National Institute for Health and Care Excellence

Version 1.0

Pancreatic Cancer in adults:

diagnosis and management

Appendix I

GRADE tables

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Draft for Consultation

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

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

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

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 All NICE guidance is subject to regular review and may be updated or withdrawn.

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Not applicable for this review.

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Not applicable for this review.

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Not applicable for this review.

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Not applicable for this review.

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Not applicable for this review.

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Not applicable for this review.

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Not applicable for this review.

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I.8.1 NCPB versus medical management alone

Table 1: Full GRADE profile for neurolytic celiac plexus blockade versus medical management alone in adults with pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NCPB versus medical management (MM)		Relative (95% CI)	Absolute		
Overall survival (follow-up 6 months)												
1[29]	randomised trials	no serious	no serious	no serious indirectness	serious[24]	none	50	50	HR 0.80 (0.50-1.28)	Median survival for patients with stage III disease was 5.5 months for NCPB and 6.1 months for analgesic therapy. For patients with stage IV disease, the median survival was 2.9 months for	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NCPB versus medical management (MM)		Relative (95% CI)	Absolute		
										NCPB and 3.4 months for analgesic therapy.		
Reduction in opioid medication: Opioid use at 2 weeks (follow-up 2 weeks; Better indicated by lower values)												
2[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	no serious imprecision	none	39	37	-	MD 64.52 lower (99.45 to 29.59 lower)	LOW	CRITICAL
Reduction in opioid medication: Opioid use at 4 weeks (Better indicated by lower values)												
4[4]	randomised trials	serious	serious[3]	no serious indirectness	no serious imprecision	none	60	60	-	MD 51.07 lower (82.71 to 19.43 lower)	LOW	CRITICAL
Reduction in opioid medication: Opioid use the day before to death (Better indicated by lower values)												
4[4]	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	57	54	-	MD 48.52 lower (68.82 to 28.22 lower)	LOW	CRITICAL
Reduction in opioid medication: Percentage change in analgesic medications use and 3 months - NSAIDs (Better indicated by lower values)												
1[6]	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	68	32	-	MD 54.6 lower (54.82 to	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NCPB versus medical management (MM)		Relative (95% CI)	Absolute		
										54.38 lower)		
Reduction in opioid medication: Percentage change in analgesic medications use and 3 months - Morphine (Better indicated by lower values)												
1[6]	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	68	32	-	MD 76.6 lower (76.8 to 76.4 lower)	MODERATE	CRITICAL
Reduction in opioid medication: Percentage change in analgesic medications use and 3 months - Oxycodone (Better indicated by lower values)												
1[6]	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	68	32	-	MD 68.4 lower (68.7 to 68.1 lower)	MODERATE	CRITICAL
Reduction in opioid medication: Absolute change in morphine use at 1 month (Better indicated by lower values)												
1[6]	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	very serious[9]	none	49	49	-	MD 1 lower (48.5 lower to 46.5 higher)	VERY LOW	CRITICAL
Reduction in opioid medication: Absolute change in morphine use at 3 months (Better indicated by lower values)												
1[10]	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	very serious[9]	none	49	49	-	MD 50 lower (118.52 lower to	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NCPB versus medical management (MM)		Relative (95% CI)	Absolute		
										18.52 higher)		
Pain Relief/ improved analgesia: Pain scores at 2 weeks (Better indicated by lower values)												
3[11]	randomised trials	serious[2]	serious[12]	no serious indirectness	no serious imprecision	none	53	56	-	SMD 0.34 lower (1.09 lower to 0.4 higher)	LOW	CRITICAL
Pain Relief/ improved analgesia: Pain scores at 4 weeks (Better indicated by lower values)												
4[13]	randomised trials	serious[14]	no serious inconsistency	no serious indirectness	no serious imprecision	none	88	85	-	MD 0.43 lower (0.73 to 0.14 lower)	MODERATE	CRITICAL
Pain Relief/ improved analgesia: Pain scores at 8 weeks (Better indicated by lower values)												
6[10,13,15]	randomised trials	serious[14]	no serious inconsistency	serious[9]	no serious imprecision	none	141	138	-	SMD 1.09 lower (2.33 lower to 0.15 higher)	LOW	CRITICAL
Patients reporting effective pain management - 2 weeks												
1[15]	randomised trials	serious[16]	no serious inconsistency	serious[17]	very serious[18]	none	5/14 (35.7%)	6/19 (31.6%)	RR 1.13 (0.36 to 2.23)	41 more per 1000 (from 202 fewer to 388 more)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NCPB versus medical management (MM)		Relative (95% CI)	Absolute		
Patients reporting effective pain management - 8 weeks												
1[15]	randomised trials	serious[16]	no serious inconsistency	serious[17]	very serious[18]	none	5/9 (55.6%)	5/12 (41.7%)	RR 1.33 (0.44 to 2.1)	138 more per 1000 (from 233 fewer to 458 more)	VERY LOW	CRITICAL
Absolute Change in Pain score at 1 and 3 months - 1 Month (Better indicated by lower values)												
1[10]	randomised trials	serious[19]	no serious inconsistency	no serious indirectness	no serious imprecision	none	49	49	-	MD 1 lower (1.73 to 0.27 lower)	MODERATE	CRITCAL
Absolute Change in Pain score at 1 and 3 months - 3 months (Better indicated by lower values)												
1[10]	randomised trials	serious[19]	no serious inconsistency	no serious indirectness	no serious imprecision	none	49	49	-	MD 2.3 lower (3.09 to 1.51 lower)	MODERATE	CRITICAL
Adverse effects: constipation												
6[20]	randomised trials	serious[21]	no serious inconsistency	no serious indirectness	no serious imprecision	none	16/81 (19.8%)	42/80 (52.5%)	RR 0.38 (0.25 to 0.59)	325 fewer per 1000 (from 215 fewer to 394 fewer)	MODERATE	CRITICAL
Adverse effects: diarrhoea												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NCPB versus medical management (MM)		Relative (95% CI)	Absolute		
4[22]	randomised trials	serious[23]	no serious inconsistency	no serious indirectness	serious[24]	none	9/61 (14.8%)	2/60 (3.3%)	RR 3.25 (0.95 to 11.13)	75 more per 1000 (from 2 fewer to 338 more)	LOW	CRITICAL
QOL scores at 1 month - Appetite (Better indicated by lower values)												
1[25]	randomised trials	serious[26]	no serious inconsistency	no serious indirectness	very serious[18]	none	29	27	-	MD 0.3 higher (0.57 lower to 1.17 higher)	VERY LOW	CRITICAL
QOL scores at 1 month - Sleep (Better indicated by lower values)												
1[25]	randomised trials	serious[26]	no serious inconsistency	no serious indirectness	very serious[18]	none	29	27	-	MD 0.5 higher (0.55 lower to 1.55 higher)	VERY LOW	CRITICAL
QOL scores at 1 month - communication (Better indicated by lower values)												
1[25]	randomised trials	serious[26]	no serious inconsistency	no serious indirectness	serious[24]	none	29	27	-	MD 1.1 lower (2.27 lower to 0.07 higher)	LOW	CRITICAL
QOL scores at 3 months - Appetite (Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NCPB versus medical management (MM)		Relative (95% CI)	Absolute		
1[25]	randomised trials	serious[25]	no serious inconsistency	no serious indirectness	very serious[18]	none	29	27	-	MD 0.3 lower (1.48 lower to 0.88 higher)	VERY LOW	CRITICAL
QOL scores at 3 months - Sleep (Better indicated by lower values)												
1[25]	randomised trials	serious[26]	no serious inconsistency	no serious indirectness	very serious[18]	none	29	27	-	MD 0.2 higher (1 lower to 1.4 higher)	VERY LOW	CRITICAL
QOL scores at 3 months - Communication (Better indicated by lower values)												
1[25]	randomised trials	serious[26]	no serious inconsistency	no serious indirectness	very serious[18]	none	29	27	-	MD 0.4 higher (0.65 lower to 1.45 higher)	VERY LOW	CRITICAL
QOL scores at 3 months - Physical function (Better indicated by lower values)												
1[6]	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	68	32	-	MD 11.6 higher (8.26 to 14.94 higher)	MODERATE	CRITICAL
QOL scores at 3 months - Role function (Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NCPB versus medical management (MM)		Relative (95% CI)	Absolute		
1[6]	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	very serious[18]	none	68	32	-	MD 1.6 higher (1.77 lower to 4.97 higher)	VERY LOW	CRITICAL
QOL scores at 3 months - Emotional function (Better indicated by lower values)												
1[6]	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	68	32	-	MD 18 higher (14.53 to 21.47 higher)	MODERATE	CRITICAL
QOL scores at 3 months - Cognitive function (Better indicated by lower values)												
1[6]	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	very serious[18]	none	68	32	-	MD 2.9 higher (3.76 lower to 9.56 higher)	VERY LOW	CRITICAL
QOL scores at 3 months - Social function (Better indicated by lower values)												
1[6]	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	very serious[18]	none	68	32	-	MD 1 higher (3.57 lower to 5.57 higher)	VERY LOW	CRITICAL
QOL scores - Digestive Disease questionnaire-15: 1 month (Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NCPB versus medical management (MM)		Relative (95% CI)	Absolute		
1[10]	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	serious[24]	none	49	49	-	MD 8 higher (0.07 to 15.93 higher)[27]	LOW	CRITICAL
QOL scores - Digestive Disease questionnaire-15: 3 months (Better indicated by lower values)												
1[10]	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	serious[24]	none	49	49	-	MD 1 higher (9.73 lower to 11.73 higher)[27]		CRITICAL
QOL scores – Global quality at 3 months (Better indicated by lower values)												
1[6]	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	68	32	-	MD 14.3 higher (14.1 to 14.5 higher)[28]	LOW	CRITICAL
QOL scores – Symptom at 3 months - Fatigue (Better indicated by lower values)												
1[6]	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	68	32	-	MD 16.7 higher (11.97 to 21.43 higher)[28]	LOW	CRITICAL
QOL scores – Symptom at 3 months - Nausea/vomiting (Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NCPB versus medical management (MM)		Relative (95% CI)	Absolute		
1[6]	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	very serious[18]	none	68	32	-	MD 1.6 higher (2.59 lower to 5.79 higher)[28]	VERY LOW	CRITICAL
QOL scores – Symptom at 3 months - Pain (Better indicated by lower values)												
1[6]	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	68	32	-	MD 33.9 lower (38.64 to 29.16 lower)[28]	LOW	CRITICAL
QOL scores – Symptom at 3 months - Dyspnea (Better indicated by lower values)												
1[6]	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	very serious[18]	none	68	32	-	MD 0.3 higher (7.15 lower to 7.75 higher)[28]	VERY LOW	CRITICAL
QOL scores – Symptom at 3 months - Insomnia (Better indicated by lower values)												
1[6]	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	serious[18]	none	68	32	-	MD 40.9 lower (46.6 to 35.2 lower)[28]	VERY LOW	CRITICAL
QOL scores – Symptom at 3 months - Appetite loss (Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NCPB versus medical management (MM)**		**Relative (95% CI)**	**Absolute**		
1[6]	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	68	32	-	MD 28.8 lower (35.28 to 22.32 lower)[28]	LOW	CRITICAL
QOL scores – Symptom at 3 months - Constipation (Better indicated by lower values)												
1[6]	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	very serious[18]	none	68	32	-	MD 1.2 higher (7.12 lower to 9.52 higher)[28]	VERY LOW	CRITICAL
QOL scores – Symptom at 3 months - Financial difficulties (Better indicated by lower values)												
1[6]	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	very serious[18]	none	68	32	-	MD 1.1 lower (3.03 lower to 0.83 higher)[28]	VERY LOW	CRITICAL
QOL scores – Symptom 3 months - Diarrhea (Better indicated by lower values)												
1[6]	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	very serious[18]	none	68	32	-	MD 0.7 lower (2.12 lower to 0.72 higher)[28]	VERY LOW	CRITICAL

1 *[1] Mercadante et al, 1993 and Zhang et al, 2010*
2 *[2] Evidence was downgraded by 1 due to unclear selection bias in all studies and potential risk of performance bias (no blinding of outcome assessors) in Mercadante et al.*

1993

[3] *Seriuos inconsistency: I2=80%*

[4] *Mercadante et al,1993; Kawamata et al,1996; Polati et al, 1998; Zhang et al, 2008*

[5] *Evidence was downgraded by 1 due to potential risk of performance bias (no blinding of outcome assessors) in 2 studies (Mercadante et al,1993; Kawamata et al,1996) and potential selection bias in all studies*

[6] *Gao et al, 2014*

[7] *The quality of the evidence was downgraded because of the uncertain risk of selection and potential risk of performance bias (no blinding of outcome assessors)*

[8] *The quality of the evidence was downgraded due to potential risk of contamination bias: 2 patients from the control group received open-label CPN at 43 and 52 days*

[9] *The quality of the evidence was further downgraded from moderate to low due to imprecision in the effect size estimates (95%CI crossed two default MIDs)*

[10] *Wyse et al, 2011*

[11] *Jonshon 2009; Mercadante et al, 1993; Zhang et al, 2008.*

[12] *Serious inconsistency: I2=71%*

[13] *Kamawata et al, 1996, Wong 1994; Mercadante et al, 1993; Zhang et al, 2008.*

[14] *The quality of the evidence was downgraded from high to moderate because of the unclear risk of selection bias in two studies (Mercadante et al, 1993; and Zhang et al, 2008) and potential risk of performance bias (Kamawata et al, 1996; Mercadante et al, 1993)*

[15] *Johnson et al, 2009*

[16] *The quality of the evidence was downgraded from high to moderate because of the potential risk of performance bias (no blinding of outcome assessors) and unclear risk of attrition bias*

[17] *The quality of the evidence was further downgraded from moderate to low due to indirectness in Johnson et al, 2009 (the cohort included 65 patients (only 58 with PC)*

[18] *Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs*

[19] *The quality of the evidence was downgraded due to potential risk of contamination bias: 2 patients from the control group received open-label CPN at 43 and 52 days*

[20] *Kawamata et al, 1996; Lillimoe 1993; Mercadante et al, 1993; Polati et al, 1998; Wong et al, 2004; Zhang et al, 2008*

[21] *Evidence was downgraded by 1 due to performance bias: no blinding of outcome assessors in 2 studies (Mercadante et al, 1993; Kawamata et al, 1996) and unclear selection bias in 5 studies (Lillemoe et al, 1993; Mercadante et al, 1993; Polati et al, 1998; Kawamata et al, 1996; Zhang et al, 2008)*

[22] *Kawamata et al, 1996; Mercadante et al, 1993; Polati et al, 1998; Zhang et al, 2008*

[23] *Evidence was downgraded by 1 due to performance bias: no blinding of outcome assessors in 2 studies (Mercadante et al, 1993; Kawamata et al, 1996) and unclear selection bias in all studies (Mercadante et al, 1993; Polati et al, 1998; Kawamata et al, 1996; Zhang et al, 2008)*

[24] *The committee decided to consider all survival outcomes that were clinically important, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not clinically important.*

[25] *Zhang et al, 2008*

[26] *The quality of the evidence was downgraded from high to moderate because of the potential risk of attrition bias and unclear risk of selection bias*

[27] *The QOL scores were collected by means of the Digestive Disease questionnaire-15*

[28] *The QOL scores were collected by means of the questionnaire "Changes in function and symptom scores on European Organization for Research and Treatment of Cancer QLQ-C30"*

[29] *Wong et al, 2004*

I.8.21 Early NCPB versus late NCPB

2 **Table 2: Full GRADE profile for early NCPB versus late NCPB in adults with pancreatic cancer**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early NCPB versus late NCPB	Control	Relative (95% CI)	Absolute		
Reduction in opioid medication: Oral morphine use at 16 weeks (Better indicated by lower values)												
1[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	none	17	6	-	MD 55.82 higher (40.91 to 70.73 higher)	MODERATE	CRITICAL
Reduction in opioid medication: Oral morphine use at 24 weeks (Better indicated by lower values)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	14	8	-	MD 62.41 higher (46.07 to 78.75 higher)	MODERATE	CRITICAL
Reduction in opioid medication: Oral Tramodol Hydrochloride use at 16 weeks (Better indicated by lower values)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	5	16	-	MD 209.68 higher (143.2 to 276.16 higher)	MODERATE	CRITICAL
Reduction in opioid medication: Oral Tramodol Hydrochloride use at 24 weeks (Better indicated by lower values)												
1[1]	randomised trials	no serious	no serious inconsistency	serious[2]	serious[4]	none	2	10	-	MD 160 higher (1.9	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early NCPB versus late NCPB	Control	Relative (95% CI)	Absolute		
		risk of bias								to 318.1 higher)		
Pain Relief/ improved analgesia: Pain scores at 16 weeks (Better indicated by lower values)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	30	30	-	MD 21.3 higher (18.88 to 23.72 higher)[5]	MODERATE	CRITICAL
Pain Relief/ improved analgesia: Pain scores at 24 weeks (Better indicated by lower values)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	30	30	-	MD 26 higher (22.34 to 29.66 higher)[5]	MODERATE	CRITICAL
Adverse effects: nausea												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[6]	none	10/30 (33.3%)	1/30 (3.3%)	RR 10 (1.36 to 73.33)	300 more per 1000 (from 12 more to 1000 more)	LOW	CRITICAL
Adverse effects: constipation												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[4]	none	16/30 (53.3%)	8/30 (26.7%)	RR 2 (1.01 to 3.95)	267 more per 1000 (from 3	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early NCPB versus late NCPB	Control	Relative (95% CI)	Absolute		
										more to 787 more)		
Adverse effects: pluritus												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[3]	none	3/30 (10%)	1/30 (3.3%)	RR 3 (0.33 to 27.23)	67 more per 1000 (from 22 fewer to 874 more)	VERY LOW	CRITICAL

[1] *Amr et al, 2013*
[2] *The quality of the evidence was downgraded from high to moderate due to potential indirectness (as the randomised trial was conducted in Egypt and the outcomes may not be transferrable to the UK settings)*
[3] *Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs*
[4] *Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed 1 default MID*
[5] *Pain relief was assessed using the visual analogue scale (VAS) pain score*
[6] *The low sample size doesn't allow for precision in the effect estimates*

I.8.3 NCPB plus medical management versus thoracic splanchnicectomy plus medical management

Table 3: Full GRADE profile for NCPB plus medical management versus thoracic splanchnicectomy plus medical management in adults with pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NCPB + MM versus thoracic splanchnicectomy + MM	Control	Relative (95% CI)	Absolute		
Pain Relief/ improved analgesia: Pain scores at 2 weeks (Better indicated by lower values)												

1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	very serious[4]	none	14	14	-	MD 0.16 higher (1.31 lower to 1.63 higher)[5]	VERY LOW	CRITICAL
Pain Relief/ improved analgesia: Pain scores at 8 weeks (Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	very serious[4]	none	7	11	-	MD 1.02 lower (2.95 lower to 0.91 higher)[5]	VERY LOW	CRITICAL
Patients reporting effective pain management at 2 weeks												
1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	very serious[4]	none	5/14 (35.7%)	4/14 (28.6%)	RR 1.25 (0.35 to 2.56)[6]	71 more per 1000 (from 186 fewer to 446 more)	VERY LOW	CRITICAL
Patients reporting effective pain management at 2 months												
1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	very serious[4]	none	5/9 (55.6%)	4/11 (36.4%)	RR 1.53 (0.47 to 2.43)[6]	193 more per 1000 (from 193 fewer to 520 more)	VERY LOW	CRITICAL

[1] *Jonshon et al, 2009*
[2] *The quality of the evidence was downgraded from high to moderate because of the potential risk of performance bias (no blinding of outcome assessors) and unclear risk of attrition bias*
[3] *The quality of the evidence was further downgraded from moderate to low due to indirectness in the study population (the cohort included 65 patients (only 58 with PC)*
[4] *Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs*
[5] *Pain scores were assessed using a 4-point Likert scale*
[6] *Patients reporting effective pain relief was assessed as one or more of the following: (i) a Brief Pain Inventory (BPI) 'worst' pain rated over the last week as 0-4 (none or mild), (ii) a reduction of >50% between the mean of the three BPI items ('worst', 'least' and 'average') obtained at the baseline assessment and that obtained at the 2-month assessment, (iii) a decrease from baseline to 2 months of at least 2 points in the response to the question 'During the past week, have you had pain?'.*

I.8.3.1 Thoracic splanchnicectomy plus medical management versus medical management alone

Table 4: Full GRADE profile for thoracic splanchnicectomy plus medical management versus medical management alone in adults with pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Thoracic splanchnicectomy + MM versus MM**	**Control**	**Relative (95% CI)**	**Absolute**		
Pain Relief/ improved analgesia: Pain scores at 2 and 8 weeks - Pain scores at 2 weeks (Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	very serious[4]	none	14	19	-	MD 0.3 lower (1.81 lower to 1.21 higher)	VERY LOW	CRITICAL
Pain Relief/ improved analgesia: Pain scores at 2 and 8 weeks - Pain scores at 8 weeks (Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	very serious[4]	none	11	11	-	MD 0.52 lower (2.11 lower to 1.07 higher)	VERY LOW	CRITICAL
Patients reporting effective pain management at 2 and 8 weeks - At 2 months												
1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	very serious[4]	none	4/14 (28.6%)	6/19 (31.6%)	RR 0.91 (0.26 to 2.04)[5]	28 fewer per 1000 (from 234 fewer to 328 more)	VERY LOW	CRITICAL
Patients reporting effective pain management at 2 and 8 weeks - At 8 months												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Thoracic splanchnicectomy + MM versus MM	Control	Relative (95% CI)	Absolute		
1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	very serious[4]	none	4/11 (36.4%)	5/12 (41.7%)	RR 0.87 (0.23 to 1.81)[5]	54 fewer per 1000 (from 321 fewer to 338 more)	VERY LOW	CRITICAL

[1] *Johnson et al, 2009*
[2] *The quality of the evidence was downgraded from high to moderate because of the potential risk of performance bias (no blinding of outcome assessors) and unclear risk of attrition bias*
[3] *The quality of the evidence was further downgraded from moderate to low due to indirectness in study population (the cohort included 65 patients (only 58 with PC)*
[4] *Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs*
[5] *Patients reporting effective pain relief was assessed as one or more of the following: (i) a Brief Pain Inventory (BPI) 'worst' pain rated over the last week as 0-4 (none or mild), (ii) a reduction of >50% between the mean of the three BPI items ('worst', 'least' and 'average') obtained at the baseline assessment and that obtained at the 2-month assessment, (iii) a decrease from baseline to 2 months of at least 2 points in the response to the question 'During the past week, have you had pain?'.*

I.8.49 EUS- guided NCPB: 1 injection versus EUS- guided NCPB: 2 injections

Table 5: Full GRADE profile for EUS-guided NCPB: 1 injection versus 2 injections in adults with pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EUS- guided NCPB: 1 injection versus EUS-guided NCPB: 2 injections	Control	Relative (95% CI)	Absolute		
Reduction in pain medication												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EUS- guided NCPB: 1 injection versus EUS-guided NCPB: 2 injections	Control	Relative (95% CI)	Absolute		
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	9/29 (31%)	7/21 (33.3%)	RR 0.93 (0.36 to 1.8)	23 fewer per 1000 (from 213 fewer to 267 more)	VERY LOW	CRITICAL
Patients with pain relief												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	20/29 (69%)	17/21 (81%)	RR 0.85 (0.46 to 1.1)	121 fewer per 1000 (from 437 fewer to 81 more)	VERY LOW	CRITICAL
Patients reporting a block effective (subjective)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	20/29 (69%)	13/21 (61.9%)	RR 1.11 (0.66 to 1.42)	68 more per 1000 (from 210 fewer to 260 more)	VERY LOW	CRITICAL
Patient with a complete pain relief												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/29 (6.9%)	2/21 (9.5%)	RR 0.72 (0.1 to 3.83)	27 fewer per 1000 (from 86 fewer to 270 more)	VERY LOW	CRITICAL

1 *[1] LeBlanc et al, 2013*
2 *[2] The quality of the evidence was downgraded from high to moderate because of the unclear risk of attrition bias (insufficient reporting of attritions/exclusions), the unclear risk*

ofperformance bias (no details given on blinding of outcome assessors) and the high risk of selective reporting bias (All outcomes of interest [Pain score and analgesic use overtime] are reported completely, but no details about the time frame of the outcome measurement)

[3] Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs

I.8.54 NCPB versus splanchnic nerve blocks

Table 6: Full GRADE profile for NCPB versus splanchnic neurolytic blockade in adults with pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NCPB versus splanchnic nerve blocks	Control	Relative (95% CI)	Absolute		
Reduction in opioid medication: total daily codeine consumption												
1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	serious[4]	none	-	-	-[5]	-	VERY LOW	CRITICAL
Pain Relief/ improved analgesia: Pain scores (VAS)												
1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	serious[4]	none	-	-	-[6]	-	VERY LOW	CRITICAL

[1] Suleyman Ozyalcin et al. 2004

[2] The quality of the evidence was downgraded from high to moderate because of the unclear risk of attrition bias (insufficient reporting of attritions/exclusions) and the high risk of selective reporting bias (all outcomes of interest [Pain score, analgesic use overtime and survival rates] are reported incompletely)

[3] The quality of the evidence was downgraded from moderate to low due to potential indirectness (as the randomised trial was conducted in Turkey and the outcomes may not be transferrable to the UK settings)

[4] The quality of evidence was further downgraded from low to very low due to imprecision in the effect estimates (not possible to estimate how precise the effect estimates: no information regarding uncertainty of the estimates reported)

*[5] Data are reported as medians (mg - COD consumption) and p values overtime: "There are significant differences between two groups at 2nd (4 weeks), 4th (8 weeks), and 5th (10 weeks) controls (respectively; p=0.041, p=0.021, p=0.028). **There are highly significant differences between two groups at 1st (2 weeks), 3rd (6 weeks), controls (respectively; p=0.003, p=0.005)"*

