;* ***HR:*** *Hazard Ratio*

1. High risk of attrition bias (1 study) and selective reporting (1 study)
2. Significant heterogeneity
3. Two studies included also patients with LAPC
4. Confidence interval includes both benefit and harm
5. High risk of performance and detection bias
6. Study included patients with LAPC
7. No significant differences (includes both beneficial and harmful effect)

Question: Re-resection compared to best supportive or palliative care for advanced PC

Bibliography: Chin V, Nagrial A, Sjoquist K, O'Connor CA, Chantrill L, Biankin A, Yip D. Pharmacologic and radiotherapeutic interventions for advanced pancreatic cancer. Cochrane Database of SRs 2017 *(under review)*[3].

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**re-resection**	**best supportive or palliative care**	**Relative (95% CI)**	**Absolute (95% CI)**		
Overall survival - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

5.5 Stakeholder meeting

The Stakeholder meeting was held on February 20, 2017. Recommendations were scored (1-5) and discussed (Table 7). Patient organisations were consulted (Table 8).

Table 7 – Scoring of recommendations by Stakeholders

Recurrence								
Recommendations	**Level of Evidence**	**Strength of recommendation**						
1. If patients with advanced pancreatic cancer (LAPC or metastatic) are treated with chemotherapy, gemcitabine in monotherapy is to be preferred over 5-FU in monotherapy.	moderate	strong	5	5	4	5	5	
2. If fit patients with metastatic PC are treated with chemotherapy, combination therapy with gemcitabine and nab-paclitaxel, or the FOLFIRINOX combination are to be preferred over gemcitabine in	high	strong	5	5	5	5	5	
3. Do not recommend re-resection in patients with recurrent or metastatic PC.	NA	strong	5	5	4	5	2	**Some individual selected patients with recurrence or oligometastatic disease can still be considered for surgery in referral centres-only selected cases**

Table 8 – Opinion of patient organisation

Voor Kom op tegen Kanker is het belangrijk dat de patiënt op elk ogenblik voldoende geïnformeerd wordt over zijn medische toestand, dit in een voor de patiënt begrijpelijke taal. Hierbij ook informatie over de behandelingsmogelijkheden met de voor- en nadelen. Ook dat de clinici rekening houden met de waarden en de voorkeuren van de patiënt. (p 21 van part 1, ook op p 30) Alsook dat hij of zij voldoende pychosociale ondersteuning krijgen alsook hun naasten. Er moet ook rekening gehouden worden met de kwaliteit van leven van de patiënt (komt niet terug in de uitgevoerde studies die geselecteerd werden, werd toen niet onderzocht).

Voor zeldzame tumoren zoals pancreaskanker er één is, is gebleken uit vroegere KCE studie dat de resultaten van de behandeling beter zijn in een ziekenhuis die meer dan 20 pancreasoperaties per jaar uitvoeren. Als Kom op tegen Kanker pleiten we voor expertise ziekenhuizen die preferentieel deze pathologie behandelen. (zie p 20 van part 1.) Dit was niet weerhouden vermits dit eerder een zaak is van de organisatie van zorg dan van good clinical practice guidelines.

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