*[6] Data reported as medians (VAS scores) and p values overtime: "*There are significant differences between two groups at 2nd (4 weeks), 4th (8 weeks), and 5th (10 weeks) controls (respectively; p=0.041, p=0.021, p=0.028). **There are highly significant differences between two groups at 1st (2 weeks), 3rd (6 weeks), controls (respectively; p=0.003, p=0.005)"*

I.9 Nutritional Interventions

I.9.1 Standard Enteral nutrition versus enteral immunonutrition

Table 7: Full GRADE profile for standard enteral nutrition versus enteral immunonutrition before and after surgery

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Enteral immunonutrition (EIN) versus Standard Enteral nutrition (SEN) before and after surgery	Control	Relative (95% CI)	Absolute		
Treatment related morbidity - postoperative complications - Patients with infectious complications												
1[1]	randomised trials	serious	no serious inconsistency	serious[3]	very serious[4]	none	5/15 (33.3%)	6/15 (40%)	RR 0.83 (0.32 to 2.15)	68 fewer per 1000 (from 272 fewer to 460 more)	VERY LOW	CRITICAL
Treatment related morbidity - postoperative complications - Patients with non-infectious complications												
1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	very serious[4]	none	6/15 (40%)	6/15 (40%)	RR 1 (0.42 to 2.4)	0 fewer per 1000 (from 232 fewer to 560 more)	VERY LOW	CRITICAL
Health Related Quality of Life - Karnofsky score at 2 weeks after surgery, change from baseline (Better indicated by higher values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	very serious[4]	none	17	20	-	MD 2 lower (7.33 lower to	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Enteral immunonutrition (EIN) versus Standard Enteral nutrition (SEN) before and after surgery	Control	Relative (95% CI)	Absolute		
										3.33 higher)		
Nutritional status at 2 weeks after surgery - BMI (kg/m2), change from baseline (Better indicated by higher values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	very serious[4]	none	17	20	-	SMD 1.5 lower (3.93 lower to 0.93 higher)	VERY LOW	CRITICAL
Nutritional status at 2 weeks after surgery - mid-arm circumference (cm), change from baseline (Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	very serious[4]	none[4]	17	20	-	MD 0.6 lower (2.92 lower to 1.72 higher)	VERY LOW	CRITICAL
Nutritional status at 2 weeks after surgery - corrected arm muscle area (cm2), change from baseline (Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	very serious[4]	none	17	20	-	MD 1.6 lower (7.09 lower to 3.89 higher)	VERY LOW	CRITICAL

1 [1] *Hamza et al. 2015*

[2] Evidence was downgraded by 1 due to attrition bias (Data were missing for 5 of the 42 randomised patients: G1 n=3 DG n=2 were missed because inadequate intake and metastatic disease, respectively. For these reasons, missing data were judged to affect the true outcome of the trial) and unclear risk of performance bias
[3] Evidence was downgraded by 1 due to indirectness of the study population (only 26 of 47 participants had PC)
[4] Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs

Table 8: Full GRADE profile for standard enteral nutrition versus enteral immunonutrition after surgery

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Enteral immunonutrition (EIN) versus Standard Enteral nutrition (SEN) after surgery**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Treatment related morbidity - postoperative complications - Patients with infectious complications												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	6/71 (8.5%)	11/73 (15.1%)	RR 0.56 (0.22 to 1.44)	66 fewer per 1000 (from 118 fewer to 66 more)	LOW	CRITICAL
Treatment related morbidity - postoperative complications - Patients with non-infectious complications												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	18/71 (25.4%)	21/73 (28.8%)	RR 0.88 (0.51 to 1.51)	35 fewer per 1000 (from 141 fewer to 147 more)	LOW	CRITICAL
Treatment related morbidity - postoperative mortality												

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Enteral immunonutrition (EIN) versus Standard Enteral nutrition (SEN) after surgery**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	2/71 (2.8%)	1/73 (1.4%)	RR 2.06 (0.19 to 22.18)	15 more per 1000 (from 11 fewer to 290 more)	LOW	CRITICAL
Treatment related morbidity - Jejunostomy and enteral nutritional related complications - Tube clogging/kinking												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	3/71 (4.2%)	5/73 (6.8%)	RR 0.62 (0.15 to 2.49)	26 fewer per 1000 (from 58 fewer to 102 more)	LOW	CRITICAL
Treatment related morbidity - Jejunostomy and enteral nutritional related complications - Tube dislodgment												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	2/71 (2.8%)	1/73 (1.4%)	RR 2.06 (0.19 to 22.18)	15 more per 1000 (from 11 fewer to	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Enteral immunonutrition (EIN) versus Standard Enteral nutrition (SEN) after surgery	Control	Relative (95% CI)	Absolute		
										290 more)		
Treatment related morbidity - Jejunostomy and enteral nutritional related complications - Tube breakage												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	0/71 (0%)	1/73 (1.4%)	RR 0.34 (0.01 to 8.27)	9 fewer per 1000 (from 14 fewer to 100 more)	LOW	CRITICAL
Treatment related morbidity - Jejunostomy and enteral nutritional related complications - Local skin infection												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	0/71 (0%)	1/73 (1.4%)	RR 0.34 (0.01 to 8.27)	9 fewer per 1000 (from 14 fewer to 100 more)	LOW	CRITICAL
Treatment related morbidity - Jejunostomy and enteral nutritional related complications - Abdominal cramps												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	10/71 (14.1%)	11/73 (15.1%)	RR 0.93 (0.42 to 2.06)	11 fewer per 1000 (from 87	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Enteral immunonutrition (EIN) versus Standard Enteral nutrition (SEN) after surgery	Control	Relative (95% CI)	Absolute		
										fewer to 160 more)		
Treatment related morbidity - Jejunostomy and enteral nutritional related complications - Abdominal distention												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	10/71 (14.1%)	9/73 (12.3%)	RR 1.14 (0.49 to 2.64)	17 more per 1000 (from 63 fewer to 202 more)	LOW	CRITICAL
Treatment related morbidity - Jejunostomy and enteral nutritional related complications - Vomiting												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	0/71 (0%)	2/73 (2.7%)	RR 0.21 (0.01 to 4.21)	22 fewer per 1000 (from 27 fewer to 88 more)	LOW	CRITICAL
Treatment related morbidity - Jejunostomy and enteral nutritional related complications - Diarrhoea												
1[1]	randomised trials	no serious	no serious inconsistency	no serious indirectness	very serious[2]	none	7/71 (9.9%)	9/73 (12.3%)	RR 0.8 (0.31	25 fewer per	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Enteral immunonutrition (EIN) versus Standard Enteral nutrition (SEN) after surgery	Control	Relative (95% CI)	Absolute	Quality	Importance
		risk of bias							to 2.03)	1000 (from 85 fewer to 127 more)		

[1] *Gianotti et al. 2000*
[2] *Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs*

I.9.24 Enteral immunonutrition versus Standard nutrition (no intervention)

Table 9: Full GRADE profile for enteral immunonutrition versus standard nutrition (no intervention)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Enteral immunonutrition (EIN) versus no intervention (standard nutrition) after surgery	Control	Relative (95% CI)	Absolute	Quality	Importance
Treatment related morbidity - postoperative complications												

1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	-	-	LOW	CRITICAL
Treatment related morbidity - postoperative mortality												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	-	-	LOW	CRITICAL
Nutritional status at 30 days after surgery - Absoulte change in weight (kg) from baseline (Better indicated by lower values)												
1[1]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	17	14	-	MD 0.97 higher (1.37 lower to 3.32 higher)	VERY LOW	CRITICAL
PROMS - Satisfaction with nutritional treatment at 1 month after surgery (Better indicated by lower values)												
1[1]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	15	15	-	MD 0.04 higher (0.34 lower to 0.41 higher)	VERY LOW	CRITICAL

1 *[1] Gade et al. 2016*
2 *[2] Evidence was downgraded by 2 due to selective outcome reporting bias (data were unclearly reported on the postoperative complications, so that it was not possible to judge*
3 *the certainty of the evidence) and unclear risk of performance and selection bias*
4 *[3] Evidence was downgraded by 1 due to unclear risk of performance and selection bias*
5 *[4] Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs*

6

I.9.37 Parenteral nutrition versus standard enteral nutrition after surgery

8 **Table 10: Full GRADE profile for parenteral nutrition versus standard enteral nutrition after surgery**

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Parenteral nutrition (PN) versus SEN after surgery	Control	Relative (95% CI)	Absolute		
Treatment related morbidity - postoperative complications - Patients with infectious complications												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	15/68 (22.1%)	11/73 (15.1%)	RR 1.46 (0.72 to 2.96)	69 more per 1000 (from 42 fewer to 295 more)	LOW	CRITICAL
Treatment related morbidity - postoperative complications - Patients with non-infectious complications												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	25/68 (36.8%)	21/73 (28.8%)	RR 1.28 (0.79 to 2.06)	81 more per 1000 (from 60 fewer to 305 more)	LOW	CRITICAL
Treatment related morbidity - postoperative complications - Total patients with complications (infectious+ non-infectious)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	40/68 (58.8%)	32/73 (43.8%)	RR 1.34 (0.97 to 1.86)	149 more per 1000 (from 13 fewer to 377 more)	LOW	CRITICAL
Treatment related morbidity - postoperative mortality												
2[4]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	4/98 (4.1%)	1/101 (1.0%)	RR 4.29 (0.49 to 37.47)	45 more per 1000 (from 7 fewer to 500 more)	LOW	CRITICAL

1 *[1] Gianotti et al. 2000*
2 *[2] Evidence was downgraded by 1 due to very serious imprecision as 95%CI crossed two default MIDs*
3 *[3] Gianotti et al. 2000; Liu et al. 2011*

4

I.9.41 Parenteral nutrition versus enteral immunonutrition after surgery

2 **Table 11: Full GRADE profile for parenteral nutrition versus enteral immunonutrition after surgery**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Parenteral nutrition (PN) versus enteral immunonutrition (EIN) after surgery	Control	Relative (95% CI)	Absolute		
Treatment related morbidity - postoperative complications - Patients with infectious complications												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	15/68 (22.1%)	6/71 (8.5%)	RR 2.61 (1.08 to 6.33)	136 more per 1000 (from 7 more to 450 more)	MODERATE	CRITICAL
Treatment related morbidity - postoperative complications - Patients with non-infectious complications												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	25/68 (36.8%)	18/71 (25.4%)	RR 1.45 (0.87 to 2.41)	114 more per 1000 (from 33 fewer to 357 more)	MODERATE	CRITICAL
Treatment related morbidity - postoperative complications - Total patients with complications (infectious+ non-infectious)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	40/68 (58.8%)	24/71 (33.8%)	RR 1.74 (1.19 to 2.55)	250 more per 1000 (from 64 more to 524 more)	MODERATE	CRITICAL

Treatment related morbidity - Postoperative mortality												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	4/68 (5.9%)	2/71 (2.8%)	RR 2.09 (0.4 to 11.03)	31 more per 1000 (from 17 fewer to 283 more)	LOW	CRITICAL

[1] *Gianotti et al. 2000*
[2] *Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed two default MID*
[3] *Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs*

I.9.54 Parenteral nutrition versus no intervention after surgery

Table 12: Full GRADE profile for parenteral nutrition versus no intervention after surgery

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Parenteral nutrition (PN) versus no intervention after surgery**	**Control**	**Relative (95% CI)**	**Absolute**		
Treatment related morbidity - major complications - Deep infection												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	4/60 (6.7%)	4/57 (7%)	RR 0.95 (0.25 to 3.62)	4 fewer per 1000 (from 53 fewer to 184 more)	VERY LOW	CRITICAL
Treatment related morbidity - major complications - Fistula												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	8/60 (13.3%)	5/57 (8.8%)	RR 1.52 (0.53 to 4.37)	46 more per 1000 (from 41 fewer to 296 more)	VERY LOW	CRITICAL

Treatment related morbidity - major complications - Abscess												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/60 (20%)	2/57 (3.5%)	RR 5.7 (1.33 to 24.36)	165 more per 1000 (from 12 more to 820 more)	LOW	CRITICAL
Treatment related morbidity - major complications - Peritonitis												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	7/60 (11.7%)	2/57 (3.5%)	RR 3.33 (0.72 to 15.34)	82 more per 1000 (from 10 fewer to 503 more)	VERY LOW	CRITICAL
Treatment related morbidity - major complications - Hemorrhage												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	1/60 (1.7%)	2/57 (3.5%)	RR 0.48 (0.04 to 5.1)	18 fewer per 1000 (from 34 fewer to 144 more)	VERY LOW	CRITICAL
Treatment related morbidity - major complications - Intestinal obstruction												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	4/60 (6.7%)	0/57 (0%)	RR 8.56 (0.47 to 155.45)	-	VERY LOW	CRITICAL
Treatment related morbidity - major complications - Anastomotic breakdown												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	7/60 (11.7%)	3/57 (5.3%)	RR 2.22 (0.6 to 8.16)	64 more per 1000 (from 21 fewer to 377 more)	VERY LOW	CRITICAL
Treatment related morbidity - major complications - Aspiration												

1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	0/60 (0%)	1/57 (1.8%)	RR 0.32 (0.01 to 7.62)	12 fewer per 1000 (from 17 fewer to 116 more)	VERY LOW	CRITICAL
Treatment related morbidity - major complications - Pneumonia												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	5/60 (8.3%)	6/57 (10.5%)	RR 0.79 (0.26 to 2.45)	22 fewer per 1000 (from 78 fewer to 153 more)	VERY LOW	CRITICAL
Treatment related morbidity - major complications - Pulmonary embolus												
1[1]	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	very serious[4]	none	0/60 (0%)	1/57 (1.8%)	RR 0.32 (0.01 to 7.62)	12 fewer per 1000 (from 17 fewer to 116 more)	VERY LOW	CRITICAL
Treatment related morbidity - major complications - Myocardial infarction												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	2/60 (3.3%)	1/57 (1.8%)	RR 1.9 (0.18 to 20.38)	16 more per 1000 (from 14 fewer to 340 more)	VERY LOW	CRITICAL
Treatment related morbidity - major complications - Reoperation												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	6/60 (10%)	3/57 (5.3%)	RR 1.9 (0.5 to 7.24)	47 more per 1000 (from 26 fewer to 328 more)	VERY LOW	CRITICAL
Treatment related morbidity - major complications - Total major complications (excluding death)												

1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	23/60 (38.3%)	12/57 (21.1%)	RR 1.82 (1 to 3.31)	173 more per 1000 (from 0 more to 486 more)	LOW	CRITICAL
Treatment related morbidity - minor complications - Superficial wound infection												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	5/60 (8.3%)	1/57 (1.8%)	RR 4.75 (0.57 to 39.42)	66 more per 1000 (from 8 fewer to 674 more)	VERY LOW	CRITICAL
Treatment related morbidity - minor complications - Cellulitis												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	1/60 (1.7%)	0/57 (0%)	RR 2.85 (0.12 to 68.62)	-	VERY LOW	CRITICAL
Treatment related morbidity - minor complications - Prolonged ileus												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	13/60 (21.7%)	5/57 (8.8%)	RR 2.47 (0.94 to 6.49)	129 more per 1000 (from 5 fewer to 482 more)	VERY LOW	CRITICAL
Treatment related morbidity - minor complications - Gastric atony												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	2/60 (3.3%)	1/57 (1.8%)	RR 1.9 (0.18 to 20.38)	16 more per 1000 (from 14 fewer to 340 more)	VERY LOW	CRITICAL
Treatment related morbidity - minor complications - Atelectasis												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	15/60 (25%)	12/57 (21.1%)	RR 1.19 (0.61 to 2.31)	40 more per 1000 (from 82	VERY LOW	CRITICAL

										fewer to 276 more)		
Treatment related morbidity - minor complications - Pleural effusion												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	12/60 (20%)	13/57 (22.8%)	RR 0.88 (0.44 to 1.76)	27 fewer per 1000 (from 128 fewer to 173 more)	VERY LOW	CRITICAL
Treatment related morbidity - minor complications - Catheter sepsis												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	5/60 (8.3%)	1/57 (1.8%)	RR 4.75 (0.57 to 39.42)	66 more per 1000 (from 8 fewer to 674 more)	VERY LOW	CRITICAL
Treatment related morbidity - minor complications - Urinary tract infection												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	4/60 (6.7%)	6/57 (10.5%)	RR 0.63 (0.19 to 2.13)	39 fewer per 1000 (from 85 fewer to 119 more)	VERY LOW	CRITICAL
Treatment related morbidity - minor complications - PN related complication												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	2/60 (3.3%)	0/57 (0%)	RR 4.75 (0.23 to 96.93)	-	VERY LOW	CRITICAL
Treatment related morbidity - minor complications - Liver function abnormality												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	0/60 (0%)	0/57 (0%)	-	-	VERY LOW	CRITICAL
Treatment related morbidity - minor complications - Total minor complications												

1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	32/60 (53.3%)	24/57 (42.1%)	RR 1.27 (0.86 to 1.86)	114 more per 1000 (from 59 fewer to 362 more)	VERY LOW	CRITICAL
Treatment related morbidity - Postoperative mortality												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	4/60 (6.7%)	1/57 (1.8%)	RR 3.8 (0.44 to 32.99)	49 more per 1000 (from 10 fewer to 561 more)	VERY LOW	CRITICAL
Overall Survival at median follow up of 18 months (Better indicated by higher values)												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	60	57	-	not pooled	LOW	CRITICAL

[1] *Brennan et al. 1994*
[2] *The quality of the evidence was downgraded from high to low because of the unclear risk of detection, performance bias and of attrition bias (No details were given in the text)*
[3] *Evidence was further downgraded by 1 due to serious imprecision as 95%CI crossed one default MID*
[4] *Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs*

I.9.6 Oral nutritional supplements (n-3 fatty acids) versus isocaloric-isonitrogenous supplement (without n-3 fatty acids)

Table 13: Full GRADE profile for oral n-3 fatty acid nutritional supplements versus isocaloric-isonitrogenous supplements

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral nutritional supplements (n-3 fatty acids)	Control	Relative (95% CI)	Absolute		

						(without n-3 fatty acids)						
Nutritional status - Change in weight loss (kg/month) at 8 weeks (Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	50	60	-	MD 0.12 higher (0.09 lower to 0.33 higher)	LOW	CRITICAL
Nutritional status - Change in lean body mass (kg) at 8 weeks (Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	41	56	-	MD 0.15 higher (0.02 to 0.28 higher)	LOW	CRITICAL
Change in resting energy expenditure at 8 weeks (Better indicated by lower values)												
1[4]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	7	12	-	MD 14 higher (81.8 lower to 109.8 higher)	LOW	CRITICAL
Change in total energy expenditure at 8 weeks (Better indicated by lower values)												
1[4]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	7	12	-	MD 187 higher (114.38 lower to 488.38 higher)	MODERATE	CRITICAL
Change in physical activity level at 8 weeks (Better indicated by lower values)												
1[4]	randomised trials	no serious	no serious inconsistency	no serious indirectness	serious[3]	none	7	12	-	MD 0.17 higher (0.05	MODERATE	CRITICAL

		risk of bias								lower to 0.39 higher)		
Health Related Quality of Life at 8 weeks (Better indicated by lower values)												
1[1]	randomised trials	very serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0	-	-	not pooled	LOW	CRITICAL

[1] *Fearon et al. 2003*
[2] *The quality of the evidence was downgraded from high to moderate because of the potential risk of attrition bias (more than 55% of patients were not available for analysis at the last follow-up, and there was not reported enough information to judge whether the true outcome of the trial would have been affected)*
[3] *Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID*
[4] *Moses et al. 2004*
[5] *Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs*
[6] *The quality of the evidence was downgraded from high to moderate because of the potential risk of attrition bias and selective reporting for this outcome*

I.9.7 Oral nutritional supplements versus placebo

Table 14: Full GRADE profile for oral nutritional supplements (oral L-Carnitine therapy) versus placebo

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oral nutritional supplements (oral L-Carnitine therapy) versus placebo**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Nutritional status - % change of BMI at 12 weeks (Better indicated by lower values)												
1[1]	randomised trials[1]	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	28	34	-	MD 4.9 higher (2.71 to 7.09 higher)	LOW	CRITICAL
Nutritional status - % change of BCM at 12 weeks (Better indicated by lower values)												
1[1]	randomised trials[1]	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	38	34	-	MD 8.8 higher	LOW	CRITICAL

										(7.20 to 10.40 higher)		
Health Related Quality of Life - EORTC-QLQ-C30/PAN26 - cognitive funtion at 6 weeks follow-up (Better indicated by lower values)												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	38	34	-	not pooled	LOW	CRITICAL
Health Related Quality of Life - EORTC-QLQ-C30/PAN26 - global health status at 12 weeks follow-up (Better indicated by lower values)												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	38	34	-	not pooled	LOW	CRITICAL
Overall Survival at follow up of 1500 days (Better indicated by lower values)												
1[1]	randomised trials[1]	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	38	34	-	0 higher (0 to 0 higher)	LOW	CRITICAL

[1] Kraft et al. 2012

[2] The quality of the evidence was downgraded from high to low because of the potential risk of attrition bias (Even tough in the report was stated that "Dropout rates and reasons were not different between both treatment arms", the high dropout rate (data missing on 43 of the 72 randomized patients [59%] is still significant) and the selective reporting of findings.

[3] Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID

I.9.8 Pancreatic enzyme replacement therapy (PERT) versus placebo

Table 15: Full GRADE profile for pancreatic enzyme replacement therapy versus placebo

Quality assessment							No of patients		Effect				
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pancreatic enzyme replacement therapy (PERT) versus placebo**	**Control**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**

Nutritional status - Percentage change in body weight (%) at 8 weeks follow-up (Better indicated by lower values)												
2[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	45	43	-	MD 2.89 higher (0.51 to 5.27 higher)	MODERATE	CRITICAL
Nutritional status - Absolute change in body weight (Kg) at 8 weeks follow-up (Better indicated by lower values)												
2[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	45	43	-	MD 1.64 higher (0.7 lower to 3.98 higher)	MODERATE	CRITICAL
Nutritional status - Daily dietary intake of total calories at 8 weeks follow-up (Better indicated by lower values)												
1[3]	randomised trials	no serious risk of bias	no serious inconsistency	serious[4]	serious[2]	none	11	10	-	MD 1.76 higher (0.19 to 3.33 higher)	LOW	CRITICAL
Health related quality of life - Global Health status (follow-up 8 weeks; measured with: EORTC-QLQ-C30 - Korean version; Better indicated by higher values)												
1[5]	randomised trials	no serious risk of bias	no serious inconsistency	serious[7]	serious[2]	none	32	30	-	not pooled	LOW	CRITICAL
Health related quality of life - Functional scale (follow-up 8 weeks; measured with: EORTC-QLQ-C30 - Korean version; Better indicated by higher values)												
1[5]	randomised trials	no serious risk of bias	no serious inconsistency	serious[7]	serious[2]	none	32	30	-	not pooled	LOW	CRITICAL
Health related quality of life - Physical (follow-up 8 weeks; measured with: EORTC-QLQ-C30 - Korean version; Better indicated by higher values)												

1[5]	randomised trials	no serious risk of bias	no serious inconsistency	serious[7]	serious[2]	none	32	30	-	not pooled	LOW	CRITICAL
Health related quality of life - Role (follow-up 8 weeks; measured with: EORTC-QLQ-C30 - Korean version; Better indicated by higher values)												
1[5]	randomised trials	no serious risk of bias	no serious inconsistency	serious[7]	serious[2]	none	32	30	-	not pooled	LOW	CRITICAL
Health related quality of life - Emotional (follow-up 8 weeks; measured with: EORTC-QLQ-C30 - Korean version; Better indicated by higher values)												
1[5]	randomised trials	no serious risk of bias	no serious inconsistency	serious[7]	serious[2]	none	32	30	-	not pooled	LOW	CRITICAL
Health related quality of life - Cognitive (follow-up 8 weeks; measured with: EORTC-QLQ-C30 - Korean version; Better indicated by higher values)												
1[5]	randomised trials	no serious risk of bias	no serious inconsistency	serious[7]	serious[2]	none	32	30	-	not pooled	LOW	CRITICAL
Health related quality of life - Social (follow-up 8 weeks; measured with: EORTC-QLQ-C30 - Korean version; Better indicated by higher values)												
1[5]	randomised trials	no serious risk of bias	no serious inconsistency	serious[7]	serious[2]	none	32	30	-	not pooled	LOW	CRITICAL
Health related quality of life - Symptom scale (follow-up 8 weeks; measured with: EORTC-QLQ-C30 - Korean version; Better indicated by lower values)												
1[5]	randomised trials	no serious risk of bias	no serious inconsistency	serious[7]	serious[2]	none	32	30	-	not pooled	LOW	CRITICAL
Health related quality of life - Fatigue (follow-up 8 weeks; measured with: EORTC-QLQ-C30 - Korean version; Better indicated by lower values)												

1[5]	randomised trials	no serious risk of bias	no serious inconsistency	serious[7]	serious[2]	none	32	30	-	not pooled	LOW	CRITICAL
Health related quality of life - Nausea and vomiting (follow-up 8 weeks; measured with: EORTC-QLQ-C30 - Korean version; Better indicated by lower values)												
1[5]	randomised trials	no serious risk of bias	no serious inconsistency	serious[7]	serious[4]	none	32	30	-	not pooled	LOW	CRITICAL
Health related quality of life - Pain (follow-up 8 weeks; measured with: EORTC-QLQ-C30 - Korean version; Better indicated by lower values)												
1[5]	randomised trials	no serious risk of bias	no serious inconsistency	serious[7]	serious[2]	none	32	30	-	not pooled	LOW	CRITICAL
Health related quality of life - Dyspnea (follow-up 8 weeks; measured with: EORTC-QLQ-C30 - Korean version; Better indicated by lower values)												
1[5]	randomised trials	no serious risk of bias	no serious inconsistency	serious[7]	serious[2]	none	32	30	-	not pooled	LOW	CRITICAL
Health related quality of life - Insomnia (follow-up 8 weeks; measured with: EORTC-QLQ-C30 - Korean version; Better indicated by lower values)												
1[5]	randomised trials	no serious risk of bias	no serious inconsistency	serious[7]	serious[2]	none	32	30	-	not pooled	LOW	CRITICAL
Health related quality of life - Appetite loss (follow-up 8 weeks; measured with: EORTC-QLQ-C30 - Korean version; Better indicated by lower values)												
1[5]	randomised trials[5]	no serious risk of bias	no serious inconsistency	serious[7]	serious[2]	none	32	30	-	not pooled	LOW	CRITICAL

Health related quality of life - Constipation (follow-up 8 weeks; measured with: EORTC-QLQ-C30 - Korean version; Better indicated by lower values)												
1[5]	randomised trials	no serious risk of bias	no serious inconsistency	serious[7]	serious[2]	none	32	30	-	not pooled	LOW	CRITICAL
Health related quality of life - Diarrhoea (follow-up 8 weeks; measured with: EORTC-QLQ-C30 - Korean version; Better indicated by lower values)												
1[5]	randomised trials	no serious risk of bias	no serious inconsistency	serious[7]	serious[2]	none	32	30	-	not pooled	LOW	CRITICAL
Health related quality of life - Financial difficulties (follow-up 8 weeks; measured with: EORTC-QLQ-C30 - Korean version; Better indicated by lower values)												
1[5]	randomised trials	no serious risk of bias	no serious inconsistency	serious[7]	serious[2]	none	32	30	-	not pooled	LOW	CRITICAL
Overall survival												
1[5]	randomised trials	serious[6]	no serious inconsistency	serious[7]	Not estimable	none	-	-	not pooled	not pooled	LOW	CRITICAL

[1] *Bruno et al. 1998; Woo et al. 2016*
[2] *Evidence for this outcome was downgraded by 1 due to imprecision as 95%CI crossed one default MID*
[3] *Bruno et al. 1998*
[4] *Evidence was downgraded by 1 due indirectness (2 of the 24 participants did not have PC)*
[5] *Woo et al. 2016*
[6] *Evidence for this outcome was downgraded by 1 due to potential selective reporting of findings.*
[7] *The quality of the evidence was downgraded from moderate to low due to potential indirectness (as the randomised trial was conducted in Korea and the outcomes may not be transferrable to the UK settings).*

I.9.91 PERT versus pancrelipase replacement therapy

2 **Table 16: Full GRADE profile for pancreatic enzyme replacement therapy versus pancrelipase replacement therapy**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pancreatic enzyme replacement therapy (PERT) versus pancrelipase replacement therapy	Control	Relative (95% CI)	Absolute		
Nutritional status - BMI (kg/m2) at 6 and 12 months follow-up - at 6 months follow-up (Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	29	28	-	MD 0.95 higher (0.68 lower to 2.58 higher)	VERY LOW	CRITICAL
Nutritional status - BMI (kg/m2) at 6 and 12 months follow-up - at 12 months follow-up (Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	29	28	-	MD 0.51 higher (1.11 lower to 2.13 higher)	VERY LOW	CRITICAL
Treatment related morbidity - NAFLD at 1 year follow-up												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	6/29 (20.7%)	11/28 (39.3%)	RR 0.53 (0.23 to 1.23)	185 fewer per 1000 (from 302 fewer to 90 more)	LOW	CRITICAL

3 *[1] Satoi et al. 2016*

[2] *The quality of the evidence was downgraded from high to moderate because of the unclear risk of performance bias (no information blinding of outcome assessors) and unclear risk of selection bias*
[3] *Evidence was further downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs*
[4] *Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID*

I.10 Biliary obstruction

I.10.1 Plastic stent versus self-expanding metal stent

Table 17: Full GRADE profile for plastic stent versus self-expanding metal stent in adults with pancreatic cancer and biliary obstruction

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Plastic	SEMS	Relative (95% CI)	Absolute		
Treatment-related mortality												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	1/51 (2%)	0/49 (0%)	RR 2.88 (0.12 to 69.16)	-	VERY LOW	CRITICAL
Overall Survival												
3	randomised trials	serious[3,4,5]	no serious inconsistency	serious[1,6]	serious[7,8]	none	0/125 (0%)[9]	0/122 (0%)[9]	HR 1 (0.75 to 1.31)	-	VERY LOW	CRITICAL
								0%		-		
Time to stent dysfunction for unresectable PC - primary and/or secondary stent												
3	randomised trials	serious[3,4,5,10]	no serious inconsistency	serious[6,11]	serious[12]	none	0/115 (0%)[9]	0/114 (0%)[9]	HR 2.59 (1.67 to 4)	-	VERY LOW	CRITICAL
								0%		-		

Time to stent dysfunction for unresectable PC - Covered or Partially Covered SEMS (Primary Stent only)												
2	randomised trials	serious[3,4,13]	no serious inconsistency	serious[14]	serious[12]	none	59/115 (51.3%)	28/109 (25.7%)	HR 2.26 (1.45 to 3.53)	232 more per 1000 (from 93 more to 392 more)	VERY LOW	CRITICAL
Time to stent dysfunction for unresectable PC - Uncovered SEMS (Primary Stent only)												
1	randomised trials	serious[3,13]	no serious inconsistency	serious[14]	serious[12]	none	23/57 (40.4%)	10/60 (16.7%)	HR 3 (1.45 to 6.2)	255 more per 1000 (from 66 more to 510 more)	VERY LOW	CRITICAL
Time to stent dysfunction for unresectable PC - Partially Covered SEMS (Secondary Stent only)												
1	randomised trials	serious[3,13]	no serious inconsistency	serious[14]	serious[12]	none	8/16 (50%)	2/17 (11.8%)	HR 6.69 (1.39 to 32.07)	449 more per 1000 (from 42 more to 864 more)	VERY LOW	CRITICAL
Time to stent dysfunction for unresectable PC - Uncovered SEMS (Secondary Stent only)												
1	randomised trials	serious[13]	no serious inconsistency	serious[14]	serious[12]	none	8/16 (50%)	1/15 (6.7%)	HR 9.97 (3.46 to 28.74)	431 more per 1000 (from 146 more to 796 more)	VERY LOW	CRITICAL
Stent Dysfunction - Stent Occlusion												
6	randomised trials	serious[3,4,5,15,16,17]	no serious inconsistency	serious[1,6,18,19]	no serious imprecision	none	98/225 (43.6%)	47/246 (19.1%)	RR 2.25 (1.67 to 3.02)	239 more per 1000 (from 128 more to 386 more)	LOW	CRITICAL
Stent Dysfunction - Stent Migration												

1	randomised trials	serious[3,4]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/58 (1.7%)	5/55 (9.1%)	RR 0.19 (0.02 to 1.57)	74 fewer per 1000 (from 89 fewer to 52 more)	VERY LOW	CRITICAL
Stent Dysfunction - Stent Occlusion or Migration												
1	randomised trials	serious[3,13]	no serious inconsistency	serious[14]	serious[12]	none	23/57 (40.4%)	19/114 (16.7%)	RR 2.42 (1.44 to 4.06)	237 more per 1000 (from 73 more to 510 more)	VERY LOW	CRITICAL
Stent Occlusion - any type of SEMS												
4	randomised trials	serious[3,5,15,16,17]	no serious inconsistency	serious[6,18,19]	serious[12]	none	45/116 (38.8%)	25/142 (17.6%)	RR 2.2 (1.45 to 3.35)	211 more per 1000 (from 79 more to 414 more)	VERY LOW	CRITICAL
Stent Occlusion - Covered SEMS												
2	randomised trials	serious[3,4]	no serious inconsistency	serious[1]	serious[12]	none	53/109 (48.6%)	22/104 (21.2%)	RR 2.3 (1.51 to 3.49)	275 more per 1000 (from 108 more to 527 more)	VERY LOW	CRITICAL
Stent Occlusion - unresectable patients												
5	randomised trials	serious[3,4,5,16,17]	no serious inconsistency	serious[1,6,18]	no serious imprecision	none	87/204 (42.6%)	37/213 (17.4%)	RR 2.36 (1.7 to 3.28)	236 more per 1000 (from 122 more to 396 more)	LOW	CRITICAL
Stent Occlusion - resectable, borderline resectable or locally advanced												

1	randomised trials	serious[3,15,19]	no serious inconsistency	no serious indirectness	serious[20]	none	11/21 (52.4%)	10/33 (30.3%)	RR 1.73 (0.89 to 3.34)	221 more per 1000 (from 33 fewer to 709 more)	LOW	CRITICAL
Pancreatitis												
7	randomised trials	serious[3,4,5,10,13,15,16]	no serious inconsistency	serious[1,6,18,19]	very serious[2]	none	5/319 (1.6%)	9/401 (2.2%)	RR 0.81 (0.32 to 2.04)	4 fewer per 1000 (from 15 fewer to 23 more)	VERY LOW	CRITICAL
Pancreatitis - any SEMS												
4	randomised trials	serious[3,10,13,15,16]	no serious inconsistency	serious[11,14,18,19]	very serious[2]	none	5/194 (2.6%)	7/279 (2.5%)	RR 1.02 (0.36 to 2.92)	1 more per 1000 (from 16 fewer to 48 more)	VERY LOW	CRITICAL
Pancreatitis - covered SEMS												
2	randomised trials	serious[3,4]	no serious inconsistency	serious[1]	very serious[2]	none	0/109 (0%)	2/104 (1.9%)	RR 0.32 (0.03 to 3.01)	13 fewer per 1000 (from 19 fewer to 39 more)	VERY LOW	CRITICAL
Pancreatitis - unresectable patients												
5	randomised trials	serious[3,4,5,10,13,16]	no serious inconsistency	serious[1,11,14,18]	very serious[2]	none	5/282 (1.8%)	3/350 (0.86%)	RR 1.52 (0.51 to 4.59)	0 more per 100 (from 0 fewer to 3 more)	VERY LOW	CRITICAL
Pancreatitis - resectable, borderline resectable or locally advanced patients												

1	randomised trials	serious[3,15]	no serious inconsistency	serious[19]	very serious[2]	none	0/21 (0%)	6/33 (18.2%)	RR 0.12 (0.01 to 2.01)	160 fewer per 1000 (from 180 fewer to 184 more)	VERY LOW	CRITICAL
Cholangitis - unresectable patients												
4	randomised trials	serious[3,5,10,16]	no serious inconsistency	serious[1,6,11]	no serious imprecision	none	17/167 (10.2%)	5/167 (3%)	RR 3.1 (1.28 to 7.48)	63 more per 1000 (from 8 more to 194 more)	LOW	CRITICAL
Cholangitis - any SEMS												
2	randomised trials	serious[3,5,16]	no serious inconsistency	serious[6,18]	very serious[2]	none	5/75 (6.7%)	3/77 (3.9%)	RR 1.71 (0.5 to 5.89)	28 more per 1000 (from 19 fewer to 191 more)	VERY LOW	CRITICAL
Cholangitis - covered SEMS												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	2/51 (3.9%)	0/49 (0%)	RR 4.81 (0.24 to 97.68)	-	VERY LOW	CRITICAL
Cholangitis - partially-covered SEMS												
1	randomised trials	serious[3,10]	no serious inconsistency	serious[11]	serious[20]	none	10/41 (24.4%)	2/41 (4.9%)	RR 5 (1.17 to 21.43)	195 more per 1000 (from 8 more to 997 more)	VERY LOW	CRITICAL
Cholecystitis - unresectable patients												
4	randomised trials	serious[3,4,5,10,13]	no serious inconsistency	serious[6,11,14]	very serious[2]	none	2/188 (1.1%)	7/260 (2.7%)	RR 0.47 (0.15 to 1.53)	14 fewer per 1000 (from 23	VERY LOW	CRITICAL

										fewer to 14 more)		
Cholecystitis - any SEMS												
2	randomised trials	serious[3,5,13]	no serious inconsistency	serious[6,14]	very serious[2]	none	2/89 (2.2%)	1/164 (0.61%)	RR 2.56 (0.33 to 20.1)	10 more per 1000 (from 4 fewer to 116 more)	VERY LOW	CRITICAL
Cholecystitis - partially-covered SEMS												
1	randomised trials	serious[3,10]	no serious inconsistency	serious[11]	very serious[2]	none	0/41 (0%)	2/41 (4.9%)	RR 0.2 (0.01 to 4.04)	39 fewer per 1000 (from 48 fewer to 148 more)	VERY LOW	CRITICAL
Cholecystitis - Covered SEMS												
1	randomised trials	serious[3,4]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/58 (0%)	4/55 (7.3%)	RR 0.11 (0.01 to 1.91)	65 fewer per 1000 (from 72 fewer to 66 more)	VERY LOW	CRITICAL
# patients with cholestatic symptoms to 2-year FU (follow-up 2 years)												
1	randomised trials	serious[3,10]	no serious inconsistency	serious[11]	very serious[2]	none	14/39 (35.9%)	10/40 (25%)	RR 1.44 (0.73 to 2.84)	110 more per 1000 (from 67 fewer to 460 more)	VERY LOW	CRITICAL
Post-ES Haemorrhage												
1	randomised trials	serious[3,16]	no serious inconsistency	serious[18]	very serious[2]	none	1/59 (1.7%)	0/59 (0%)	RR 3 (0.12 to 72.18)	-	VERY LOW	CRITICAL
								0%		-		
Hospitalisation (measured with: Days; Better indicated by lower values)												

2	randomised trials	serious[3,10,16]	no serious inconsistency	serious[11,18]	serious[20]	none	98	99	-	SMD 0.49 higher (0.21 to 0.77 higher)	VERY LOW	CRITICAL
# >=30% decrease in serum bilirubin												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[20]	none	15/16 (93.8%)	18/18 (100%)	RR 0.94 (0.79 to 1.1)	60 fewer per 1000 (from 210 fewer to 100 more)	LOW	CRITICAL
% Reduction in total serum bilirubin levels (Better indicated by higher values)												
1	randomised trials	serious[3,10]	no serious inconsistency	serious[11]	serious[21,22]	none	39	40	-	MD 10.3 lower (32.51 lower to 11.91 higher)	VERY LOW	CRITICAL
Total Serum Bilirubin - rate of change (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[20]	none	49	49	-	SMD 0.23 lower (0.62 lower to 0.17 higher)	LOW	CRITICAL

1 Soderlund et al. 2006 sample included 78% pancreatic cancer patients.
2 Crosses 2 default MIDs for dichotomous outcomes (0.8 and 1.25).
3 Overall high risk of bias.
4 Isayama et al. 2001 (all patients received endoscopic sphincterotomy).
5 Schmidt et al. 2015 (selective reporting of outcomes; study terminated early due to high rate of stent failure in plastic [winged] stent group).
6 Schmidt et al 2015 sample included 67% pancreatic cancer patients.
7 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant.
8 Not statistically significant.
9 Not all included studies provided data regarding number of patients who were still alive or experienced stent dysfunction.
10 Moses et al. 2013 (unclear randomisation method; selective reporting of outcomes).

11 Moses et al. 2013 sample included 68% pancreatic cancer patients.
12 Small sample size for dichotomous outcomes (<300 events).
13 Walter et al. 2015 (unclear whether blinding would affect outcome; selective reporting of outcomes).
14 Walter et al. 2015 included 75% pancreatic cancer patients.
15 Gardner et al. 2016 (unclear allocation concealment and blinding of outcome assessment; selective reporting of outcomes; participants were receiving 1 of 3 neoadjuvant chemoradiotherapy regimens).
16 Kaassis et al. 2003 (unclear randomisation method and allocation concealment; selective reporting of outcomes; significant difference in % weight loss at baseline; some patients also received sphincterotomy).
17 Travis et al. 1997 (unclear randomisation method, allocation concealment, blinding of personnel/participants/outcome assessment; imbalance in group numbers and selective reporting of outcomes).
18 Kaassis et al. 2003 sample included 75% pancreatic cancer patients.
19 Gardner et al. 2016 includes both resectable (19%), borderline resectable (26%), and unresectable (55%) pancreatic cancer patients.
20 Crosses 1 default MID for dichotomous (0.8 or 1.25) or continuous outcomes (0.5 or -0.5).
21 MID for this outcome assumed to be 21.81/-21.81 (0.5 SD of control group at follow up; data from Moses et al. 2013).
22 Crosses 1 MID for this outcome.

I.10.2 Covered SEMS versus uncovered SEMS

Table 18: Full GRADE profile for covered SEMS versus uncovered SEMS in adults with pancreatic cancer and biliary obstruction

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SEMS: Covered	Uncovered	Relative (95% CI)	Absolute		
Stent Dysfunction												
5	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	73/350 (20.9%)	91/351 (25.9%)	RR 0.81 (0.61 to 1.05)	49 fewer per 1000 (from 101 fewer to 13 more)	VERY LOW	CRITICAL
Stent Dysfunction by cause - Sludge formation												
3	randomised trials	serious[4]	no serious inconsistency	serious[5]	serious[6]	none	25/300 (8.3%)	10/300 (3.3%)	RR 2.43 (1.22 to 4.85)	48 more per 1000 (from 7 more to 128 more)	VERY LOW	CRITICAL
Stent Dysfunction by cause - Stent migration												

2	randomised trials	serious[7]	no serious inconsistency	serious[8]	very serious[9]	none	6/260 (2.3%)	0/260 (0%)	RR 13 (0.74 to 229.23)	-	VERY LOW	CRITICAL
Stent Dysfunction by cause - Tumour ingrowth												
3	randomised trials	serious[10]	serious	serious[8]	serious[3]	none	14/300 (4.7%)	40/300 (13.3%)	RR 0.36 (0.2 to 0.64)	85 fewer per 1000 (from 48 fewer to 107 fewer)	VERY LOW	CRITICAL
Stent Dysfunction by cause - Tumour overgrowth												
3	randomised trials	serious[11]	no serious inconsistency	serious[8]	serious[6]	none	23/300 (7.7%)	12/300 (4%)	RR 1.88 (0.97 to 3.66)	35 more per 1000 (from 1 fewer to 106 more)	VERY LOW	CRITICAL
Adverse Events												
4	randomised trials	serious[12]	no serious inconsistency	serious[2]	very serious[9]	none	23/334 (6.9%)	26/334 (7.8%)	RR 0.89 (0.52 to 1.51)	9 fewer per 1000 (from 37 fewer to 40 more)	VERY LOW	CRITICAL
Adverse Events by type - Cholangitis												
1	randomised trials	serious[13]	no serious inconsistency	serious[8]	very serious[9]	none	8/200 (4%)	12/200 (6%)	RR 0.67 (0.28 to 1.6)	20 fewer per 1000 (from 43 fewer to 36 more)	VERY LOW	CRITICAL
Adverse Events by type - Cholecystitis												
2	randomised trials	serious[14]	no serious inconsistency	no serious indirectness	very serious[9]	none	3/260 (1.2%)	4/260 (1.5%)	RR 0.75 (0.17 to 3.31)	4 fewer per 1000 (from 13 fewer to 36 more)	VERY LOW	CRITICAL
Adverse Events by type - Haemorrhage												

2	randomised trials	serious[15]	no serious inconsistency	serious[8]	very serious[9]	none	2/240 (0.83%)	3/240 (1.3%)	RR 0.71 (0.14 to 3.52)	4 fewer per 1000 (from 11 fewer to 32 more)	VERY LOW	CRITICAL
Adverse Events by type - Pancreatitis												
3	randomised trials	serious[11]	no serious inconsistency	serious[2]	very serious[9]	none	5/294 (1.7%)	4/294 (1.4%)	RR 1.2 (0.37 to 3.89)	3 more per 1000 (from 9 fewer to 39 more)	VERY LOW	CRITICAL
Adverse Events by type - Peritoneal irritation												
1	randomised trials	serious[16]	no serious inconsistency	no serious indirectness	very serious[9]	none	3/40 (7.5%)	2/40 (5%)	RR 0 (0.26 to 8.5)	50 fewer per 1000 (from 37 fewer to 375 more)	VERY LOW	CRITICAL
Adverse Events by type - Retroperitoneal perforation												
1	randomised trials	serious[13]	no serious inconsistency	serious[8]	very serious[9]	none	1/200 (0.5%)	1/200 (0.5%)	RR 1 (0.06 to 15.88)	0 fewer per 1000 (from 5 fewer to 74 more)	VERY LOW	CRITICAL
Adverse Events by type - Sepsis												
1	randomised trials	serious[17]	no serious inconsistency	serious[18]	very serious[9]	none	1/34 (2.9%)	0/34 (0%)	RR 3 (0.13 to 71.15)	-	VERY LOW	CRITICAL

1 Overall high risk of bias due to selective reporting and other source of bias. Kullman et al. 2010 contributed almost 50% to this outcome and had risk of bias due to significant difference in mean age of groups, number with hepatic or metastasis (at baseline) and number with unknown causes of stent failure.
2 Two of the studies (Kullman et al. 2010; Ung et al. 2013) used samples that had less than 85% pancreatic cancer patients.
3 Small sample size for dichotomous outcomes (<300 events).
4 Overall all 3 studies had high/unclear risk of bias mainly due to selective reporting. Two of these, which contributed approximately 57% and 38% to outcome, were at high risk due to other sources of bias: in Kitano et al. 2013, there was significant difference in the length of stents used in each group, whilst majority of sample had had prior biliary drainage; in Kullman et al 2010 there were significant differences in mean age of groups and number with hepatic or metastasis (at baseline) and number with unknown causes of stent failure).
5 Sample in Kullman et al. 2010, which contributed 38% to the outcome, had 77% pancreatic cancer patients.
6 Crosses 1 default MID for dichotomous outcomes (0.8 or 1.25).
7 Both studies had high risk of bias due to selective reporting and other sources of bias. Kullman et al. 2010 contributed 100% to this outcome and there were significant differences between the groups in mean age and hepatic or other metastasis at baseline and in number of patients with unknown causes of stent failure.

8 Sample in Kullman et al. 2010 had 77% pancreatic cancer patients.
9 Crosses 2 default MID for dichotomous outcomes (0.8 and 1.25).
10 Overall high risk of bias due to selective reporting and other source of bias. Kullman et al. 2010 contributed almost 52% to this outcome and had risk of bias due to significant difference in mean age of groups, number with hepatic or metastasis (at baseline) and number with unknown causes of stent failure. Kitano et al. 2013 contributed approximately 38% to this outcome and similar risk of bias due to significant differences in the length of stent used in each group and fact that majority of sample had had prior biliary drainage.
11 Overall high risk of bias due to selective reporting and other source of bias. Kullman et al. 2010 contributed 80% to this outcome and had risk of bias due to significant difference in mean age of groups, number with hepatic or metastasis (at baseline) and number with unknown causes of stent failure.
12 Overall high risk of bias due to selective reporting and other source of bias. Kullman et al. 2010 contributed almost 80% to this outcome and had risk of bias due to significant difference in mean age of groups, number with hepatic or metastasis (at baseline) and number with unknown causes of stent failure.
13 Kullman et al. 2010 is at high risk of bias due to selective reporting and other sources of bias. There were significant differences between the groups in mean age and hepatic or other metastasis at baseline and in number of patients with unknown causes of stent failure.
14 Both studies, each of which contributed 50% to this outcome, had high risk of bias due to selective reporting and other sources of bias (in Kullman et al. 2010, there were significant differences between the groups in mean age and hepatic or other metastasis at baseline and in number of patients with unknown causes of stent failure; in Kitano et al. 2013, there was significant difference in length of stents used in each group, and majority of sample had received prior biliary drainage).
15 Overall high or unclear risk of bias. Krokidis et al. 2011, which contributed approximately 57% to this outcome, at risk due to selective reporting, and unclear randomisation method/allocation concealment.
16 Krokidis et al. 2011 had overall high or unclear risk of bias due to selective reporting, and unclear randomisation method/allocation concealment.
17 Ung et al. 2013 had high risk of bias due to unclear randomisation method, selective reporting, and fact that more than 80% of the sample died with patent stents.
18 Sample in Ung et al. 2013 had 84% pancreatic cancer patients.

I.10.3 Partially covered SEMS versus uncovered SEMS

Table 19: Full GRADE profile for partially covered SEMS versus uncovered SEMS in adults with pancreatic cancer and biliary obstruction

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SEMS: Partially covered	Uncovered	Relative (95% CI)	Absolute		
Stent Dysfunction - Any cause												
2	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29/122 (23.8%)	21/121 (17.4%)	RR 1.35 (0.81 to 2.23)	61 more per 1000 (from 33 fewer to 213 more)	VERY LOW	CRITICAL
Stent Dysfunction - Stent migration												

1	randomised trials	serious[4]	no serious inconsistency	serious[5]	serious[3]	none	8/68 (11.8%)	0/61 (0%)	RR 15.28 (0.9 to 259.23)	-	VERY LOW	CRITICAL
Adverse events - Any cause												
1	randomised trials	serious[4]	no serious inconsistency	serious[5]	serious[3]	none	42/68 (61.8%)	27/61 (44.3%)	RR 1.4 (1 to 1.96)	177 more per 1000 (from 0 more to 425 more)	VERY LOW	CRITICAL
Adverse events - Pancreatitis												
2	randomised trials	serious[6]	no serious inconsistency	serious[2]	very serious[7]	none	1/139 (0.72%)	1/136 (0.74%)	RR 0.97 (0.14 to 6.58)	0 fewer per 1000 (from 6 fewer to 41 more)	VERY LOW	CRITICAL
Adverse events - Cholecystitis												
2	randomised trials	serious[4]	no serious inconsistency	serious[5]	very serious[7]	none	3/117 (2.6%)	3/120 (2.5%)	RR 0.98 (0.21 to 4.59)	0 fewer per 1000 (from 20 fewer to 90 more)	VERY LOW	CRITICAL
Adverse events - Other												
2	randomised trials	serious[8]	no serious inconsistency	serious[2]	very serious[7]	none	23/139 (16.5%)	19/136 (14%)	RR 1.14 (0.66 to 1.99)	20 more per 1000 (from 47 fewer to 138 more)	VERY LOW	CRITICAL

1 Telford et al. 2010, which contributed 55% to this outcome, had high/unclear risk of bias due to insufficient information about allocation concealment, imbalance in numbers due to failure to attain adequately powered groups, and selective reporting.
2 Both studies used samples comprised of less than 85% pancreatic cancer patients.
3 Crosses 1 default MID for dichotomous outcomes (0.8 or 1.25).
4 Telford et al. 2010 had high/unclear risk of bias due to insufficient information about allocation concealment, imbalance in numbers due to failure to attain adequately powered groups, and selective reporting.
5 Telford et al. 2010 had 82% pancreatic cancer patients.
6 Telford et al. 2010, which contributed approximately 77% to this outcome, had high/unclear risk of bias due to insufficient information about allocation concealment, imbalance in numbers due to failure to attain adequately powered groups, and selective reporting.
7 Crosses 2 default MID for dichotomous outcomes (0.8 and 1.25).
8 Telford et al. 2010, which contributed 65% to this outcome, had high/unclear risk of bias due to insufficient information about allocation concealment, imbalance in numbers due to failure to attain adequately powered groups, and selective reporting.

I.10.41 Paclitaxel-eluting self-expanding metal stent vs covered self-expanding metal stent

2 **Table 20: Full GRADE profile for paclitaxel-eluting self-expanding metal stent versus covered SEMS in adults with an unresectable**
3 **distal malignant biliary obstruction**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Paclitaxel-eluting SEMS	Covered SEMS for unresectable PC	Relative (95% CI)	Absolute		
Time to stent dysfunction- All patients												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	0/26 (0%)[4]	0/26 (0%)[4]	HR 0.53 (0.16 to 1.78)	- 0%	VERY LOW	CRITICAL
Time to stent dysfunction - Pancreatic cancer patients												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness[2]	very serious[3]	none	0/13 (0%)[4]	0/12 (0%)[4]	HR 0.52 (0.1 to 3.09)	- 0%	VERY LOW	CRITICAL
Overall Survival - All patients												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[5,6]	none	0/26 (0%)[4]	0/26 (0%)[4]	HR 1.19 (0.65 to 2.18)	- 0%	VERY LOW	CRITICAL
Overall Survival - Pancreatic cancer patients												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[5,6]	none	0/13 (0%)[4]	0/12 (0%)[4]	HR 0.85 (0.35 to 2.06)	- 0%	LOW	CRITICAL
Stent Dysfunction - Stent Occulsion												

1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	5/24 (20.8%)	8/25 (32%)	RR 0.65 (0.25 to 1.71)	112 fewer per 1000 (from 240 fewer to 227 more)	VERY LOW	CRITICAL
Cholangitis symptoms (assessed with: <30 days after surgery)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	3/24 (12.5%)	0/25 (0%)	RR 7.28 (0.4 to 133.89)	-	VERY LOW	CRITICAL
Pancreatitis (assessed with: <30 days after surgery)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	1/24 (4.2%)	1/25 (4%)	RR 1.04 (0.07 to 15.73)	2 more per 1000 (from 37 fewer to 589 more)	VERY LOW	CRITICAL

1 Song et al. 2011: overall high risk of bias (unclear allocation concealment, blinding of outcome assessment and selective reporting; no power calculation; randomised participants were patients with unresectable distal malignant biliary obstruction who did not wish to undergo chemotherapy nor radiotherapy).
2 There were only 51% pancreatic cancer patients in this study. Since this was the only study that compared paclitaxel-eluting SEMS with another type of SEMS, it was decided to include this study though downgrade one level for indirectness.
3 Crosses 2 default MIDs for dichotomous outcomes (0.8 and 1.25).
4 Study did not report number of deaths nor number of stent failures.
5 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant.
6 Not statistically significant.

I.10.5 Preoperative endoscopic biliary drainage (PEBD) then surgery versus surgery

Table 21: Full GRADE profile for preoperative endoscopic biliary drainage then surgery versus surgery in adults with suspected pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative Endoscopic	Surgery	Relative (95% CI)	Absolute		

							Biliary Drainage>Surgery					
Mortality at 120 days												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	15/102 (14.7%)	12/94 (12.8%)	RR 1.15 (0.57 to 2.33)	19 more per 1000 (from 55 fewer to 170 more)	VERY LOW	CRITICAL
Mortality at 2 years												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	77/95 (81.1%)	76/90 (84.4%)	RR 0.96 (0.84 to 1.09)	34 fewer per 1000 (from 135 fewer to 76 more)	VERY LOW	CRITICAL
Treatment-related mortality												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	9/102 (8.8%)	4/94 (4.3%)	RR 2.07 (0.66 to 6.51)	46 more per 1000 (from 14 fewer to 234 more)	VERY LOW	CRITICAL
Overall Survival at 2 years												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[5,6]	none	77/95 (81.1%)	76/90 (84.4%)	HR 0.98 (0.72 to 1.34)	6 fewer per 1000 (from 106 fewer to 73 more)	VERY LOW	CRITICAL
Overall Survival at 2 years – resectable patients after resection												
1	randomised trials	very serious[1,7]	no serious inconsistency	serious[2]	serious[5,6]	none	53/91 (58.2%)	60/89 (67.4%)	HR 0.79 (0.54 to 1.18)	82 fewer per 1000 (from 221	VERY LOW	CRITICAL

										fewer to 52 more)		
Overall Survival at 2 years – unresectable patients after palliative surgery												
1	randomised trials	very serious[1,7]	no serious inconsistency	serious[2]	serious[5,6]	none	38/91 (41.8%)	29/89 (32.6%)	HR 1.02 (0.63 to 1.67)	2 more per 1000 (from 85 fewer to 31 more)	VERY LOW	CRITICAL
Delay to surgery (measured with: Weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4,8]	none	102	94	-	MD 4 higher (3.58 to 4.42 higher)	VERY LOW	CRITICAL
Hospitalisation due to protocol-specific complication												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	34/102 (33.3%)	11/94 (11.7%)	RR 2.85 (1.53 to 5.29)	216 more per 1000 (from 62 more to 502 more)	VERY LOW	CRITICAL
Rate of serious complications (<120 days after randomisation)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	75/102 (73.5%)	37/94 (39.4%)	HR 1.86 (1.41 to 2.45)	212 more per 1000 (from 112 more to 313 more)	VERY LOW	CRITICAL
Total protocol-specified complications												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	75/102 (73.5%)	37/94 (39.4%)	RR 1.87 (1.42 to 2.46)	342 more per 1000 (from 165 more to	VERY LOW	CRITICAL

										575 more)		
Pre-surgery Pancreatitis												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[9]	none	7/102 (6.9%)	0/94 (0%)	RR 13.83 (0.8 to 238.96)	-	VERY LOW	CRITICAL
Pre-surgery Cholangitis												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	27/102 (26.5%)	2/94 (2.1%)	RR 12.44 (3.04 to 50.89)	243 more per 1000 (from 43 more to 1000 more)	VERY LOW	CRITICAL
Pre-surgery Post-ERCP Haemorrhage												
1	randomised trials	serious[1]	no serious inconsistency	serious	very serious[3]	none	2/102 (2%)	0/94 (0%)	RR 4.61 (0.22 to 94.83)	-	VERY LOW	CRITICAL
Pre-surgery Perforation												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	2/102 (2%)	0/94 (0%)	RR 4.61 (0.22 to 94.83)	-	VERY LOW	CRITICAL
Stent Dysfunction - Stent Occlusion												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	15/102 (14.7%)	1/94 (1.1%)	RR 13.82 (1.86 to 102.63)	136 more per 1000 (from 9 more to 1000 more)	VERY LOW	CRITICAL
Total Surgery-related Complications												

1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[9]	none	48/102 (47.1%)	35/94 (37.2%)	RR 1.26 (0.91 to 1.76)	97 more per 1000 (from 34 fewer to 283 more)	VERY LOW	CRITICAL
Total Surgery-related Complications for unresectable PC												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	18/33 (54.5%)	5/28 (17.9%)	RR 3.05 (1.3 to 7.17)	366 more per 1000 (from 54 more to 1000 more)	VERY LOW	CRITICAL
Surgery-related Haemorrhage												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	2/102 (2%)	4/94 (4.3%)	RR 0.46 (0.09 to 2.46)	23 fewer per 1000 (from 39 fewer to 62 more)	VERY LOW	CRITICAL
Surgery-related Cholangitis												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	3/102 (2.9%)	3/94 (3.2%)	RR 0.92 (0.19 to 4.45)	3 fewer per 1000 (from 26 fewer to 110 more)	VERY LOW	CRITICAL
Surgery-related Pneumonia												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	9/102 (8.8%)	5/94 (5.3%)	RR 1.66 (0.58 to 4.77)	35 more per 1000 (from 22 fewer to 201 more)	VERY LOW	CRITICAL

1 Eshuis et al. 2010/van der Gaag 2010: overall unclear risk of bias (unclear allocation concealment and selective reporting).
2 After surgical exploration, sample was found to include 92% pancreatic cancer patients; sample also includes participants with either resectable or unresectable tumours. Five patients in surgery only group also underwent preoperative biliary drainage due to unavailability of surgical facility (3 patients), intercurrent cholangitis after ERCP (1 patient) and hyperglycemia (1 patient).
3 Crosses 2 default MIDs for dichotomous outcomes (0.8 and 1.25).
4 Small sample size for dichotomous (<300 events) or continuous (<400 participants) outcome.
5 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant.
6 Not statistically significant.
7 Randomisation of patients were not stratified by resectability status.
8 MID for this outcome assumed to be 0.61/-0.61 weeks (0.5 SD of control arm at follow up, calculated from data in van der Gaag et al. 2010).
9 Crosses 1 default MID for dichotomous outcomes (0.8 or 1.25).

I.10.6.3 Endoscopic sphincterotomy then stent versus stent

Table 22: Full GRADE profile for endoscopic sphincterotomy then stent versus stent in adults with unresectable pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Endoscopic Sphincterotomy ->Stent	Stent only for unresectable PC	Relative (95% CI)	Absolute		
Deaths due to PC progression												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	67/100 (67%)	78/100 (78%)	RR 0.86 (0.72 to 1.02)	109 fewer per 1000 (from 218 fewer to 16 more)	MODERATE	CRITICAL
Stent Dysfunction - Stent Occulsion												
3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	25/229 (10.9%)	27/227 (11.9%)	RR 0.91 (0.55 to 1.52)	11 fewer per 1000 (from 54 fewer to 62 more)	VERY LOW	CRITICAL

Stent Dysfunction - Stent Migration												
3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	13/229 (5.7%)	7/227 (3.1%)	RR 1.84 (0.75 to 4.54)	26 more per 1000 (from 8 fewer to 109 more)	VERY LOW	CRITICAL
Early Complications <=30 days												
2	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[3]	none	16/188 (8.5%)	13/188 (6.9%)	RR 1.24 (0.61 to 2.5)	17 more per 1000 (from 27 fewer to 104 more)	VERY LOW	CRITICAL
Total stent-related Early Complications (<=30 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	15/100 (15%)	15/100 (15%)	RR 1 (0.52 to 1.93)	0 fewer per 1000 (from 72 fewer to 139 more)	LOW	
Pancreatitis <=30 days												
3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	11/225 (4.9%)	10/225 (4.4%)	RR 1.11 (0.49 to 2.54)	5 more per 1000 (from 23 fewer to 68 more)	VERY LOW	CRITICAL
Pancreatitis <=30 days related to stent placement												
2	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[3]	none	11/188 (5.9%)	10/188 (5.3%)	RR 1.11 (0.49 to 2.54)	6 more per 1000 (from 27 fewer to 82 more)	VERY LOW	CRITICAL

Perforation <=30 days												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	0/96 (0%)	1/98 (1%)	RR 0.34 (0.01 to 8.25)	7 fewer per 1000 (from 10 fewer to 74 more)	LOW	
Cholecystitis <=30 days												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	1/91 (1.1%)	4/93 (4.3%)	RR 0.26 (0.03 to 2.24)	32 fewer per 1000 (from 42 fewer to 53 more)	LOW	CRITICAL
Total Late Complications related to stent placement (>30 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	6/100 (6%)	5/100 (5%)	RR 1.2 (0.38 to 3.81)	10 more per 1000 (from 31 fewer to 140 more)	LOW	CRITICAL
Cholangitis >30 days												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[3]	none	16/92 (17.4%)	15/90 (16.7%)	RR 1.04 (0.55 to 1.98)	7 more per 1000 (from 75 fewer to 163 more)	VERY LOW	CRITICAL
Cholecystitis >30 days												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	1/91 (1.1%)	4/93 (4.3%)	RR 0.26 (0.03 to 2.24)	32 fewer per 1000 (from 42 fewer to 53 more)	LOW	CRITICAL

1 *1 Crosses 1 default MID for dichotomous outcomes (0.8 or 1.25).*

2 Majority of studies (2 of 3) are unclear or high risk of bias (Artifon et al. 2008; Giorgio et al. 2004): Artifon et al. 2008 (unclear allocation concealment, selective reporting of outcomes); Giorgio et al. 2004 (unclear randomisation method, allocation concealment).
3 Crosses 2 default MIDs for dichotomous outcomes (0.8 and 1.25).
4 Unclear risk of bias for Giorgio et al. 2004 (unclear randomisation method, allocation concealment).

I.10.75 Endoscopic sphincterotomy then stent versus surgical bypass

Table 23: Full GRADE profile for endoscopic sphincterotomy then stent versus surgical bypass in adults with unresectable pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Endoscopic Sphincterotomy ->Stent	Surgical bypass for unresectable PC	Relative (95% CI)	Absolute		
Relief of biliary obstruction												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	15/15 (100%)	15/15 (100%)	RR 1 (0.88 to 1.13)	0 fewer per 1000 (from 120 fewer to 130 more)	LOW	CRITICAL
Treatment-related morbidity												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/15 (20%)	4/15 (26.7%)	RR 0.75 (0.2 to 2.79)	67 fewer per 1000 (from 213 fewer to 477 more)	VERY LOW	CRITICAL
Treatment-related hospital readmissions												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	9/15 (60%)	6/15 (40%)	RR 1.5 (0.71 to 3.16)	200 more per 1000 (from 116 fewer to 864 more)	VERY LOW	CRITICAL
Bilirubin level <2.5 mg/dL on day 30												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	8/15 (53.3%)	8/15 (53.3%)	RR 1 (0.51 to 1.95)	0 fewer per 1000 (from 261 fewer to 507 more)	VERY LOW	CRITICAL
Serum bilirubin level at 30 days (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4,5]	none	15	15	-	MD 0.3 lower (1.06 lower to 0.46 higher)	LOW	CRITICAL
Stent-related complications												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/15 (26.7%)	0/15 (0%)	RR 9 (0.53 to 153.79)	-	VERY LOW	CRITICAL
Treatment-related early onset complications (assessed with: Definition of 'early' not provided)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/15 (20%)	5/15 (33.3%)	RR 0.6 (0.17 to 2.07)	133 fewer per 1000 (from 277	VERY LOW	CRITICAL

										fewer to 357 more)		
Treatment-related late onset complications (assessed with: Definition of 'late' not provided)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/15 (20%)	4/15 (26.7%)	RR 0.75 (0.2 to 2.79)	67 fewer per 1000 (from 213 fewer to 477 more)	VERY LOW	CRITICAL
Post-operative complications												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/15 (33.3%)	7/15 (46.7%)	RR 0.71 (0.29 to 1.75)	135 fewer per 1000 (from 331 fewer to 350 more)	VERY LOW	CRITICAL
Pneumonia												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/15 (0%)	2/15 (13.3%)	RR 0.2 (0.01 to 3.85)	107 fewer per 1000 (from 132 fewer to 380 more)	VERY LOW	CRITICAL
Post-ERCP Pancreatitis												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/15 (6.7%)	0/15 (0%)	RR 3 (0.13 to 68.26)	- -	VERY LOW	CRITICAL

Quality of Life - SF-36 at 30 days (Better indicated by higher values)												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	serious[6]	none	15	15	-	SMD 0.78 higher (0.04 to 1.52 higher)	LOW	CRITICAL
Quality of Life - SF-36 at 60 days (Better indicated by higher values)												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	serious[6]	none	15	15	-	SMD 0.75 higher (0.01 to 1.49)	LOW	CRITICAL

1 Artifon et al. 2006: overall high/unclear risk of bias (unclear allocation concealment; selective reporting of survival and QoL outcomes; no power calculation/small sample size).
2 Small sample size (<300 events).
3 Crosses 2 default MIDs for dichotomous outcomes (0.8 and 1.25).
4 MIDs for this outcome assumed to be 0.5 SD or -0.5 SD of control arm at baseline calculated as 5.64/-5.64 (from data in Artifon et al. 2006).
5 Small sample size for continuous outcome (<400 participants).
6 Crosses 1 default MID for continuous outcomes (0.5 or -0.5).

I.10.8 Endoscopic ultrasound-guided choledochoduodenostomy (EUS-CD) and stent versus percutaneous transhepatic biliary drainage (PTBD))

Table 24: Full GRADE profile for endoscopic ultrasound-guided choledochoduodenostomy and stent versus percutaneous transhepatic biliary drainage in adults with an unresectable malignant biliary obstruction where either ERCP or EUS-guided transpapillary rendezvous has failed

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EUS-CD	Percutaneous transhepatic biliary drainage	Relative (95% CI)	Absolute		
Total serum bilirubin - at 7 days (Better indicated by lower values)												

1	randomised trials	serious[1]	no serious inconsistency	very serious[2]	serious[3]	none	13	12	-	SMD 0.53 lower (1.33 lower to 0.27 higher)	VERY LOW	CRITICAL
Total serum bilirubin - at 30 days (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	very serious[2]	serious[3]	none	13	12	-	SMD 0.42 higher (0.37 lower to 1.22 higher)	VERY LOW	CRITICAL
Treatment-related complications - Total												
1	randomised trials	serious[1]	no serious inconsistency	very serious[2]	very serious[4]	none	2/13 (15.4%)	3/12 (25%)	RR 0.62 (0.12 to 3.07)	95 fewer per 1000 (from 220 fewer to 517 more)	VERY LOW	CRITICAL
SF-36 Overall - at 7 days (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	very serious[2]	serious[3]	none	13	12	-	SMD 0.29 lower (1.08 lower to 0.5 higher)	VERY LOW	CRITICAL
SF-36 Overall - at 30 days (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	very serious[2]	serious[3]	none	13	12	-	SMD 0.31 lower (1.1 lower to 0.48 higher)	VERY LOW	CRITICAL

1 *1 Artifon et al. 2012: overall high risk of bias (inadequate randomisation method, unclear allocation concealment, selective reporting of outcomes, no power calculation/small*
2 *sample size; participants not blinded for QoL outcomes).*
3 *2 Sample has 64% pancreatic cancer patients.*
4 *3 Crosses 1 default MID for continuous outcomes (0.5 or -0.5).*
5 *4 Crosses 2 default MIDs for dichotomous outcomes (0.8 and 1.25).*

I.10.9 Endoscopic ultrasound-guided choledochoduodenostomy and stent versus surgical bypass

Table 25: Full GRADE profile for endoscopic ultrasound-guided choledochoduodenostomy and stent versus surgical bypass in adults with an unresectable malignant biliary obstruction where ERCP has failed

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EUS-CD	Surgical bypass	Relative (95% CI)	Absolute		
Reduction>=50% from baseline in total serum bilirubin after 7 days												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	10/14 (71.4%)	14/15 (93.3%)	RR 0.77 (0.54 to 1.09)	215 fewer per 1000 (from 429 fewer to 84 more)	VERY LOW	CRITICAL
Total serum bilirubin - at 7 days (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4,5]	none	14	15	-	MD 1.71 higher (0.24 lower to 3.66 higher)	VERY LOW	CRITICAL
Total serum bilirubin - at 30 days (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4,6]	none	14	15	-	MD 0.26 higher (0.37 lower to 0.89 higher)	VERY LOW	CRITICAL
Total serum bilirubin - at 60 days (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4,6]	none	11	14	-	MD 0.06 higher (0.31 lower to 0.43 higher)	VERY LOW	CRITICAL
Total serum bilirubin - at 90 days (Better indicated by lower values)												

1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4,6]	none	7	6	-	MD 0.01 higher (0.58 lower to 0.6 higher)	VERY LOW	CRITICAL
Treatment-related complications												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[7]	none	3/14 (21.4%)	2/15 (13.3%)	RR 1.61 (0.31 to 8.24)	81 more per 1000 (from 92 fewer to 965 more)	VERY LOW	CRITICAL
Overall Survival 90 days after surgery												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[8,9]	none	6/14 (42.9%)	9/15 (60%)	HR 0.64 (0.23 to 1.8)	156 fewer per 1000 (from 410 fewer to 208 more)	VERY LOW	CRITICAL
SF-36 Functional Capacity - at 7 days (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[4,10]	none	14	15	-	MD 6.3 higher (5.12 lower to 17.72 higher)	VERY LOW	CRITICAL
SF-36 Functional Capacity - at 30 days (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4,11]	none	14	15	-	MD 10.7 higher (0.93 to 20.47 higher)	VERY LOW	CRITICAL
SF-36 Functional Capacity - at 60 days (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4,11]	none	12	14	-	MD 9.9 higher (1.04 to 18.76 higher)	VERY LOW	CRITICAL
SF-36 Functional Capacity - at 90 days (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[4,10]	none	7	6	-	MD 1.8 lower (9.86 lower to 6.26 higher)	VERY LOW	CRITICAL

SF-36 Physical Health - at 7 days (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[4,10]	none	14	15	-	MD 1.5 higher (11.76 lower to 14.76 higher)	VERY LOW	CRITICAL
SF-36 Physical Health - at 30 days (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[4,10]	none	14	15	-	MD 4.9 lower (18.55 lower to 8.75 higher)	VERY LOW	CRITICAL
SF-36 Physical Health - at 60 days (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[4,10]	none	12	14	-	MD 6.8 higher (5.67 lower to 19.27 higher)	VERY LOW	CRITICAL
SF-36 Physical Health - at 90 days (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[4,10]	none	7	6	-	MD 10.1 lower (33.62 lower to 13.42 higher)	VERY LOW	CRITICAL
SF-36 Pain - at 7 days (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4,6]	none	14	15	-	MD 3.7 lower (17.22 lower to 9.82 higher)	VERY LOW	CRITICAL
SF-36 Pain - at 30 days (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4,6]	none	14	15	-	MD 2.7 higher (9.6 lower to 15 higher)	VERY LOW	CRITICAL
SF-36 Pain - at 60 days (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4,11]	none	12	14	-	MD 4.4 lower (17.51 lower to 8.71 higher)	VERY LOW	CRITICAL
SF-36 Pain - at 90 days (range of scores: 0-100; Better indicated by higher values)												

1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4,11]	none	7	6	-	MD 15.3 lower (27.76 to 2.84 lower)	VERY LOW	CRITICAL
SF-36 General Health - at 7 days (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4,11]	none	14	15	-	MD 3.4 lower (10.15 lower to 3.35 higher)	VERY LOW	CRITICAL
SF-36 General Health - at 30 days (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4,11]	none	14	15	-	MD 4.1 lower (11.85 lower to 3.65 higher)	VERY LOW	CRITICAL
SF-36 General Health - at 60 days (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4,11]	none	12	14	-	MD 3.3 lower (10.58 lower to 3.98 higher)	VERY LOW	CRITICAL
SF-36 General Health - at 90 days (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[4,10]	none	7	6	-	MD 4.5 higher (7.44 lower to 16.44 higher)	VERY LOW	CRITICAL
SF-36 Vitality - at 7 days (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[4,10]	none	14	15	-	MD 2.7 higher (5.64 lower to 11.04 higher)	VERY LOW	CRITICAL
SF-36 Vitality - at 30 days (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4,11]	none	14	15	-	MD 7.6 higher (2.43 lower to 17.63 higher)	VERY LOW	CRITICAL
SF-36 Vitality - at 60 days (range of scores: 0-100; Better indicated by higher values)												

1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[4,10]	none	12	14	-	MD 2.1 higher (8.61 lower to 12.81 higher)	VERY LOW	CRITICAL
SF-36 Vitality - at 90 days (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4,11]	none	7	6	-	MD 14.6 higher (3.2 lower to 32.4 higher)	VERY LOW	CRITICAL
SF-36 Social Role Functioning - at 7 days (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[4,10]	none	14	15	-	MD 0.3 lower (9.69 lower to 9.09 higher)	VERY LOW	CRITICAL
SF-36 Social Role Functioning - at 30 days (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4,11]	none	14	15	-	MD 0.3 higher (7.56 lower to 8.16 higher)	VERY LOW	CRITICAL
SF-36 Social Role Functioning - at 60 days (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[4,10]	none	12	14	-	MD 1.1 lower (12.32 lower to 10.12 higher)	VERY LOW	CRITICAL
SF-36 Social Role Functioning - at 90 days (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[4,10]	none	7	7	-	MD 1.5 higher (9.73 lower to 12.73 higher)	VERY LOW	CRITICAL
SF-36 Emotional Role Functioning - at 7 days (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[4,10]	none	14	15	-	MD 2.5 higher (11.19 lower to 16.19 higher)	VERY LOW	CRITICAL
SF-36 Emotional Role Functioning - at 30 days (range of scores: 0-100; Better indicated by higher values)												

1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[4,10]	none	14	15	-	MD 0.9 higher (15.69 lower to 17.49 higher)	VERY LOW	CRITICAL
SF-36 Emotional Role Functioning - at 60 days (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[4,10]	none	12	14	-	MD 9.5 higher (11.05 lower to 30.05 higher)	VERY LOW	CRITICAL
SF-36 Emotional Role Functioning - at 90 days (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4,10]	none	7	6	-	MD 8.7 higher (15.33 lower to 32.73 higher)	VERY LOW	CRITICAL
SF-36 Mental Health - at 7 days (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4,11]	none	14	15	-	MD 9.1 higher (1.49 to 16.71 higher)	VERY LOW	CRITICAL
SF-36 Mental Health - at 30 days (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4,11]	none	14	15	-	MD 12.9 higher (4.63 to 21.17 higher)	VERY LOW	CRITICAL
SF-36 Mental Health - at 60 days (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4,11]	none	12	14	-	MD 8.9 higher (0.92 lower to 18.72 higher)	VERY LOW	CRITICAL
SF-36 Mental Health - at 90 days (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[4,10]	none	7	7	-	MD 1.9 higher (9.98 lower to 13.78 higher)	VERY LOW	CRITICAL

1 *1 Artifon et al. 2015: Overall high risk of bias (no power calculation; no blinding for QoL outcomes).*
2 *2 Cause of biliary obstruction unclear/number of pancreatic cancer patients unclear*
3 *3 Crosses 1 default MID for dichotomous outcomes (0.8 or 1.25).*

4 MIDs for these outcomes assumed to be 0.5 SD or -0.5 SD of control arm at baseline (calculated from data in Artifon et al. 2015). The MIDs for total bilirubin levels were 2.81/-2.81. For the SF-36 subscales, the MIDs were calculated to be 4.95/-4.95 for Functional Capacity, 5.5/-5.2 for Physical Health, 17.3/-17.3 for Pain, 5.35/-5.35 for General Health, 5.45/-5.45 for Vitality, 7.75/-7.75 for Social Role Functioning, 7.65/-7.65 for Emotional Role Functioning, and 6.6/-6.6 for Mental Health.

5 Crosses 1 MID for total bilirubin levels (2.81 or -2.81).

6 Small sample size for continuous outcome (<400 participants).

7 Crosses 2 default MIDs for dichotomous outcomes (0.8 and 1.25).

8 The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant.

9 Not statistically significant.

10 Crosses 2 MIDs for relevant SF-36 subscale.

11 Crosses 1 MID for relevant SF-36 subscale.

I.11 Duodenal obstruction

I.11.1 Prophylactic GJJ and hepaticojejunostomy versus hepaticojejunostomy only

Table 26: Full GRADE profile for prophylactic GJJ and hepaticojejunostomy versus hepaticojejunostomy only in adults with unresectable pancreatic cancer and gastric outlet obstruction

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prophylactic GJJ + HJJ	HJJ only	Relative (95% CI)	Absolute		
Relief of obstruction (Gastric outlet obstruction) (follow-up 1 months)												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2/80 (2.5%)	20/72 (27.8%)	RR 0.11 (0.03 to 0.4)	247 fewer per 1000 (from 167 fewer to 269 fewer)	LOW	CRITICAL
Adverse events (Perioperative morbidity) - Peri-operative mortality (follow-up 1 months)												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/80 (1.3%)	0/72 (0%)	RR 2.43 (0.1 to 57.57)	-	VERY LOW	CRITICAL
Adverse events (Perioperative morbidity) - Cholangitis (follow-up 1 months)												

1[1]	randomised trials	serious[2,4]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/44 (9.1%)	2/43 (4.7%)	RR 1.95 (0.38 to 10.12)	44 more per 1000 (from 29 fewer to 424 more)	VERY LOW	CRITICAL
Adverse events (Perioperative morbidity) - Bile leak (follow-up 1 months)												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/80 (5%)	3/72 (4.2%)	RR 1.23 (0.28 to 5.34)	10 more per 1000 (from 30 fewer to 181 more)	VERY LOW	CRITICAL
Adverse events (Perioperative morbidity) - Gastroenteral leak (follow-up 1 months)												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/80 (1.3%)	1/72 (1.4%)	RR 0.81 (0.05 to 12.33)	3 fewer per 1000 (from 13 fewer to 157 more)	VERY LOW	CRITICAL
Adverse events (Perioperative morbidity) - Delayed gastric emptying (follow-up 1 months)												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	7/80 (8.8%)	2/72 (2.8%)	RR 2.71 (0.52 to 14.08)	48 more per 1000 (from 13 fewer to 363 more)	VERY LOW	CRITICAL
Adverse events (Perioperative morbidity) - Wound infection (follow-up 1 months)												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/80 (6.3%)	1/72 (1.4%)	RR 3.09 (0.52 to 18.36)	29 more per 1000 (from 7 fewer to 241 more)	VERY LOW	CRITICAL
Adverse events (Perioperative morbidity) - Chest complications (follow-up 1 months)												
2[2]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/80 (2.5%)	4/72 (5.6%)	RR 0.44 (0.08 to 2.35)	31 fewer per 1000 (from 51	VERY LOW	CRITICAL

										fewer to 75 more)		
Adverse events (Perioperative morbidity) - Cardiac complications (follow-up 1 months)												
1[1]	randomised trials	serious[2,4]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/36 (11.1%)	2/29 (6.9%)	RR 1.61 (0.32 to 8.19)	42 more per 1000 (from 47 fewer to 496 more)	VERY LOW	CRITICAL
Overall survival												
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[5]	none	-	-	Not estimable	-	LOW	CRITICAL
Health Related Quality of Life (EORTC QoL) (assessed with: EORTC)												
1[4]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	-	-	LOW	CRITICAL

[1] *Lillemoe et al. 1999, Van Heek et al. 2003*
[2] *Potential risk of performance bias (no blinding of outcome assessors) in both RCTs. Van Heek et al. 2003 also had incomplete data (3 patients lost to follow up) and potential selective reporting of outcomes (no data provided for quality of life ouctomes).*
[3] *95% CI crosses 2 default MIDs (0.8 and 1.25).*
[4] *van Heek et al. 2003*
[5] *The GC decided to downgrade survival outcomes by one level if the difference in survival was not statistically significant.*

I.11.2 GJJ versus duodenal stent placement

Table 27: Full GRADE profile for GJJ versus duodenal stent placement in adults with pancreatic cancer and gastric outlet obstruction

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GJJ	Duodenal stent placement	Relative (95% CI)	Absolute		
Relief of obstruction (Days with GOOSS score >= 2 after intervention - median)												

1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	-	-	LOW	CRITICAL
Change in symptoms - Persistent obstructive symptoms - Persistent obstructive symptoms												
1[1]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	3/18 (16.7%)	3/21 (14.3%)	RR 1.17 (0.27 to 5.08)	24 more per 1000 (from 104 fewer to 583 more)	VERY LOW	CRITICAL
Change in symptoms - Persistent obstructive symptoms - Recurrent obstructive symptoms												
1[1]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	1/18 (5.6%)	5/21 (23.8%)	RR 0.23 (0.03 to 1.82)	183 fewer per 1000 (from 231 fewer to 195 more)	VERY LOW	CRITICAL
Nutritional status - Days to restore ability to eat (median)												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	-	-	LOW	CRITICAL
Adverse events - Minor complications												
1[1]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	5/18 (27.8%)	4/21 (19%)	RR 1.46 (0.46 to 4.63)	88 more per 1000 (from 103 fewer to 691 more)	VERY LOW	CRITICAL
Adverse events - Major complications												
1[1]	randomised trials[5]	serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	0/18 (0%)	4/21 (19%)	RR 0.13 (0.01 to 2.24)	166 fewer per 1000 (from 189 fewer to 236 more)	VERY LOW	CRITICAL
Overall survival												
1[6]	randomised trials	serious[3]	no serious inconsistency	serious[7]	serious[8]	none	-	-	HR 0.81 (0.27 to 2.4)	-	VERY LOW	CRITICAL

Health Related Quality of Life: SF-36 - Physical Health score (follow-up 1 months; Better indicated by lower values)												
1[6]	randomised trials	serious[3]	no serious inconsistency	serious[7]	very serious[9,10]	none	13	12	-	MD 7.9 lower (22.74 lower to 6.94 higher)	VERY LOW	CRITICAL
Health Related Quality of Life: SF-36 - Mental Health score (follow-up 1 months; Better indicated by lower values)												
1[6]	randomised trials	serious[3]	no serious inconsistency	serious[7]	very serious[9,10]	none	13	12	-	MD 0.7 higher (18.29 lower to 19.69 higher)	VERY LOW	CRITICAL
PROMS - Self-report Pain (Visual Analog Scale) (follow-up 1 months; Better indicated by lower values)												
1[6]	randomised trials	serious[3]	no serious inconsistency	serious[7]	serious[9,11]	none	13	12	-	MD 2 higher (0.36 lower to 4.36 higher)	VERY LOW	CRITICAL

[1] Jeurnink et al. 2010
[2] The quality of the evidence was downgraded because of the unclear risk of selection bias and the potential risk of performance bias (no blinding of outcome assessors) and potential selective reporting for this outcome.
[3] The quality of the evidence was downgraded because of the unclear risk of selection bias and the potential risk of performance bias (no blinding of outcome assessors).
[4] 95% CI crosses 2 default MID (0.8 and 1.25).
[5] Follow-up not clear.
[6] Metha et al. 2006
[7] Metha et al. 2006 sample had less than 66% pancreatic cancer patients.
[8] The GC decided to downgrade survival outcomes by one level for imprecision only if the difference in survival was statistically significant.
[9] MIDs for SF-36 subscales and pain score were calculated as +/- 0.5 SD of control arm at baseline and were as follows: +/- 6.41 for physical health subscale; +/- 11.78 for mental health subscale; +/- 1,39 for pain score.
[10] 95% CI crosses 2 MIDs for this outcome.
[11] 95% CI crosses 1 MID for this outcome.

I.11.3 Type I GJJ (proximal to the Jejunal limb: Ligament of Treitz) versus Type II GJJ (Pylorus)

Table 28: Full GRADE profile for Type I GJJ (proximal to the Jejunal limb: Ligament of Treitz) versus Type II GJJ (Pylorus) in adults with pancreatic cancer and gastric outlet obstruction

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Type I GJJ proximal to the Jejunal limb: Ligament of Treitz	Type II GJJ Pylorus	Relative (95% CI)	Absolute	Quality	Importance
Change in symptoms - GOO overall (follow-up 1 months; assessed with: GOO)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	7/15 (46.7%)	2/15 (13.3%)	RR 3.5 (0.86 to 14.18)	333 more per 1000 (from 19 fewer to 1000 more)	VERY LOW	CRITICAL
Change in symptoms (GOO) - Anorexia (follow-up 1 months; assessed with: GOO)												
1[4]	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[5]	none	1/15 (6.7%)	0/15 (0%)	RR 3 (0.13 to 68.26)	-	VERY LOW	CRITICAL
Change in symptoms (GOO) - Epigastric fullness (follow-up 1 months; assessed with: GOO)												
1[4]	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[5]	none	2/15 (13.3%)	1/15 (6.7%)	RR 2 (0.2 to 19.78)	67 more per 1000 (from 53 fewer to 1000 more)	VERY LOW	CRITICAL
Change in symptoms (GOO) - Nausea (follow-up 1 months; assessed with: GOO)												
1[4]	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[5]	none	1/15 (6.7%)	0/15 (0%)	RR 3 (0.13 to 68.26)	-	VERY LOW	CRITICAL

Change in symptoms (GOO) - Vomiting (follow-up 1 months; assessed with: GOO)												
1[4]	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[5]	none	3/15 (20%)	0/15 (0%)	RR 7 (0.39 to 124.83)	-	VERY LOW	CRITICAL
Nutritional status - Gastric emptying time (follow-up 1 months; Better indicated by lower values)												
1[4]	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[6,7]	none	15	15	-	MD 40.8 higher (67.85 lower to 149.45 higher)	VERY LOW	CRITICAL
Nutritional status - Patients with delayed gastric emptying (follow-up 10 days)												
1[4]	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious	none	3/15 (20%)	1/15 (6.7%)	RR 3 (0.35 to 25.68)	133 more per 1000 (from 43 fewer to 1000 more)	VERY LOW	CRITICAL

[1] *Quality of evidence was downgraded by 1 point owing to unclear risk of performance bias and unclear selective reporting*
[2] *Sample had <66% pancreatic cancer patients.*
[3] *95% CI crosses 1 default MID (0.8 or 1.25).*
[4] *Shyr et al. 1997*
[5] *95% CI crosses 2 default MIDs (0.8 and 1.25).*
[6] *MIDs for nutritional status (gastric emptying time) were calculated as +/- SD of control group immediately after resumption of oral diet and was +/- 75.91 min.*
[7] *95% CI crosses 1 MID for this outcome.*

I.11.4 Type I GJJ (proximal to the Jejunal limb: Ligament of Treitz) versus Type III GJJ (proximal to Roux-limb Jejunum)

Table 29: Full GRADE profile for Type I GJJ (proximal to the Jejunal limb: Ligament of Treitz) versus Type III GJJ (proximal to Roux-limb Jejunum)) in adults with pancreatic cancer and gastric outlet obstruction

Quality assessment							No of patients		Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Type I GJJ proximal to the Jejunal limb: Ligament of Treitz	Type III GJJ proximal to Roux-limb Jejunum	Relative (95% CI)	Absolute		
Change in symptoms - GOO overall (follow-up 1 months)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	7/15 (46.7%)	2/15 (13.3%)	RR 3.5 (0.86 to 14.18)	333 more per 1000 (from 19 fewer to 1000 more)	VERY LOW	CRITICAL
Change in symptoms (GOO) - Anorexia (assessed with: GOO)												
1[4]	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[5]	none	1/15 (6.7%)	1/15 (6.7%)	RR 1 (0.07 to 14.55)	0 fewer per 1000 (from 62 fewer to 903 more)	VERY LOW	CRITICAL
Change in symptoms (GOO) - Epigastric fullness (follow-up 1 months; assessed with: GOO)												
1[4]	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[5]	none	2/15 (13.3%)	1/15 (6.7%)	RR 2 (0.2 to 19.78)	67 more per 1000 (from 53 fewer to 1000 more)	VERY LOW	CRITICAL
Change in symptoms (GOO) - Nausea (follow-up 1 months; assessed with: GOO)												
1[4]	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[5]	none	1/15 (6.7%)	0/15 (0%)	RR 3 (0.13 to 68.26)	-	VERY LOW	CRITICAL
Change in symptoms (GOO) - Vomiting (follow-up 1 months; assessed with: GOO)												
1[4]	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[5]	none	3/15 (20%)	0/15 (0%)	RR 7 (0.39 to 124.83)	-	VERY LOW	CRITICAL
Nutritional status - Gastric emptying time (follow-up 1 months; Better indicated by lower values)												

1[4]	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[6,7]	none	15	15	-	MD 86.4 lower (192.05 lower to 19.25 higher)	VERY LOW	CRITICAL
Nutritional status - Patients with delayed gastric emptying (follow-up 10 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[5]	none	3/15 (20%)	1/15 (6.7%)	RR 3 (0.35 to 25.68)	133 more per 1000 (from 43 fewer to 1000 more)	VERY LOW	CRITICAL

[1] *Quality of evidence was downgraded by 1 point owing to unclear risk of performance bias and unclear selective reporting*
[2] *Sample had <66% pancreatic cancer patients.*
[3] *95% CI crosses 1 default MID (0.8 or 1.25).*
[4] *Shyr et al. 1997*
[5] *95% CI crosses 2 default MIDs (0.8 and 1.25).*
[6] *MIDs for nutritional status (gastric emptying time) were calculated as +/- SD of control group immediately after resumption of oral diet and was +/- 71.65 min.*
[7] *95% CI crosses 1 MID for this outcome.*

I.11.5 Type II GJJ (Pylorus) versus Type III GJJ (proximal to Roux-limb Jejunum)

Table 30: Full GRADE profile for Type II GJJ (Pylorus) versus Type III GJJ (proximal to Roux-limb Jejunum) in adults with pancreatic cancer and gastric outlet obstruction

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Type II GJJ Pylorus**	**Type III GJJ proximal to Roux-limb Jejunum**	**Relative (95% CI)**	**Absolute**		
Change in symptoms - GOO overall (follow-up 1 months; assessed with: GOO)												

1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	very serious[4]	none	1/15 (6.7%)	2/15 (13.3%)	RR 0.5 (0.05 to 4.94)	67 fewer per 1000 (from 127 fewer to 525 more)	VERY LOW	CRITICAL
Change in symptoms (GOO) - Anorexia (follow-up 1 months)												
1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	no serious imprecision	none	0/15 (0%)	0/15 (0%)	-	-	LOW	CRITICAL
Change in symptoms (GOO) - Epigastric fullness (follow-up 1 months; assessed with: GOO)												
1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	serious	none	1/15 (6.7%)	1/15 (6.7%)	RR 1 (0.07 to 14.55)	0 fewer per 1000 (from 62 fewer to 903 more)	VERY LOW	CRITICAL
Change in symptoms (GOO) - Nausea (follow-up 1 months; assessed with: GOO)												
1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	serious	none	0/15 (0%)	1/15 (6.7%)	RR 0.33 (0.01 to 7.58)	45 fewer per 1000 (from 66 fewer to 439 more)	VERY LOW	CRITICAL
Change in symptoms (GOO) - Vomiting (follow-up 1 months; assessed with: GOO)												
1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	no serious imprecision	none	0/15 (0%)	0/15 (0%)	-	-	LOW	CRITICAL
Nutritional status - Gastric emptying time (follow-up 1 months; Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	serious[5,6]	none	15	15	-	MD 127.2 lower (232.85 to 21.55 lower)	VERY LOW	CRITICAL
Nutritional status - Patients with delayed gastric emptying (follow-up 10 days)												
1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	very serious[4]	none	1/15 (6.7%)	1/15 (6.7%)	RR 1 (0.07 to 14.55)	0 fewer per 1000 (from 62 fewer to 903 more)	VERY LOW	CRITICAL

1 [1] *Shyr et al. 1997*

[2] *Quality of evidence was downgraded by 1 point owing to unclear risk of performance bias and unclear selective reporting*
[3] *Sample had <66% pancreatic cancer patients.*
[4] *95% CI crosses 2 default MIDs (0.8 and 1.25).*
[5] *MIDs for nutritional status (gastric emptying time) were calculated as +/- SD of control group immediately after resumption of oral diet and was +/- 71.65 min.*
[6] *95% CI crosses 1 MID for this outcome.*

I.11.6 Duodenal stent-1 versus duodenal stent-2

Table 31: Full GRADE profile for duodenal stent-1 versus duodenal stent-2 in adults with pancreatic cancer and duodenal obstruction

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Duodenal stent-1 (WallFlex)	Duodenal stent-2 (Niti-S)	Relative (95% CI)	Absolute		
Relief of obstruction - Mean change in GOO score at 2 weeks (Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3,4]	none	14	17	-	SMD 0.37 higher (0.34 lower to 1.09 higher)	LOW	CRITICAL
Relief of obstruction - GOO recurrence (follow-up 2 weeks)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[5]	none	4/14 (28.6%)	4/17 (23.5%)	RR 1.21 (0.37 to 4)	49 more per 1000 (from 148 fewer to 706 more)	VERY LOW	CRITICAL
Change in symptoms - Mean change in NVSS score (Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3,4]	none	14	17	-	SMD 0.28 higher (0.43	LOW	CRITICAL

										lower to 0.99 higher)		
Nutritional status- Mean change in BMI at 4 weeks (Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	13	17	-	MD 0.3 lower (1.22 lower to 0.62 higher)	MODERATE	CRITICAL
Adverse events (procedure-related) (follow-up 30 days)												
1[1]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	4/14 (28.6%)	4/17 (23.5%)	RR 1.21 (0.37 to 4)	49 more per 1000 (from 148 fewer to 706 more)	VERY LOW	CRITICAL
HRQL - Mean change in Karnofsky performance score at 2 weeks (Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3,6]	none	14	13	-	MD 5.2 higher (5.47 lower to 15.87 higher)	LOW	CRITICAL
HRQL - Mean change in Performance score at 2 weeks (Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3,6]	none	14	17	-	MD 0.1 lower (0.69 lower to 0.49 higher)	LOW	CRITICAL
Overall survival												

1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[7]	none	-	-	HR 0.52 (0.26 to 1.08)	-	LOW	CRITICAL

[1] *Okuwaki et al. 2016*
[2] *Unclear randomisation method and whether blinded.*
[3] *MIDs for change in BMI, change in Karnofsky Performance Score and change in Performance Score were calculated as +/- 0.5 SD of control arm at baseline and were as follows: +/- 1.4 kg/m2 for change in BMI, +/- 9.5 for Karnofsky Performance Score, and +/- 0.55 for Performance Score. MIDs for change in GOO score and change in NVSS score were assumed to be the default MIDs for continuous outcomes expressed as an SMD (i.e. +/- 0.5) due to insufficient baseline data.*
[4] *95% CI crosses 1 default MID for SMDs (0.5 or -0.5).*
[5] *95% CI crosses 2 default MIDs (0.8 and 1.25).*
[6] *95% CI crosses 1 MID for this outcome.*
[7] *The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant.*

I.12 Neo-adjuvant treatment

I.12.1 Neoadjuvant chemoradiotherapy followed by surgery versus surgery alone

Table 32: Full GRADE profile for neoadjuvant chemoradiotherapy followed by surgery versus surgery only in patients with resectable pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CRT followed by surgery**	**Surgery alone**	**Relative (95% CI)**	**Absolute**		
Response to neoadjuvant treatment pre- surgery - radiological response (assessed with: RECIST criteria[1])												
2[2]	RCTs	serious[3]	serious[11]	no serious indirectness	no serious imprecision	none	18[8]	-	Not estimable	Radiological response to CRT was rarely seen (n = 4 partial and 1 complete response)	LOW	CRITICAL

										whereas most patients had no change (n = 8) or progression (n = 4)		
							29[16]	-		Radiological response to CRT was rarely seen (n = 4 partial) whereas most patients had no change (n = 8) or progression (n = 12) -5 missing data		
Response to neoadjuvant treatment pre-surgery - pathological response (assessed with: Rebekah criteria)												
1[8]	RCTs	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	18	-	Not estimable	Pathological response to CRT was slightly higher than the radiological (n=0 none; n=2 minimal; n=3 small; n=5 moderate and 1 large response)	LOW	CRITICAL
Complete resection rate												
3[9]	RCTs	serious[3]	no serious inconsistency	no serious indirectness	serious[5]	none	43/72 (59.7%)	66/111 (59.5%)	RR 1.16 (0.97 to 1.39)	95 more per 1000 (from 18 fewer to 232 more)	LOW	CRITICAL
Overall Survival												
2[10]	RCTs	serious[3]	serious[11]	no serious indirectness	serious[6]	none	-	-	HR 0.85 (0.58 to 1.25)	-	VERY LOW	CRITICAL

Adverse events - Postoperative complications												
2[2]	RCTs	serious[3]	serious[11]	no serious indirectness	very serious imprecision[7]	none	32/51 (62.7%)	41/53 (77.4%)	RR 0.86 (0.47 to 1.57)	108 fewer per 1000 (from 410 fewer to 441 more)	VERY LOW	CRITICAL
Adverse events - Pancreatic fistula												
1[9]	observational studies[10]	serious[11]	no serious inconsistency	no serious indirectness	very serious imprecision[7]	none	11/61 (18%)	23/71 (32.4%)	RR 0.56 (0.3 to 1.05)	143 fewer per 1000 (from 227 fewer to 16 more)	VERY LOW	CRITICAL
Adverse events - Postoperative bleeding												
3[15]	observational studies[10]	serious[14]	serious[11]	no serious indirectness	very serious imprecision[7]	none	4/198 (2%)	6/148 (4.1%)	RR 0.56 (0.12 to 2.65)	18 fewer per 1000 (from 36 fewer to 67 more)	VERY LOW	CRITICAL
Adverse events - Acute toxicity of CRT (assessed with: NCI common toxicity criteria v2.0 and RTOG/EORTC recommendations)												
2[10]	RCTs	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	18[8]		not pooled	All patients experienced toxicities. toxicities 16 patients experienced hematologic toxicities, whereas 15 patients experienced non-hematologic toxicities	LOW	CRITICAL

[1] Therasse P, Arbuck SG, Eisenhauer EA et al (2000) New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205–216

[2] Casadei et al. 2015, Golcher et al. 2015

[3] Quality of evidence was downgraded by 1 point owing to unclear risk of performance bias.

[4] Numbers are too small for precise results to be obtained

[5] 95% CI crosses 1 default MID (0.8 and 1.25)

[6] The GC decided to downgrade survival outcomes by one level if the difference in survival was not statistically significant.

[7] 95% CI crosses 2 default MIDs (0.8 and 1.25).

8 Casadei et al. 2015

[9] Casadei et al. 2015, Golcher et al. 2015, Golcher et al. 2008

[10] *Golcher et al. 2008, Golcher et al. 2015*
[11] *Quality of evidence was downgraded by 1 point owing to some inconsistency across studies*
[12] *Sho et al. 2013*
[13] *Retrospective*
[14] *The quality of the evidence was downgraded of one point because of the potential risk of performance bias due to some issues of comparability between comparison groups*
15 Sho et al. 2013, Tzeng et al. 2014, Vento et al. 2007

[13] *Golcher et al. 2015*

I.12.2 Neoadjuvant chemoradiotherapy followed by surgery in adults with resectable pancreatic cancer

Table 33: Full GRADE profile for neoadjuvant chemoradiotherapy then surgery in adults with resectable pancreatic cancer

Quality assessment							No of patients	Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Relative (95% CI)	Absolute		
5 years survival rate- Resectable PC (follow-up 5 years)											
1[1]	observational studies[3]	no serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	188	-	The 5-year survival was 57%	VERY LOW	CRITICAL
Overall Survival - Resectable PC (follow-up unclear)											
1[2]	observational studies[3]	no serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	86	-	Median survival was 34 months for the 64 patients who underwent PD and 7 months for the 22 un-resected patients (P < .001). The 5-year survival for those who did and did not undergo PD was 36% and 0%, respectively.	VERY LOW	CRITICAL
Resection rate - Resectable PC (follow-up mean 8 weeks[5])											
2[1,2]	observational studies[3]		no serious inconsistency	no serious indirectness	no serious imprecision	none	164[1]	-	R0 resection rate was 99% in those patients who underwent PD		CRITICAL

		no serious [4]							and received the intervention (p=no reported)		
							86[2]		R0 resection rate was 89% in those patients who underwent PD and received the intervention (p=no reported)	VERY LOW	
Time from initiating treatment to Surgery											
1[2]	observational studies[3]	no serious [4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	73	-	The median time from completion of preoperative therapy to surgery in the 73 patients who went to surgery was 5.6 weeks. (p=no reported)	VERY LOW	CRITICAL
Adverse effects: Hematologic toxicities (Anemia; Leukopenia; Granulocytopenia; Thrombocytopenia; Neutropenic fever) (follow-up - unclear; assessed with: assessed with: No of events with grade 3-4)											
1[2]	observational studies[3]	no serious [4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	86	-	37 patients experienced hematologic toxicities (p=no reported)	VERY LOW	CRITICAL
Adverse effects: Constitutional toxicities (Fatigue; Anorexia; Pain; Failure to thrive) (follow-up - unclear; assessed with: assessed with: No of events with grade 3-4)											
1[2]	observational studies[3]	no serious [4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	86	-	32 patients experienced constitutional toxicities(p=no reported)	VERY LOW	CRITICAL
Adverse effects: Gastrointestinal toxicities (Nausea; Emesis; Diarrhea/enteritis; Dehydration; Constipation; Abdominal pain) (follow-up - unclear; assessed with: assessed with: No of events with grade 3-4)											
1[2]	observational studies[3]	no serious [4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	86	-	30 patients experienced gastrointestinal toxicities (p=no reported)	VERY LOW	CRITICAL
Adverse effects: Liver and biliary toxicities (follow-up - unclear; assessed with: assessed with: No of events with grade 3-4)											
1[2]	observational studies[3]	no serious [4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	86	-	24 patients experienced liver and biliary toxicities (p=no reported)	VERY LOW	CRITICAL

Adverse effects: Cardiovascular toxicities (Deep venous thrombosis) (follow-up - unclear; assessed with: assessed with: No of events with grade 3-4)											
1[2]	observational studies[3]	no serious [4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	86	-	4 patients experienced cardiovascular toxicities (p=no reported)	VERY LOW	CRITICAL
Adverse effects: Pulmonary embolism toxicities (follow-up - unclear; assessed with: assessed with: No of events with grade 3-4)											
1[2]	observational studies[2]	no serious [4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	86	-	No patient experienced pulmonary embolism toxicities (p=no reported)	VERY LOW	CRITICAL
Adverse effects: Other toxicities (follow-up - unclear; assessed with: assessed with: No of events with grade 3-4)											
1[2]	observational studies[3]	no serious [4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	86	-	18 patients experienced other toxicities	VERY LOW	CRITICAL

[1] *Takashaki 2013*
[2] *Evans et al. 2008*
[3] *Single-arm phase II clinical trial (non-comparative)*
[4] *Non-randomised study with no comparator*
[5] *From the initial staging*

I.12.3 Chemoradiotherapy followed by surgery in adults with borderline resectable pancreatic cancer

Table 34: Full GRADE table for neoadjuvant chemoradiotherapy followed by surgery in adults with borderline resectable pancreatic cancer

Quality assessment							No of patients	Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Relative (95% CI)	Absolute		
Response to neoadjuvant treatment pre-surgery (assessed with: Percent frequency of complete/partial response following neoadjuvant therapy – RECIST criteria)											

7[1]	observational studies[2]	no serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	137	-	The weighted fraction of patients with complete/partial response at restaging was 13.5% [(95% CI: 7-24.6%), p=no reported]	LOW	CRITICAL
5 years survival rate- Resectable PC											
1[3]	observational studies[2]	no serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	43	-	The 5-year survival was 34%	LOW	CRITICAL
Resection rate (measured with: Percent frequency of pancreatic resection rates following neoadjuvant therapy; Better indicated by lower values)											
7[1]	observational studies[2]	no serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	137	-	R0 resection rate was 78.5 % in those patients who underwent surgery and received the neoadjuvant CRT intervention [(95% CI: 62.2-89.1%), p=no reported]	LOW	CRITICAL
Adverse events: toxicity rates (grade 3-4)											
7[1]	observational studies[2]	no serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	137	-	28.8% of patients had grade 3-4 toxicities as consequence of the neoadjuvant intervention [(95% CI: 15.2-47.7%), p=no reported]	LOW	CRITICAL

1 *[1] Festa et al. 2013 (included studies: Le Scodan et al. 2009; Leone et al. 2012; Magnin et al. 2003; Massucco et al. 2006; Mehta et al. 2001; Pipas et al. 2005; Small et al.*
2 *2011)*
3 *[2] Single-arm prospective clinical trials (non-comparative)*
4 *[3] Takashaki eta l. 2013*
5 *[4] Non-randomised study with no comparator*

I.12.4 Neoadjuvant chemoradiotherapy followed by surgery in adults with borderline resectable or resectable pancreatic cancer

Table 35: Full GRADE profile for neoadjuvant chemoradiotherapy followed by surgery in adults with borderline resectable or resectable pancreatic cancer

Quality assessment							No of patients	Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Relative (95% CI)	Absolute		
Adverse events: Leukopenia(Grade 2) (assessed with: National Cancer Institute Common Toxicity Criteria version 3[4])											
1[1]	observational studies[2]	no serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	268	-	There were the following preoperative CRT-associated leukopenia toxicities: n=127 (grade 3) n=5 (grade 4)	LOW	CRITICAL
Adverse events: Thrombocytopenia (Grade 2) (assessed with: National Cancer Institute Common Toxicity Criteria version 3[4])											
1[1]	observational studies[2]	no serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	268	-	There were the following preoperative CRT-associated thrombocytopenia toxicities: n=10 (grade 3) n=4 (grade 4)	LOW	CRITICAL
Adverse events: Gastrointestinal toxicity (Grade 2) (assessed with: National Cancer Institute Common Toxicity Criteria version 3[4])											
1[1]	observational studies[2]	no serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	268	-	There were the following preoperative CRT-associated gastrointestinal toxicities: n=0 (grade 3) n=4 (grade 4)	LOW	CRITICAL
Adverse events: Delayed gastric emptying (Grade B/C) (assessed with: International study group of pancreatic surgery criteria[5])											

1[1]	observational studies[2]	no serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	268	-	There were 23 preoperative CRT-associated delayed gastric emptying complications	LOW	CRITICAL
Adverse events: Delayed gastric emptying (Operative Mortality) (assessed with: International study group of pancreatic surgery criteria[5])											
1[1]	observational studies[2]	no serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	268	-	There was 1 death following preoperative CRT-associated complications	LOW	CRITICAL
Adverse events: Pancreatic fistula (Grade B-C) (assessed with: International study group of pancreatic fistula criteria[6])											
1[1]	observational studies[5]	no serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	268	-	There were 15 preoperative CRT-associated pancreatic fistula complications	LOW	CRITICAL

1 *[1] Takashaki et al. 2013*
2 *[2] Single-arm phase II clinical trial (non-comparative)*
3 *[3] Non-randomised study with no comparator*
4 *[4] NCI Common Terminology Criteria for Adverse Events (CTCAE) v.4. NCI Common Terminology Criteria for Adverse Events (CTCAE) v.4 data files. Available at:*
5 *http://evs.nci.nih.gov/ftp1/CTCAE/About.html.*
6 *[5] Wente MN, Bassi C, Dervenis C, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic*
7 *Surgery (ISGPS). Surgery. 2007;142:761–768.*

8 *[6] Bassi C, Dervenis C, Butturini G, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery. 2005;138:8–13*

I.12.5 9 Neoadjuvant chemotherapy then surgery

10 **Table 36: Full GRADE profile for neoadjuvant chemotherapy followed by surgery in patients with with borderline resectable**
11 **pancreatic cancer.**

Quality assessment							**No of patients**	**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**		**Relative (95% CI)**	**Absolute**		
Response to neoadjuvant treatment pre-surgery (assessed with: Percent frequency of complete/partial response following neoadjuvant therapy – RECIST criteria)											

3[1]	observational studies[2]	no serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	45	-	The weighted fraction of patients with complete/partial response at restaging was 23.6% [(95% CI: 8.0-28%), p=no reported]	VERY LOW	CRITICAL
Resection rate											
3[1]	observational studies[2]	no serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	45	-	R0 resection rate was 87.6 % in those patients who underwent surgery and received the neoadjuvant CRT intervention [(95% CI: 43.9-98.5%), p=no reported]	VERY LOW	CRITICAL
Adverse events: toxicity rates (grade 3-4)											
3[1]	observational studies[2]	no serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	45	-	35.9% of patients had grade 3-4 toxicities as consequence of the neoadjuvant intervention [(95% CI: 23.1-51.1%), p=no reported]	VERY LOW	CRITICAL

[1] *Festa et al. 2013 (included studies: Lee et al. 2012; Sahora et al. 2011a; Sahora et al. 2011b)*
[2] *Single-arm prospective clinical trials (non-comparative)*
[3] *Non-randomised study with no comparator*
[4] *Numbers are too small for precise results to be obtained*

I.12.6 Neoadjuvant chemotherapy then chemoradiotherapy followed by surgery

Table 37: Full GRADE profile for neoadjuvant chemotherapy then chemoradiotherapy followed by surgery in patients with with resectable pancreatic cancer.

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Relative (95% CI)	Absolute		
Overall Survival (follow-up 5 years)											
1[1]	observational studies[2]	no serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	79	-	Median survival for the patients who completed chemo-CRT was 18.7 months, with a median survival of 31 months for the 52 patients who underwent PD and 10.5 months for the 27 patients who did not undergo surgical resection of their primary tumour (p<.001)	LOW	CRITICAL
Resection rate (follow-up - unclear)											
1[1]	observational studies[2]	no serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	62	-	R0 resection rate was 96% in those patients who underwent PD and received the intervention (p=no reported)	LOW	CRITICAL
Time from initiating treatment to Surgery (follow-up - unclear)											
1[1]	observational studies[2]	no serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	62	-	The median time from completion of the neoadjuvant intervention to surgery in the patients who went to surgery for planned PD was 5.6 weeks (p=no reported)	LOW	CRITICAL
Adverse effects: Hematologic toxicities (Anemia; Leukopenia; Granulocytopenia; Thrombocytopenia; Neutropenic fever) (follow-up - unclear; assessed with: No of events with grade 3-4)											
1[1]	observational studies[2]	no serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	79	-	24 patients experienced hematologic toxicities	LOW	CRITICAL

Adverse effects: Constitutional toxicities (Fatigue; Anorexia; Pain; Failure to thrive) (follow-up - unclear; assessed with: No of events)											
1[1]	observational studies[2]	no serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	79	-	30 patients experienced constitutional toxicities	LOW	CRITICAL
Adverse effects: Gastrointestinal toxicities (Nausea; Emesis; Diarrhea/enteritis; Dehydration; Constipation; Abdominal pain) (follow-up - unclear; assessed with: No of events with grade 3-4)											
1[1]	observational studies[3]	no serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	79	-	20 patients experienced gastrointestinal toxicities	LOW	CRITICAL
Adverse effects: Liver and biliary toxicities (follow-up - unclear; assessed with: No of events with grade 3-4)											
1[1]	observational studies[2]	no serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	79	-	29 patients experienced liver and biliary toxicities	LOW	CRITICAL
Adverse effects: Cardiovascular toxicities (Deep venous thrombosis) (follow-up - unclear; assessed with: No of events with grade 3-4)											
1[1]	observational studies[2]	no serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	79	-	7 patients experienced cardiovascular toxicities	LOW	CRITICAL
Adverse effects: Pulmonary embolism toxicities (follow-up - unclear; assessed with: No of events with grade 3-4)											
1[1]	observational studies	no serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	79	-	3 patients experienced pulmonary embolism toxicities	LOW	CRITICAL
Adverse effects: Other toxicities (follow-up - unclear; assessed with: No of events with grade 3-4)											
1[1]	observational studies[2]	no serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	79	-	19 patients experienced other toxicities	LOW	CRITICAL

1 *[1] Varadhachary et al. 2008*
2 *[2] Single-arm phase II clinical trial (non-comparative)*
3 *[3] Non-randomised study with no comparator*

I.13 Resectable and borderline resectable pancreatic cancer

I.13.1 Minimally invasive (laparoscopic and robotic) pancreaticoduodenectomy versus open pancreaticoduodenectomy

Table 38: Full GRADE profile for minimally invasive (laparoscopic and robotic) pancreaticoduodenectomy versus open pancreaticoduodenectomy in adults with resectable or borderline resectable pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minimally invasive (laparoscopic and robotic) pancreaticoduodenectomy	Open pancreaticoduodenectomy	Relative (95% CI)	Absolute		
Postoperative Mortality												
9	observational studies	no serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	9/268 (3.4%)	26/500 (5.2%)	RR 0.88 (0.4 to 1.92)	6 fewer per 1000 (from 31 fewer to 48 more)	VERY LOW	CRITICAL
R0 resection rate												
9	observational studies	no serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	227/253 (89.7%)	342/419 (81.6%)	RR 1.08 (1.02 to 1.14)	65 more per 1000 (from 16 more to 114 more)	VERY LOW	CRITICAL

Operation Time (mins) (Better indicated by lower values)												
6	observational studies	no serious	serious[4]	serious[2]	serious[5,6]	none	160	375	-	MD 109.99 higher (2.74 to 217.24 higher)	VERY LOW	CRITICAL
Delayed Gastric Emptying												
8	observational studies	no serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	28/285 (9.8%)	53/473 (11.2%)	RR 1.04 (0.63 to 1.72)	4 more per 1000 (from 41 fewer to 81 more)	VERY LOW	CRITICAL
Pancreatic Fistula												
13	observational studies	no serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	72/366 (19.7%)	116/606 (19.1%)	RR 1.04 (0.8 to 1.34)	8 more per 1000 (from 38 fewer to 65 more)	VERY LOW	CRITICAL
Reoperation												
8	observational studies	no serious[1]	no serious inconsistency	serious[2]	serious[7]	none	32/320 (10%)	45/525 (8.6%)	RR 0.75 (0.45 to 1.23)	21 fewer per 1000 (from 47 fewer to 20 more)	VERY LOW	CRITICAL

Blood loss (ml) (Better indicated by lower values)												
5	observational studies	no serious[1]	serious[8]	serious[2]	serious[9]	none	87	93	-	MD 398.6 lower (746.26 to 50.95 lower)	VERY LOW	CRITICAL
Retrieved lymph nodes (Better indicated by higher values)												
4	observational studies	no serious[1]	serious[10]	serious[2]	no serious imprecision	none	93	135	-	MD 1.23 higher (2.29 lower to 4.75 higher)	VERY LOW	CRITICAL

[1] *Not Randomised*
[2] *Not all malignancy was pancreatic malignancy*
[3] *95% CI crosses 2 default MIDs (0.8 and 1.25).*
[4] *High heterogeneity between studies (I2=96%)*
[5] *MID is +/- 54 mins (Median SD of control arm at follow up=108 mins).*
[6] *95% CI crosses 1 MID for this outcome.*
[7] *95% CI crosses 1 default MID (0.8 or 1.25).*
[8] *Between studies heterogeneity I2=93%*
[9] *MID for this outcome is +/- 97.3 ml (Median SD of control arm at follow up=194.5 ml).*
[10] *Between studies heterogeneity I2=63%*

I.13.2 Pylorus preserving Whipple versus classic Whipple

Table 39: Full GRADE profile for pylorus-preserving Whipple versus classic Whipple in adults with resectable or borderline resectable pancreatic cancer

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pylorus Preserving Whipple	Classic Whipple	Relative (95% CI)	Absolute		
Overall Survival (follow-up 1-115 months[1])												
3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness[3]	serious[4]	none	98/167 (58.7%)	105/168 (62.5%)	HR 0.73 (0.43 to 1.22)	114 fewer per 1000 (from 281 fewer to 73 more)	LOW	CRITICAL
Postoperative Mortality (follow-up 1-115 months[5])												
7	randomised trials	serious[2]	no serious inconsistency	serious[6]	very serious[7]	none	9/231 (3.9%)	14/233 (6%)	RR 0.7 (0.31 to 1.55)	18 fewer per 1000 (from 41 fewer to 33 more)	VERY LOW	CRITICAL
R0 Resection Rate												
3	randomised trials	serious[2]	no serious inconsistency	serious[6]	serious[8]	none	142/177 (80.2%)	149/182 (81.9%)	RR 0.99 (0.74 to 1.05)	8 fewer per 1000 (from 213 fewer to 41 more)	VERY LOW	CRITICAL
Operation Time (Better indicated by lower values)												
7	randomised trials	serious[2]	no serious inconsistency	serious[6]	serious[9]	none	238	234	-	MD 45.22 lower (74.67 to 15.78 lower)	VERY LOW	CRITICAL
Delayed Gastric Emptying (follow-up 1-115 weeks[5])												
7	randomised trials	serious[2]	serious[10]	serious[6]	serious[8]	none	72/229 (31.4%)	84/230 (36.5%)	RR 2.15 (0.98 to 4.71)	420 more per 1000 (from 7 fewer to 1000 more)	VERY LOW	CRITICAL

Pancreatic Fistula (follow-up 1-115 months)												
7	randomised trials	serious[2]	no serious inconsistency	serious[6]	very serious[7]	none	21/232 (9.1%)	22/236 (9.3%)	RR 0.97 (0.56 to 1.69)	3 fewer per 1000 (from 41 fewer to 64 more)	VERY LOW	CRITICAL
Biliary Leakage (follow-up 1-115 months[5])												
5	randomised trials	serious[2]	no serious inconsistency	serious[6]	very serious[7]	none	5/191 (2.6%)	4/189 (2.1%)	RR 0.95 (0.18 to 5.16)	1 fewer per 1000 (from 17 fewer to 88 more)	VERY LOW	CRITICAL
Necessity for Reoperation												
3	randomised trials	serious[2]	no serious inconsistency	serious[6]	very serious[7]	none	16/163 (9.8%)	18/157 (11.5%)	RR 0.82 (0.44 to 1.53)	21 fewer per 1000 (from 64 fewer to 61 more)	VERY LOW	CRITICAL
Intraoperative Blood Loss (follow-up 1-115 months[5]; Better indicated by lower values)												
5	randomised trials	serious[2,9]	no serious inconsistency	serious[6]	serious[9,11]	none	202	202	-	MD 0.37 lower (0.77 lower to 0.04 higher)	VERY LOW	CRITICAL
Surgical site infection												
4	randomised trials	serious[2]	no serious inconsistency	serious[6]	serious[4]	none	10/119 (8.4%)	13/132 (9.8%)	RR 0.86 (0.39 to 1.88)	14 fewer per 1000 (from 60 fewer to 87 more)	VERY LOW	CRITICAL
Hospital Stay (days) (Better indicated by lower values)												
5	randomised trials	serious[2]	no serious inconsistency	serious[6]	no serious imprecision[4,9]	none	188	178	-	MD 0.26 higher	LOW	CRITICAL

										(2.04 lower to 2.56 higher)		

[1] *Lin et al Not Reported; Seiler et al 4-93 months; Tran et al 1-115 months;*
[2] *Inadequate reporting of sequence generation and allocation concealment. Small sample size (Lin et al), no power calculations, no intention to treat analysis,*
[3] *Subgroup analysis of pancreatic head carcinoma*
[4] *The GC decided to downgrade survival outcomes by one level for imprecision only if there was a significant difference between the groups.*
[5] *Follow-up not reported in all studies*
[6] *Includes patients with periampullary cancer*
[7] *95% CI crosses both default MIDs (0.8 and 1.25).*
[8] *95% CI crosses 1 default MID (0.8 or 1.25).*
[9] *Distribution of continuous outcomes is known to be skewed and may introduce bias to the analysis. MID for continuous outcomes, calculated from median SD of control arm at follow up, are as follows: operating time is +/- 26.8 mins (Median SD=53.5 min); intraoperative blood loss is +/- 0.202 litres (Median SD=0.404 litres); hospital stay is +/- 6.9 days (Median SD=13.8 days).*
[10] *Heterogeneity I2>50%*
[11] *95% CI crosses 1 MID.*

I.13.3 Minimally invasive laparoscopic distal pancreatectomy versus open pancreatectomy

Table 40: Full GRADE profile for minimally invasive laparoscopic distal pancreatectomy versus open pancreatectomy in adults with resectable or borderline resectable pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Laparoscopic distal pancreatectomy	Open Pancreatectomy	Relative (95% CI)	Absolute		
Mortality												
17	observational studies	no serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	3/748 (0.4%)	13/975 (1.3%)	RR 0.63 (0.2 to 2.01)	5 fewer per 1000 (from 11 fewer to 13 more)	VERY LOW	CRITICAL
Positive Margins												

7	observational studies	no serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	15/470 (3.2%)	45/861 (5.2%)	RR 0.61 (0.26 to 1.48)	20 fewer per 1000 (from 39 fewer to 25 more)	VERY LOW	CRITICAL
Pancreatic Fistula (All)												
18	observational studies	no serious[1]	no serious inconsistency	serious[2]	serious[4]	none	131/773 (16.9%)	213/1041 (20.5%)	RR 0.93 (0.77 to 1.13)	14 fewer per 1000 (from 47 fewer to 27 more)	VERY LOW	CRITICAL
Pancreatic Fistula Grade B-C												
6	observational studies	no serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	39/302 (12.9%)	80/532 (15%)	RR 0.90 (0.63 to 1.29)	15 fewer per 1000 (from 56 fewer to 44 more)	VERY LOW	CRITICAL
Reoperation Rates												
5	observational studies	no serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	7/334 (2.1%)	16/513 (3.1%)	RR 0.79 (0.29 to 2.15)	7 fewer per 1000 (from 22 fewer to 36 more)	VERY LOW	CRITICAL
Operative Blood Loss (Better indicated by lower values)												
16	observational studies	no serious[1]	serious[5]	serious[2]	serious[6,7]	none	492	849	-	MD 332.22 lower (480.99 to 183.65 lower)	VERY LOW	CRITICAL
Surgical Site Infection												

11	observational studies	no serious [1]	no serious inconsistency	serious[2]	no serious imprecision	none	15/520 (2.9%)	48/607 (7.9%)	RR 0.49 (0.28 to 0.87)	40 fewer per 1000 (from 10 fewer to 57 fewer)	VERY LOW	CRITICAL
Operation Time (Better indicated by lower values)												
18	observational studies	no serious [1]	serious[8]	serious[2]	no serious imprecision [6]	none	616	946	-	MD 8.88 higher (6.46 lower to 24.24 higher)	VERY LOW	CRITICAL
Length of hospital stay (Better indicated by lower values)												
20	observational studies	no serious [1]	serious[9]	serious[2]	serious[6,7]	none	731	1080	-	MD 3.88 lower (4.92 to 2.83 lower)	VERY LOW	CRITICAL
Time to Oral Intake (Better indicated by lower values)												
6	observational studies	no serious [1]	serious[10]	serious[2]	serious[3]	none	219	169	-	MD 1.48 lower (2.43 to 0.53 lower)	VERY LOW	CRITICAL

[1] *Not randomised comparisons*

[2] *Population not all pancreatic cancer patients*

[3] *95% CI crosses 2 default MIDs (0.8 and 1.25).*

[4] *95% CI crosses 1 MID (0.8 or 1.25).*

[5] *Between Studies heterogeneity I2=81%*

[6] *MIDs for continuous outcomes, calculated from median SD of control arm at follow up, are as follows: operative blood loss is +/- 291.5 litres (Median SD=583 litres); operation time is +/- 33.3 mins(Median SD=66.7 mins); length of hospital stay is +/- 2.9 days (median SD=5.7 days); time to oral intake is +/- 2.8 days (median SD=5.4 days).*

[7] *95% CI crosses 1 MID for this outcome.*

[8] *Between Studies heterogeneity I2=81%*

[9] *Between studies heterogeneity I2=84%*

[10] *Between studies heterogeneity I2=68%*

I.13.41 Robotic pancreatectomy versus open pancreatectomy

2 **Table 41: Full GRADE profile for robotic pancreatectomy versus open pancreatectomy in adults with resectable or borderline**
3 **resectable pancreatic cancer**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Robotic pancreatectomy	Open pancreatectomy	Relative (95% CI)	Absolute		
Overall Complication Rate												
7[1]	observational studies	no serious[2]	no serious inconsistency	serious[3]	serious[4]	none	41/137 (29.9%)	74/203 (36.5%)	RR 0.71 (0.52 to 0.97)	106 fewer per 1000 (from 11 fewer to 175 fewer)	VERY LOW	CRITICAL
Postoperative Mortality												
7[1]	observational studies	no serious[2]	no serious inconsistency	serious[3]	very serious[4]	none	4/137 (2.9%)	3/203 (1.5%)	RR 1.67 (0.45 to 6.16)	10 more per 1000 (from 8 fewer to 76 more)	VERY LOW	CRITICAL
Positive Margin Rate												
4	observational studies	no serious[2]	no serious inconsistency	serious[3]	serious[5]	none	3/66 (4.5%)	13/58 (22.4%)	RR 0.31 (0.11 to 0.9)	155 fewer per 1000 (from 22 fewer to 199 fewer)	VERY LOW	CRITICAL

Operation Time (mins) (Better indicated by lower values)												
3	observational studies	no serious [2]	serious[6]	serious[3]	serious[4]	none	57	57	-	MD 117.71 higher (139.76 lower to 375.18 higher)	VERY LOW	CRITICAL
Length of hospital stay (days) (Better indicated by lower values)												
3	observational studies	no serious [2]	no serious inconsistency	serious[3]	serious[4]	none	57	57	-	MD 4.71 lower (9.45 lower to 0.03 higher)	VERY LOW	CRITICAL
Pancreatic Fistula												
5	observational studies	no serious [2]	no serious inconsistency	serious[3]	very serious[4]	none	13/105 (12.4%)	17/104 (16.3%)	RR 0.82 (0.42 to 1.39)	29 fewer per 1000 (from 95 fewer to 64 more)	VERY LOW	CRITICAL

[1] *5 full studies/2 abstracts*
[2] *Not randomised*
[3] *Includes patients with benign disease and malignancies other than pancreatic cancer (N=138 patients with malignant disease)*
[4] *95% CI crosses 2 default MIDs (0.8 and 1.25).*
[5] *95% CI crosses 1 default MID (0.8 or 1.25).*
[6] *High heterogeneity between studies (I2=96%)*

I.13.5 Extended lymphadenectomy versus standard lymphadenectomy

Table 42: Full GRADE profile for extended lymphadenectomy versus standard lymphadenectomy in adults with resectable or borderline resectable pancreatic cancer

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Extended lymphadenectomy	Standard lymphadenectomy	Relative (95% CI)	Absolute		
Overall Survival (follow-up 60-96 months)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness[2]	serious[3]	none	172/205 (83.9%)	182/207 (87.9%)	HR 1.09 (0.84 to 1.41)	21 more per 1000 (from 49 fewer to 70 more)	LOW	CRITICAL
Lymph nodes (positve) (follow-up 60-96 months)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness[2]	serious[4]	none	117/139 (84.2%)	132/141 (93.6%)	HR 1.04 (0.76 to 1.42)	7 more per 1000 (from 60 fewer to 44 more)	LOW	CRITICAL
Lymph Nodes (negative) (follow-up 60-96 months)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness[2]	very serious[4]	none	52/66 (78.8%)	51/66 (77.3%)	HR 1.06 (0.58 to 1.94)	19 more per 1000 (from 196 fewer to 171 more)	VERY LOW	CRITICAL
No postoperative adjuvant treatment (follow-up 77-96 months)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness[2]	very serious[4]	none	88/89 (98.9%)	80/89 (89.9%)	RR 1.16 (0.67 to 1.98)	144 more per 1000	VERY LOW	CRITICAL

										(from 297 fewer to 881 more)		
Margin Status Negative												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	184/213 (86.4%)	173/215 (80.5%)	RR 1.06 (0.93 to 1.21)	48 more per 1000 (from 56 fewer to 169 more)	MODERATE	CRITICAL
Margin Status (positive)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness[2]	very serious[4]	none	24/213 (11.3%)	40/215 (18.6%)	RR 0.65 (0.33 to 1.31)	65 fewer per 1000 (from 125 fewer to 58 more)	VERY LOW	CRITICAL

[1] *Inadequate reporting of randomisation and allocation concealment, no assessor blinding, incomplete outcome data*
[2] *Only data relevant to patients with pancreatic cancer were extracted and included in the systematic review*
[3] *The GC decided to downgrade survival outcomes by one level for imprecision only if there was a significant difference between the groups.*
[4] *95% CI crosses 2 default MIDs (0.8 and 1.25).*

I.13.6 Arterial resection versus no arterial resection

Table 43: Full GRADE profile for arterial resection versus no arterial resection in adults with resectable or borderline resectable pancreatic cancer

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Arterial Resection	No Arterial Resection	Relative (95% CI)	Absolute		
1-year Overall survival												
12	observational studies	no serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	83/170 (48.8%)	1081/1640 (65.9%)	RR 0.83 (0.67 to 1.02)	112 fewer per 1000 (from 218 fewer to 13 more)	VERY LOW	CRITICAL
3-year Overall survival												
12	observational studies	no serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	17/166 (10.2%)	408/1638 (24.9%)	RR 0.46 (0.23 to 0.94)	135 fewer per 1000 (from 15 fewer to 192 fewer)	VERY LOW	CRITICAL
Post operative mortality												
14	observational studies	no serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	26/191 (13.6%)	67/1902 (3.5%)	RR 4.40 (2.52 to 7.69)	120 more per 1000 (from 54 more to 236 more)	VERY LOW	CRITICAL
Reoperation Rate												
7	observational studies	no serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	27/118 (22.9%)	151/1440 (10.5%)	RR 2.42 (1.36 to 4.3)	149 more per 1000 (from 38 more to 346 more)	VERY LOW	CRITICAL
R0 Resection Rate												
9	observational studies	no serious[1]	serious[3]	no serious indirectness	serious[4]	none	79/126 (62.7%)	997/1345 (74.1%)	RR 0.91 (0.67 to 1.23)	67 fewer per 1000 (from 245	VERY LOW	CRITICAL

										fewer to 170 more)		
Positive lymph nodes												
6	observational studies	no serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	60/89 (67.4%)	668/1112 (60.1%)	RR 1.13 (0.94 to 1.36)	78 more per 1000 (from 36 fewer to 216 more)	VERY LOW	CRITICAL
Postoperative morbidity												
7	observational studies	no serious[1]	serious[5]	no serious indirectness	serious[4]	none	45/97 (46.4%)	508/1282 (39.6%)	RR 1.32 (0.92 to 1.89)	127 more per 1000 (from 32 fewer to 353 more)	VERY LOW	CRITICAL

[1] *Not randomised studies*
[2] *The GC decided to downgrade survival outcomes by one level for imprecision only if there was a significant difference between the groups.*
[3] *I2 81% indicating between studies heterogeneity*
[4] *95% CI crosses 1 default MID (0.8 or 1.25).*
[5] *I2 was 64% indicating between studies heterogeneity*

I.13.7 Venous resection versus no venous resection

Table 44: Full GRADE profile for venous resection versus no venous resection in adults with resectable or borderline resectable pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Venous resection**	**No venous resection**	**Relative (95% CI)**	**Absolute**		
1-year overall survival												
6	observational studies	no serious[1]	serious[2]	no serious indirectness	no serious imprecision[3]	none	-	-	Not estimable	-	VERY LOW	CRITICAL

5-year overall survival												
4	observational studies	no serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[3]	none	-	-	Not estimable	-	VERY LOW	CRITICAL
5-year overall survival (b)												
11	observational studies	no serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	60/484 (12.4%)	180/1048 (17.2%)	RR 0.68 (0.45 to 1.01)	55 fewer per 1000 (from 94 fewer to 2 more)	VERY LOW	CRITICAL
Post operative mortality												
28	observational studies	no serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	64/1584 (4%)	226/7040 (3.2%)	RR 1.53 (1.16 to 2.02)	17 more per 1000 (from 5 more to 33 more)	VERY LOW	CRITICAL
Reoperation Rate												
11	observational studies	no serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	128/1010 (12.7%)	485/5388 (9%)	RR 1.35 (1.13 to 1.62)	32 more per 1000 (from 12 more to 56 more)	VERY LOW	CRITICAL
R1-R2 resection rate												
18	observational studies	no serious	serious[5]	no serious indirectness	serious[4]	none	346/934 (37%)	817/2369 (34.5%)	RR 1.37 (1.2 to 1.56)	128 more per 1000 (from 69 more to 193 more)	VERY LOW	CRITICAL
Overall operative morbidity												
16	observational studies	no serious[1]	serious[6]	no serious indirectness	serious[4]	none	370/945 (39.2%)	1751/5304 (33%)	RR 1.18 (1.01 to 1.38)	59 more per 1000 (from 3	VERY LOW	CRITICAL

											more to 125 more)		

[1] *No randomised, blinding or allocation concealment*
[2] *I2=61% indicated high between studies heterogeneity*
[3] *The GC decided to downgrade survival outcomes by one level for imprecision only if there was a significant difference between the groups.*
[4] *95% CI crosses 1 default MID (0.8 or 1.25).*
[5] *I2 is 68% indicating high between studies heterogeneity*
[6] *I2 is 55% indicating high between studies heterogeneity*

I.14 Adjuvant treatment

I.14.1 Adjuvant chemotherapy versus no adjuvant therapy

Table 45: Full GRADE profile for adjuvant chemotherapy versus no adjuvant therapy in resected pancreatic cancer patients

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Chemotherapy**	**No adjuvant therapy**	**Relative (95% CI)**	**Absolute**		
Overall Survival - Chemotherapy vs No adjuvant therapy												
8	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	504/641 (78.6%)	517/621 (83.3%)	HR 0.78 (0.69 to 0.89)	81 fewer per 1000 (from 36 fewer to 124 fewer)	LOW	CRITICAL
								30%[3]		57 fewer per 1000 (from 28 fewer to 82 fewer)		
Overall Survival - 5FU+FA vs No adjuvant therapy												

3	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	174/233 (74.7%)	190/225 (84.4%)	HR 0.69 (0.56 to 0.85)	121 fewer per 1000 (from 50 fewer to 197 fewer)	LOW	CRITICAL
								30%[3]		82 fewer per 1000 (from 38 fewer to 119 fewer)		
Overall Survival - Cisplatin+5FU vs No adjuvant therapy												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[2,6]	none	35/45 (77.8%)	36/44 (81.8%)	HR 1.02 (0.64 to 1.62)[7]	6 more per 1000 (from 154 fewer to 119 more)	LOW	CRITICAL
								30%[3]		5 more per 1000 (from 96 fewer to 139 more)		
Overall Survival - Gemcitabine vs No adjuvant therapy												
2	randomised trials	very serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	201/237 (84.8%)	213/235 (90.6%)	HR 0.76 (0.63 to 0.93)	72 fewer per 1000 (from 17 fewer to 131 fewer)	LOW	CRITICAL

								30%[3]		63 fewer per 1000 (from 18 fewer to 99 fewer)		
Overall Survival - Gemcitabine, Carboplatin, Mitomycin C, 5FU+FA vs No adjuvant therapy												
1	randomised trials	very serious[9]	no serious inconsistency	no serious indirectness	serious[2,6]	none	22/45 (48.9%)	15/40 (37.5%)	HR 0.52 (0.27 to 1)[7]	158 fewer per 1000 (from 256 fewer to 0 more)	VERY LOW	CRITICAL
								30%[3]		131 fewer per 1000 (from 208 fewer to 0 more)		
Overall Survival - Mitomycin C+5FU vs No adjuvant therapy												
1	randomised trials	very serious[10]	no serious inconsistency	no serious indirectness	serious[2,6]	none	72/81 (88.9%)	63/77 (81.8%)	HR 1.15 (0.82 to 1.61)[7]	41 more per 1000 (from 65 fewer to 118 more)	VERY LOW	CRITICAL
								30%[3]		36 more per 1000 (from 46 fewer to 137 more)		
Disease-free Survival - Chemotherapy vs No adjuvant therapy												

5	randomised trials	very serious[11]	serious[12]	no serious indirectness	no serious imprecision[2]	none	351/407 (86.2%)	358/396 (90.4%)	HR 0.79 (0.68 to 0.92)	61 fewer per 1000 (from 20 fewer to 107 fewer)	VERY LOW	CRITICAL
								20%[3]		38 fewer per 1000 (from 14 fewer to 59 fewer)		
Disease-free Survival - Cisplatin+5FU vs No adjuvant therapy												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[2,6]	none	32/44 (72.7%)	34/44 (77.3%)	HR 1.06 (0.66 to 1.72)[7]	19 more per 1000 (from 149 fewer to 149 more)	LOW	CRITICAL
								20%[3]		11 more per 1000 (from 63 fewer to 119 more)		
Disease-free Survival - Gemcitabine vs No adjuvant therapy												
2	randomised trials	very serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	200/237 (84.4%)	213/235 (90.6%)	HR 0.72 (0.59 to 0.87)	88 fewer per 1000 (from 34 fewer to 154 fewer)	LOW	CRITICAL

								20%[3]		52 fewer per 1000 (from 24 fewer to 77 fewer)		
Disease-free Survival - Gemcitabine, Carboplatin, Mitomycin C, 5FU+FA vs No adjuvant therapy												
1	randomised trials	very serious[9]	no serious inconsistency	no serious indirectness	serious[2,6]	none	19/45 (42.2%)	15/40 (37.5%)	HR 0.41 (0.21 to 0.81)[7]	200 fewer per 1000 (from 58 fewer to 281 fewer)	VERY LOW	CRITICAL
								20%[3]		113 fewer per 1000 (from 35 fewer to 154 fewer)		
Disease-free Survival - Mitomycin C+5FU vs No adjuvant therapy												
1	randomised trials	very serious[10]	no serious inconsistency	no serious indirectness	serious[2,6]	none	74/81 (91.4%)	71/77 (92.2%)	HR 0.97 (0.7 to 1.34)[7]	6 fewer per 1000 (from 90 fewer to 45 more)	VERY LOW	CRITICAL
								20%[3]		5 fewer per 1000 (from 55 fewer to 58 more)		
# patients with serious adverse events - Gemcitabine vs No adjuvant therapy												

1	randomised trials	very serious[13]	no serious inconsistency	no serious indirectness	serious[14]	none	26/186 (14%)	15/182 (8.2%)	RR 1.7 (0.93 to 3.1)	58 more per 1000 (from 6 fewer to 173 more)	VERY LOW	CRITICAL
# patients with any Grade 3 or 4 haematological toxicities - 5FU+FA vs No adjuvant therapy (assessed with: UICC Common Toxicity Criteria)												
1	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	very serious[15]	none	2/75 (2.7%)	0/69 (0%)	RR 4.61 (0.22 to 94.27)	-	VERY LOW	CRITICAL
# patients with any Grade 3 or 4 non-haematological toxicities - 5FU+FA vs No adjuvant therapy (assessed with: UICC Common Toxicity Criteria)												
1	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	very serious[15]	none	9/75 (12%)	0/69 (0%)	RR 17.5 (1.04 to 295.13)	-	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Abscess - Gemcitabine vs No adjuvant therapy (assessed with: NCI Common Terminology Criteria for Adverse Events)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[15]	none	1/57 (1.8%)	0/60 (0%)	RR 3.16 (0.13 to 75.9)	-	LOW	CRITICAL
# patients with Grade 3 or 4 Alanine Aminotransferase - Gemcitabine vs No adjuvant therapy (assessed with: NCI Common Terminology Criteria for Adverse Events)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[15]	none	4/57 (7%)	0/60 (0%)	RR 9.47 (0.52 to 171.95)	-	LOW	CRITICAL
# patients with Grade 3 or 4 Anaemia - Gemcitabine vs No adjuvant therapy (assessed with: NCI Common Terminology Criteria for Adverse Events)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[15]	none	2/57 (3.5%)	0/60 (0%)	RR 5.26 (0.26 to 107.22)	-	LOW	CRITICAL

# patients with Grade 3 or 4 Anorexia - Gemcitabine vs No adjuvant therapy (assessed with: NCI Common Terminology Criteria for Adverse Events)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[15]	none	2/57 (3.5%)	0/60 (0%)	RR 5.26 (0.26 to 107.22)	-	LOW	CRITICAL
# patients with Grade 3 or 4 Aspartate Aminotransferase - Gemcitabine vs No adjuvant therapy (assessed with: NCI Common Terminology Criteria for Adverse Events)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[15]	none	3/57 (5.3%)	0/60 (0%)	RR 7.36 (0.39 to 139.44)	-	LOW	CRITICAL
# patients with Grade 3 or 4 Diarrhoea - Chemotherapy vs No adjuvant therapy (assessed with: UICC Common Toxicity Criteria; NCI Common Terminology Criteria for Adverse Events)												
2	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	very serious[15]	none	3/132 (2.3%)	0/129 (0%)	RR 3.9 (0.44 to 34.75)	-	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Diarrhoea - 5FU+FA vs No adjuvant therapy (assessed with: UICC Common Toxicity Criteria)												
1	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	very serious[15]	none	2/75 (2.7%)	0/69 (0%)	RR 4.61 (0.22 to 94.27)	-	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Diarrhoea - Gemcitabine vs No adjuvant therapy (assessed with: NCI Common Terminology Criteria for Adverse Events)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[15]	none	1/57 (1.8%)	0/60 (0%)	RR 3.16 (0.13 to 75.9)	-	LOW	CRITICAL
# patients with Grade 3 or 4 Fatigue - Gemcitabine vs No adjuvant therapy (assessed with: NCI Common Terminology Criteria for Adverse Events)												
1	randomised trials	no serious	no serious inconsistency	no serious indirectness	very serious[15]	none	1/57 (1.8%)	0/60 (0%)	RR 3.16 (0.13 to 75.9)	-	LOW	CRITICAL

		risk of bias										
# patients with Grade 3 or 4 Fever - Gemcitabine vs No adjuvant therapy (assessed with: NCI Common Terminology Criteria for Adverse Events)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[15]	none	1/57 (1.8%)	0/60 (0%)	RR 3.16 (0.13 to 75.9)	-	LOW	CRITICAL
# patients with Grade 3 or 4 Granulocytopenia - Cisplatin+5FU vs No adjuvant therapy (assessed with: WHO Toxicity criteria)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[15]	none	4/38 (10.5%)	0/44 (0%)	RR 10.38 (0.58 to 186.87)	-	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Hepatic - Cisplatin+5FU vs No adjuvant therapy (assessed with: WHO Toxicity criteria)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[15]	none	3/38 (7.9%)	0/44 (0%)	RR 8.08 (0.43 to 151.56)	-	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Leukopenia - Chemotherapy vs No adjuvant therapy (assessed with: WHO Toxicity criteria; NCI Common Terminology Criteria for Adverse Events)												
2	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[16]	none	16/95 (16.8%)	0/104 (0%)	RR 18.43 (2.45 to 138.47)	-	LOW	CRITICAL
# patients with Grade 3 or 4 Leukopenia - Cisplatin+5FU vs No adjuvant therapy (assessed with: WHO Toxicity criteria)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[15]	none	2/38 (5.3%)	0/44 (0%)	RR 5.77 (0.29 to 116.57)	-	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Leukopenia - Gemcitabine vs No adjuvant therapy (assessed with: NCI Common Terminology Criteria for Adverse Events)												
1	randomised trials	no serious	no serious inconsistency	no serious indirectness	serious[16]	none	14/57 (24.6%)	0/60 (0%)	RR 30.5 (1.86 to 499.65)	-	MODERATE	CRITICAL

		risk of bias										
# patients with Grade 3 or 4 Neutropenia - Gemcitabine vs No adjuvant therapy (assessed with: NCI Common Terminology Criteria for Adverse Events)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[16]	none	40/57 (70.2%)	0/60 (0%)	RR 85.19 (5.36 to 1353.55)	-	MODERATE	CRITICAL
# patients with Grade 3 or 4 Mucositis - Cisplatin+5FU vs No adjuvant therapy (assessed with: WHO Toxicity criteria)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[15]	none	2/38 (5.3%)	0/44 (0%)	RR 5.77 (0.29 to 116.57)	-	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Nausea/Vomiting - Chemotherapy vs No adjuvant therapy (assessed with: WHO toxicity criteria; NCI Common Terminology Criteria for Adverse Events)												
3	randomised trials	very serious[5, 9]	no serious inconsistency	no serious indirectness	serious[14]	none	7/140 (5%)	0/144 (0%)	RR 5.97 (1.1 to 32.48)	-	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Nausea/Vomiting - Cisplatin+5FU vs No adjuvant therapy (assessed with: WHO toxicity criteria)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[15]	none	5/38 (13.2%)	0/44 (0%)	RR 12.69 (0.72 to 222.32)	-	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Nausea/Vomiting - Gemcitabine, Carboplatin, Mitoxantrone, mitomycin C, 5FU+ FA vs No adjuvant therapy (assessed with: Not stated in study)												
1	randomised trials	very serious[9]	no serious inconsistency	no serious indirectness	very serious[15]	none	1/45 (2.2%)	0/40 (0%)	RR 2.67 (0.11 to 63.84)	-	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Nausea/Vomiting - Gemcitabine vs No adjuvant therapy (assessed with: NCI Common Terminology Criteria for Adverse Events)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[15]	none	1/57 (1.8%)	0/60 (0%)	RR 3.16 (0.13 to 75.9)	-	LOW	CRITICAL
# patients with Grade 3 or 4 Stomatitis - 5FU+FA vs No adjuvant therapy (assessed with: UICC Common Toxicity Criteria)												
1	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	very serious[15]	none	4/75 (5.3%)	0/69 (0%)	RR 8.29 (0.45 to 151.2)	-	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Thrombocytopenia - Gemcitabine vs No adjuvant therapy (assessed with: NCI Common Terminology Criteria for Adverse Events)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[15]	none	1/57 (1.8%)	0/60 (0%)	RR 3.16 (0.13 to 75.9)	-	LOW	CRITICAL
Quality of life - change scores - 5FU+FA vs No adjuvant therapy (measured with: ESPAC-1 QoL; Better indicated by lower values)												
1	randomised trials	very serious[4]	no serious inconsistency	serious[17]	no serious imprecision	none	238	235	-	SMD 0 higher (0.18 lower to 0.18 higher)	VERY LOW	CRITICAL
# patients with improving ESPAC-1 QoL Role Functioning scores - 5FU+FA vs No adjuvant therapy (Better indicated by lower values)												
1	randomised trials	very serious[4]	no serious inconsistency	serious[17]	no serious imprecision	none	238	235	-	SMD 0.27 higher (0.09 to 0.46 higher)	VERY LOW	CRITICAL
# patients improved >=1 ECOG PS Grade - Mitomycin C+5FU vs No adjuvant therapy												
1	randomised trials	very serious[10]	no serious inconsistency	no serious indirectness	very serious[15]	none	41/58 (70.7%)	39/55 (70.9%)	RR 1 (0.79 to 1.26)	0 fewer per 1000 (from	VERY LOW	CRITICAL

										149 fewer to 184 more)		

1 Majority of studies have high risk of bias (Lygidakis et al. 2002; Neoptolemos et al. 2001, 2004, 2009; Oettle et al. 2007/2013; Takada et al. 2002). Main reasons include: unclear risk for randomisation method/allocation concealment; unclear or high risk for selective reporting (primary outcomes not fully reported); other sources of bias (Kaplan-Meier curves cross, proportional hazards not satisfied).
2 The committee decided to consider all survival outcomes that were clinically important, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not clinically important.
3 Thirty percent 2-year overall survival rate and 20% 2-year disease-free survival rate assumed for no adjuvant therapy control group.
4 Overall high risk of bias (Neoptolemos et al. 2001, 2004 and 2009). Main reasons include: unclear risk randomisation method; selective reporting (one or more outcomes of interest reported incompletely); other sources of bias (clinicians chose which ESPAC-1 trial patients were randomised to [ESPAC-1 2x2, ESPAC-1+ chemotherapy only trial, ESPAC-1+ chemoradiotherapy only trials]); other sources of bias (Kaplan-Meier curves for overall survival cross, proportional hazards not satisfied).
5 Overall unclear risk of bias for Kosuge et al. 2006 (unclear risk allocation concealment; selective reporting (insufficient information); other sources of bias (Kaplan-Meier curves for overall and disease-free survival cross, proportional hazards not satisfied).
6 Not clinically important (p>0.5).
7 Hazard ratio estimated from Kaplan-Meier curve and/or summary statistics using method 7 in Tierney et al. (2007).
8 Overall high risk of bias (Oettle et al. 2007/2013). Main reasons include: selective reporting (one or more outcomes of interest not fully reported; other sources of bias (Kaplan-Meier curves for overall survival cross, proportional hazards not satisfied).
9 Overall high risk of bias for Lygidakis et al. 2002. Main reasons include unclear risk randomisation method/allocation method; high risk selective reporting (fails to report survival results in expected manner); other sources of bias (power calculation not reported; Kaplan-Meier curves for overall survival cross, proportional hazards not satisfied).
10 Overall high risk of bias for Takada et al. 2002. Main reasons include: unclear randomisation method/allocation concealment; selective reporting (one or more outcomes of interest not fully reported); other sources of bias (No Kaplan-Meier curve, not clear whether proportional hazards satisfied).
11 Majority of studies have high risk of bias (Lygidakis et al. 2002; Oettle et al. 2007/2013; Takada et al. 2002). Main reasons include: unclear risk for randomisation method/allocation concealment; high risk for selective reporting (primary outcomes not fully reported);
12 High heterogeneity (i2>50%).
13 Overall high risk of bias for Oettle et al. 2007/2013. Main reasons include: selective reporting (one or more outcomes of interest not fully reported.
14 Crosses 1 default MID (0.8 or 1.25).
15 Crosses 2 default MIDs (0.8 and 1.25).
16 Small sample size (<300 events).
17 Data from both ESPAC-1 2x2 trial (Neoptolemos et al. 2001, 2004) and ESPAC-1+ (Neoptolemos et al. 2009) trial. Chemotherapy group (n=238) includes 72 patients who received both chemotherapy and chemoradiotherapy, in addition to 168 patients who received chemotherapy only. Comparison group (n=235) includes 70 patients who received chemoradiotherapy only, in addition to165 patients who received no treatment after resection.

I.14.2 Adjuvant chemotherapy-1 (gemcitabine) versus adjuvant chemotherapy-2 (other)

Table 46: Full GRADE profile for adjuvant chemotherapy-1 (gemcitabine) versus adjuvant chemotherapy-2 (other) in resected pancreatic cancer patients

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemotherapy-1 (gemcitabine)	Chemotherapy-2 (other)	Relative (95% CI)	Absolute		
Overall Survival - Gemcitabine vs Other chemotherapy (Random Effects)												
4	randomised trials	serious[1]	very serious[2]	no serious indirectness	serious[3,4]	none	783/1145 (68.4%)	752/1157 (65%)	HR 1.15 (0.85 to 1.55)	51 more per 1000 (from 60 fewer to 154 more)	VERY LOW	CRITICAL
								40%[5]		44 more per 1000 (from 48 fewer to 147 more)		
Overall Survival - Gemcitabine vs 5FU+FA (Fixed Effects)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3,4]	none	365/537 (68%)	388/551 (70.4%)	HR 0.94 (0.81 to 1.09)	22 fewer per 1000 (from 77 fewer to 31 more)	MODERATE	CRITICAL
								40%[5]		19 fewer per 1000 (from 61 fewer to 27 more)		
Overall Survival - Gemcitabine vs S-1(Fixed Effects)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[3]	none	153/193 (79.3%)	114/192 (59.4%)	HR 1.75 (1.37 to 2.24)	200 more per 1000 (from	HIGH	CRITICAL

										115 more to 273 more)		
								40%[5]		191 more per 1000 (from 103 more to 282 more)		
Overall Survival - Gemcitabine vs Gemcitabine+UFT (Fixed Effects)												
1	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[3,4]	none	26/49 (53.1%)	31/50 (62%)	HR 0.75 (0.45 to 1.26)[7]	104 fewer per 1000 (from 267 fewer to 85 more)	LOW	CRITICAL
								40%[5]		82 fewer per 1000 (from 195 fewer to 75 more)		
Overall Survival - Gemcitabine vs Gemcitabine+Capecitabine (Fixed Effects)												
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision [3]	none	239/366 (65.3%)	219/364 (60.2%)	HR 1.22 (1.02 to 1.46)[7]	73 more per 1000 (from 7 more to 138 more)	MODERATE	CRITICAL

								40%[5]		64 more per 1000 (from 6 more to 126 more)		
Relapse-Free Survival - Gemcitabine vs Gemcitabine+Capecitabine												
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	serious[3,4]	none	243/366 (66.4%)	236/364 (64.8%)	HR 1.16 (0.98 to 1.37)	54 more per 1000 (from 7 fewer to 113 more)	LOW	CRITICAL
Disease-free Survival - Gemcitabine vs Other chemotherapy												
3	randomised trials	serious[1]	very serious[2]	no serious indirectness	serious[3,4]	none	591/725 (81.5%)	579/736 (78.7%)	HR 1.11 (0.99 to 1.25)	33 more per 1000 (from 3 fewer to 68 more)	VERY LOW	CRITICAL
								40%[5]		33 more per 1000 (from 3 fewer to 72 more)		
Disease-free Survival - Gemcitabine vs 5FU+FA												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3,4]	none	406/486 (83.5%)	417/499 (83.6%)	HR 0.99 (0.87 to 1.14)	3 fewer per 1000 (from 43 fewer to 37 more)	MODERATE	CRITICAL
								40%[5]		3 fewer per 1000 (from 41		

										fewer to 41 more)		
Disease-free Survival - Gemcitabine vs S-1												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision [3]	none	149/190 (78.4%)	123/187 (65.8%)	HR 1.67 (1.31 to 2.12)	175 more per 1000 (from 97 more to 239 more)	HIGH	CRITICAL
								40%[5]		174 more per 1000 (from 88 more to 261 more)		
Disease-free Survival - Gemcitabine vs Gemcitabine+UFT												
1	randomised trials	very serious[6]	no serious inconsistency	no serious indirectness	serious[3,4]	none	36/49 (73.5%)	39/50 (78%)	HR 0.91 (0.58 to 1.43)[7]	32 fewer per 1000 (from 196 fewer to 105 more)	VERY LOW	CRITICAL
								40%[5]		28 fewer per 1000 (from 144 fewer to 118 more)		
# patients with serious treatment-related adverse events - Gemcitabine vs Other (Random Effects)												

2	randomised trials	serious[8]	very serious[2]	no serious indirectness	very serious[9]	none	134/903 (14.8%)	163/910 (17.9%)	RR 0.77 (0.38 to 1.52)	41 fewer per 1000 (from 111 fewer to 93 more)	VERY LOW	CRITICAL
# patients with serious treatment-related adverse events - Gemcitabine vs 5FU+FA (Fixed Effects)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	40/537 (7.4%)	77/551 (14%)	RR 0.53 (0.37 to 0.77)	66 fewer per 1000 (from 32 fewer to 88 fewer)	HIGH	CRITICAL
# patients with serious treatment-related adverse events - Gemcitabine vs Gemcitabine+Capecitabine (Fixed Effects)												
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	serious[10]	none	94/366 (25.7%)	86/359 (24%)	RR 1.07 (0.83 to 1.38)	17 more per 1000 (from 41 fewer to 91 more)	LOW	CRITICAL
# patients with Grade 3 or 4 Alanine Aminotransferase/Aspartate Aminotransferase - Gemcitabine vs Other chemotherapy (Random Effects) (assessed with: NCI Common Toxicity Criteria)												
3	randomised trials	no serious risk of bias	very serious[2]	no serious indirectness	very serious[9]	none	257/776 (33.1%)	137/788 (17.4%)	RR 1.94 (0.26 to 14.2)	163 more per 1000 (from 129 fewer to 1000 more)	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Alanine Aminotransferase/Aspartate Aminotransferase - Gemcitabine vs S-1 (Fixed Effects) (assessed with: NCI Common Toxicity Criteria)												
1	randomised trials	no serious	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association[11]	138/190 (72.6%)	15/187 (8%)	RR 9.05	646 more per	HIGH	CRITICAL

		risk of bias							(5.53 to 14.83)	1000 (from 363 more to 1000 more)		
# patients with Grade 3 or 4 Alanine Aminotransferase/Aspartate Aminotransferase - Gemcitabine vs 5FU+FA (Fixed Effects) (assessed with: NCI Common Toxicity Criteria)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[10]	none	119/537 (22.2%)	121/551 (22%)	RR 1.01 (0.81 to 1.26)	2 more per 1000 (from 42 fewer to 57 more)	MODERATE	CRITICAL
# patients with Grade 3 or 4 Alanine Aminotransferase/Aspartate Aminotransferase - Gemcitabine vs Gemcitabine+UFT (Fixed Effects) (assessed with: NCI Common Toxicity Criteria)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[9]	none	0/49 (0%)	1/50 (2%)	RR 0.34 (0.01 to 8.15)	13 fewer per 1000 (from 20 fewer to 143 more)	LOW	CRITICAL
# patients with Grade 3 or 4 Anorexia - Gemcitabine vs Other chemotherapy (assessed with: NCI Common Toxicity Criteria)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[9]	none	12/239 (5%)	16/237 (6.8%)	RR 0.74 (0.36 to 1.53)	18 fewer per 1000 (from 43 fewer to 36 more)	LOW	CRITICAL
# patients with Grade 3 or 4 Anorexia - Gemcitabine vs Gemcitabine+UFT (assessed with: NCI Common Toxicity Criteria)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[9]	none	1/49 (2%)	1/50 (2%)	RR 1.02 (0.07 to 15.86)	0 more per 1000 (from 19 fewer to 297 more)	LOW	CRITICAL

# patients with Grade 3 or 4 Anorexia - Gemcitabine vs S-1 (assessed with: NCI Common Toxicity Criteria)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[9]	none	11/190 (5.8%)	15/187 (8%)	RR 0.72 (0.34 to 1.53)	22 fewer per 1000 (from 53 fewer to 43 more)	LOW	CRITICAL
# patients with Grade 3 or 4 Bilirubin - Gemcitabine vs S-1 (assessed with: NCI Common Toxicity Criteria)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[9]	none	1/190 (0.53%)	2/187 (1.1%)	RR 0.49 (0.05 to 5.38)	5 fewer per 1000 (from 10 fewer to 47 more)	LOW	CRITICAL
# patients with Grade 3 or 4 Creatinine - Gemcitabine vs S-1 (assessed with: NCI Common Toxicity Criteria)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[9]	none	1/190 (0.53%)	1/187 (0.53%)	RR 0.98 (0.06 to 15.62)	0 fewer per 1000 (from 5 fewer to 78 more)	LOW	CRITICAL
# patients with Grade 3 or 4 Diarrhoea - Gemcitabine vs Other chemotherapy (assessed with: NCI Common Toxicity Criteria)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association[11]	18/1093 (1.6%)	100/1097 (9.1%)	RR 0.19 (0.11 to 0.3)	74 fewer per 1000 (from 64 fewer to 81 fewer)	HIGH	CRITICAL
# patients with Grade 3 or 4 Diarrhoea - Gemcitabine vs S-1 (assessed with: NCI Common Toxicity Criteria)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[10]	none	0/190 (0%)	9/187 (4.8%)	RR 0.05 (0 to 0.88)	46 fewer per 1000 (from 6 fewer to 48 fewer)	MODERATE	CRITICAL

# patients with Grade 3 or 4 Diarrhoea - Gemcitabine vs 5FU+FA (assessed with: NCI Common Toxicity Criteria)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association[11]	12/537 (2.2%)	72/551 (13.1%)	RR 0.17 (0.09 to 0.31)	108 fewer per 1000 (from 90 fewer to 119 fewer)	HIGH	CRITICAL
# patients with Grade 3 or 4 Diarrhoea - Gemcitabine vs Gemcitabine+Capecitabine (assessed with: NCI Common Toxicity Criteria)												
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	none	6/366 (1.6%)	19/359 (5.3%)	RR 0.31 (0.13 to 0.77)	37 fewer per 1000 (from 12 fewer to 46 fewer)	MODERATE	CRITICAL
# patients with Grade 3 or 4 Fatigue/Tiredness - Gemcitabine vs Other chemotherapy (assessed with: NCI Common Toxicity Criteria)												
3	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	serious[10]	none	60/1093 (5.5%)	75/1097 (6.8%)	RR 0.81 (0.58 to 1.12)	13 fewer per 1000 (from 29 fewer to 8 more)	LOW	CRITICAL
# patients with Grade 3 or 4 Fatigue/Tiredness - Gemcitabine vs S-1 (assessed with: NCI Common Toxicity Criteria)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[9]	none	9/190 (4.7%)	10/187 (5.3%)	RR 0.89 (0.37 to 2.13)	6 fewer per 1000 (from 34 fewer to 60 more)	LOW	CRITICAL
# patients with Grade 3 or 4 Fatigue/Tiredness - Gemcitabine vs 5FU+FA (assessed with: NCI Common Toxicity Criteria)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[10]	none	32/537 (6%)	45/551 (8.2%)	RR 0.73 (0.47 to 1.13)	22 fewer per 1000 (from 43 fewer to 11 more)	MODERATE	CRITICAL

# patients with Grade 3 or 4 Fatigue/Tiredness - Gemcitabine vs Gemcitabine+Capecitabine (assessed with: NCI Common Toxicity Criteria)												
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	very serious[9]	none	19/366 (5.2%)	20/359 (5.6%)	RR 0.93 (0.51 to 1.72)	4 fewer per 1000 (from 27 fewer to 40 more)	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Febrile Neutropenia - Gemcitabine vs S-1 (assessed with: NCI Common Toxicity Criteria)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[9]	none	3/190 (1.6%)	1/187 (0.53%)	RR 2.95 (0.31 to 28.13)	10 more per 1000 (from 4 fewer to 145 more)	LOW	CRITICAL
# patients with Grade 3 or 4 Fever - Gemcitabine vs Other (assessed with: NCI Common Toxicity Criteria)												
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	very serious[9]	none	7/556 (1.3%)	11/546 (2%)	RR 0.62 (0.24 to 1.6)	8 fewer per 1000 (from 15 fewer to 12 more)	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Fever - Gemcitabine vs S-1 (assessed with: NCI Common Toxicity Criteria)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[9]	none	1/190 (0.53%)	5/187 (2.7%)	RR 0.2 (0.02 to 1.67)	21 fewer per 1000 (from 26 fewer to 18 more)	LOW	CRITICAL
# patients with Grade 3 or 4 Fever - Gemcitabine vs Gemcitabine+Capecitabine (assessed with: NCI Common Toxicity Criteria)												
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	very serious[9]	none	6/366 (1.6%)	6/359 (1.7%)	RR 0.98 (0.32 to 3.01)	0 fewer per 1000 (from 11 fewer to 34 more)	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Glucose Intolerance - Gemcitabine vs Gemcitabine+UFT (assessed with: NCI Common Toxicity Criteria)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[9]	none	49/49 (100%)	49/50 (98%)	RR 0.34 (0.01 to 8.15)	647 fewer per 1000 (from 970 fewer to 1000 more)	LOW	CRITICAL
# patients with Grade 3 or 4 Haemoglobin - Gemcitabine vs Gemcitabine+UFT (assessed with: NCI Common Toxicity Criteria)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[9]	none	4/49 (8.2%)	2/50 (4%)	RR 2.04 (0.39 to 10.64)	42 more per 1000 (from 24 fewer to 386 more)	LOW	CRITICAL
# patients with Grade 3 or 4 Hand-Foot Syndrome												
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/366 (0%)	26/359 (7.2%)	RR 0.02 (0 to 0.3)	71 fewer per 1000 (from 51 fewer to 72 fewer)	MODERATE	CRITICAL
# patients with Grade 3 or 4 Infection - Gemcitabine vs Other (assessed with: NCI Common Toxicity Criteria)												
2	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	none	32/556 (5.8%)	11/546 (2%)	RR 2.86 (1.46 to 5.6)	37 more per 1000 (from 9 more to 93 more)	MODERATE	CRITICAL
# patients with Grade 3 or 4 Infection - Gemcitabine vs S-1 (assessed with: NCI Common Toxicity Criteria)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[10]	none	8/190 (4.2%)	2/187 (1.1%)	RR 3.94 (0.85 to 18.3)	31 more per 1000 (from 2 fewer to	MODERATE	CRITICAL

										185 more)		
# patients with Grade 3 or 4 Infection - Gemcitabine vs Gemcitabine+Capecitabine (assessed with: NCI Common Toxicity Criteria)												
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	serious[10]	none	24/366 (6.6%)	9/359 (2.5%)	RR 2.62 (1.23 to 5.55)	41 more per 1000 (from 6 more to 114 more)	LOW	CRITICAL
# patients with Grade 3 or 4 Leukocytes - Gemcitabine vs Gemcitabine+UFT (assessed with: NCI Common Toxicity Criteria)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[9]	none	11/49 (22.4%)	9/50 (18%)	RR 1.25 (0.57 to 2.74)	45 more per 1000 (from 77 fewer to 313 more)	LOW	CRITICAL
# patients with Grade 3 or 4 Nausea - Gemcitabine vs Other chemotherapy (assessed with: NCI Common Toxicity Criteria)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[9]	none	18/727 (2.5%)	26/738 (3.5%)	RR 0.7 (0.39 to 1.27)	11 fewer per 1000 (from 21 fewer to 10 more)	LOW	CRITICAL
# patients with Grade 3 or 4 Nausea - Gemcitabine vs S-1 (assessed with: NCI Common Toxicity Criteria)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[9]	none	5/190 (2.6%)	7/187 (3.7%)	RR 0.7 (0.23 to 2.18)	11 fewer per 1000 (from 29 fewer to 44 more)	LOW	CRITICAL
# patients with Grade 3 or 4 Nausea - Gemcitabine vs 5FU+FA (assessed with: NCI Common Toxicity Criteria)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[9]	none	13/537 (2.4%)	19/551 (3.4%)	RR 0.7 (0.35 to 1.41)	10 fewer per 1000 (from 22	LOW	CRITICAL

										fewer to 14 more)		
# patients with Grade 3 or 4 Neutrophils - Gemcitabine vs Other chemotherapy (Random Effects) (assessed with: NCI Common Toxicity Criteria)												
2	randomised trials	no serious risk of bias	very serious[2]	no serious indirectness	no serious imprecision	none	257/727 (35.4%)	136/738 (18.4%)	RR 0.19 (1.59 to 2.31)	149 fewer per 1000 (from 109 more to 241 more)	LOW	CRITICAL
# patients with Grade 3 or 4 Neutrophils - Gemcitabine vs S-1 (Fixed Effects) (assessed with: NCI Common Toxicity Criteria)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association[11]	138/190 (72.6%)	15/187 (8%)	RR 9.05 (5.53 to 14.83)	646 more per 1000 (from 363 more to 1000 more)	HIGH	CRITICAL
# patients with Grade 3 or 4 Neutrophils - Gemcitabine vs 5FU+FA (Fixed Effects) (assessed with: NCI Common Toxicity Criteria)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[10]	none	119/537 (22.2%)	121/551 (22%)	RR 1.01 (0.81 to 1.26)	2 more per 1000 (from 42 fewer to 57 more)	MODERATE	CRITICAL
# patients with Grade 3 or 4 Platelets - Gemcitabine vs Other chemotherapy (assessed with: NCI Common Toxicity Criteria)												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[10]	none	36/1142 (3.2%)	17/1147 (1.5%)	RR 2.04 (1.17 to 3.53)	15 more per 1000 (from 3 more to 37 more)	MODERATE	CRITICAL
# patients with Grade 3 or 4 Platelets - Gemcitabine vs S-1 (assessed with: NCI Common Toxicity Criteria)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[10]	none	18/190 (9.5%)	9/187 (4.8%)	RR 1.97 (0.91 to 4.27)	47 more per 1000 (from 4 fewer to 157 more)	MODERATE	CRITICAL
# patients with Grade 3 or 4 Platelets - Gemcitabine vs 5FU+FA (assessed with: NCI Common Toxicity Criteria)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[10]	none	8/537 (1.5%)	0/551 (0%)	RR 17.44 (1.01 to 301.45)	-	MODERATE	CRITICAL
# patients with Grade 3 or 4 Platelets - Gemcitabine vs Gemcitabine+UFT (assessed with: NCI Common Toxicity Criteria)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[9]	none	3/49 (6.1%)	0/50 (0%)	RR 7.14 (0.38 to 134.71)	-	LOW	CRITICAL
# patients with Grade 3 or 4 Platelets - Gemcitabine vs Gemcitabine+Capecitabine (assessed with: NCI Common Toxicity Criteria)												
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	very serious[9]	none	7/366 (1.9%)	8/359 (2.2%)	RR 0.86 (0.31 to 2.34)	3 fewer per 1000 (from 15 fewer to 30 more)	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Stomatitis - Gemcitabine vs Other chemotherapy (assessed with: NCI Common Toxicity Criteria)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association[11]	1/727 (0.14%)	59/738 (8%)	RR 0.03 (0.01 to 0.13)	78 fewer per 1000 (from 70 fewer to 79 fewer)	HIGH	CRITICAL
# patients with Grade 3 or 4 Stomatitis - Gemcitabine vs S-1 (assessed with: NCI Common Toxicity Criteria)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[9]	none	0/190 (0%)	5/187 (2.7%)	RR 0.09 (0 to 1.61)	24 fewer per 1000 (from 27 fewer to 16 more)	LOW	CRITICAL
# patients with Grade 3 or 4 Stomatitis - Gemcitabine vs 5FU+FA (assessed with: NCI Common Toxicity Criteria)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association[11]	1/537 (0.19%)	54/551 (9.8%)	RR 0.02 (0 to 0.14)	96 fewer per 1000 (from 84 fewer to 98 fewer)	HIGH	CRITICAL
# patients with Grade 3 or 4 Vomiting - Gemcitabine vs Other chemotherapy (assessed with: NCI Common Toxicity Criteria)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[9]	none	13/727 (1.8%)	20/738 (2.7%)	RR 0.66 (0.33 to 1.32)	9 fewer per 1000 (from 18 fewer to 9 more)	LOW	CRITICAL
# patients with Grade 3 or 4 Vomiting - Gemcitabine vs S-1 (assessed with: NCI Common Toxicity Criteria)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[9]	none	2/190 (1.1%)	3/187 (1.6%)	RR 0.66 (0.11 to 3.88)	5 fewer per 1000 (from 14 fewer to 46 more)	LOW	CRITICAL
# patients with Grade 3 or 4 Vomiting - Gemcitabine vs 5FU+FA (assessed with: NCI Common Toxicity Criteria)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[9]	none	11/537 (2%)	17/551 (3.1%)	RR 0.66 (0.31 to 1.4)	10 fewer per 1000 (from 21 fewer to 12 more)	LOW	CRITICAL
# patients with Grade 3 or 4 White Blood Cell Count - Gemcitabine vs Other chemotherapy (Random Effects) (assessed with: NCI Common Toxicity Criteria)												

4	randomised trials	no serious risk of bias	very serious[2]	no serious indirectness	very serious[9]	none	166/1142 (14.5%)	94/1147 (8.2%)	RR 1.65 (0.75 to 3.63)	53 more per 1000 (from 20 fewer to 216 more)	VERY LOW	CRITICAL
# patients with Grade 3 or 4 White Blood Cell Count - Gemcitabine vs S-1 (Fixed Effects) (assessed with: NCI Common Toxicity Criteria)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[12]	74/190 (38.9%)	16/187 (8.6%)	RR 4.55 (2.76 to 7.51)	304 more per 1000 (from 151 more to 557 more)	HIGH	CRITICAL
# patients with Grade 3 or 4 White Blood Cell Count - Gemcitabine vs 5FU+FA (Fixed Effects) (assessed with: NCI Common Toxicity Criteria)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[10]	none	53/537 (9.9%)	32/551 (5.8%)	RR 1.7 (1.11 to 2.59)	41 more per 1000 (from 6 more to 92 more)	MODERATE	CRITICAL
# patients with Grade 3 or 4 White Blood Cell Count - Gemcitabine vs Gemcitabine+UFT (Fixed Effects) (assessed with: NCI Common Toxicity Criteria)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[9]	none	11/49 (22.4%)	9/50 (18%)	RR 1.25 (0.57 to 2.74)	45 more per 1000 (from 77 fewer to 313 more)	LOW	CRITICAL
# patients with Grade 3 or 4 White Blood Cell Count - Gemcitabine vs Gemcitabine+Capecitabine (Fixed Effects) (assessed with: NCI Common Toxicity Criteria)												
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	serious[10]	none	28/366 (7.7%)	37/359 (10.3%)	RR 0.74	27 fewer per 1000	LOW	CRITICAL

									(0.46 to 1.19)	(from 56 fewer to 20 more)		
EQ-5D Quality of Life - Gemcitabine vs S-1, 3 months post-randomisation (Better indicated by higher values)												
1	randomised trials	very serious[13]	no serious inconsistency	no serious indirectness	serious[14]	none	156	155	-	SMD 0.15 higher (0.08 lower to 0.37 higher)	VERY LOW	CRITICAL
EQ-5D Quality of Life - Gemcitabine vs S-1, 6 months post-randomisation (Better indicated by higher values)												
1	randomised trials	very serious[13]	no serious inconsistency	no serious indirectness	serious[14]	none	142	149	-	SMD 0.14 higher (0.09 lower to 0.37 higher)	VERY LOW	CRITICAL
EQ-5D Quality of Life - Gemcitabine vs S-1, 12 months post-randomisation (Better indicated by higher values)												
1	randomised trials	very serious[13]	no serious inconsistency	no serious indirectness	serious[10]	none	120	135	-	SMD 0.4 higher (0.15 to 0.65 higher)	VERY LOW	CRITICAL
EQ-5D Quality of Life - Gemcitabine vs S-1, 24 months post-randomisation (Better indicated by higher values)												
1	randomised trials	very serious[13]	no serious inconsistency	no serious indirectness	serious[10]	none	70	101	-	SMD 0.42 higher (0.11 to 0.72 higher)	VERY LOW	CRITICAL
Global Quality of Life - Gemcitabine vs 5FU+FA (measured with: EORTC QLQ-C30 v3; ESPAC-32; Better indicated by higher values)												

1	randomised trials	very serious[1] [5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	285	280	-	SMD 0.15 higher (0.01 lower to 0.32 higher)	LOW	CRITICAL

1 Two of 4 studies at high risk of bias: Yoshitomi et al. 2008 (high risk of bias due to other sources of bias (Kaplan-Meier curves for both overall and disease-free survival cross, proportional hazards not satisfied); Neoptolemos et al. 2017 (high risk due to no allocation concealment; no blinding of participants/personnel; relapsed patients received additional chemoradiotherapy, surgery or other treatment).
2 High heterogeneity (i2>80%).
3 The committee decided to consider all survival outcomes that were clinically important, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not clinically important.
4 Not clinically important (p>0.5).
5 Forty percent 2-year overall survival and disease-free survival rate assumed for other chemotherapy group.
6 Overall high risk of bias (Yoshitomi et al. 2008) due to high risk other sources of bias (Kaplan-Meier curves for overall and disease-free survival cross, proportional hazards not satisfied).
7 Hazard ratio estimated from Kaplan-Meier curve and summary statistics using method 7 in Tierney et al. (2007).
8 Overall high risk of bias (Neoptolemos et al. 2017: no allocation concealment; no blinding of participants/personnel; relapsed patients received additional chemoradiotherapy, surgery or other treatment).
9 Crosses 2 default MIDs (0.8 and 1.25).
10 Crosses 1 default MID (dichotomous outcomes: 0.8 or 1.25; continuous outcomes: 0.5 or -0.5).
11 Very large effect size (Risk Ratio >5 or <0.2)
12 Large effect size (Risk Ratio >2 or <0.5)
13 Overall high risk of bias (Uesaka et al. 2016). Main reason: high risk blinding of participants and personnel (participants not blinded, quality of life outcomes likely to be influenced by this).
14 Small sample size (<400 participants).
15 Overall high risk of bias (Neoptolemos et al. 2010). Main reason: high risk blinding of participants and personnel (participants not blinded, quality of life outcomes likely to be influenced by this).

I.14.3 Adjuvant chemotherapy versus adjuvant chemoradiotherapy

Table 47: GRADE profile for any adjuvant chemotherapy vs any adjuvant chemoradiotherapy in resected pancreatic cancer patients

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemotherapy	Chemoradiotherapy	Relative	Absolute		

									(95% CI)			
Overall Survival - Chemotherapy vs Chemoradiotherapy												
2	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	serious[3]	none	78/120 (65%)	88/118 (74.6%)	HR 0.79 (0.59 to 1.07)[4]	85 fewer per 1000 (from 192 fewer to 23 more)	VERY LOW	CRITICAL
								50%[5]		78 fewer per 1000 (from 164 fewer to 24 more)		
Overall Survival - 5FU+FA vs Chemoradiotherapy												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3,6]	none	52/75 (69.3%)	63/73 (86.3%)	HR 0.7 (0.49 to 1.01)	112 fewer per 1000 (from 241 fewer to 3 more)	VERY LOW	CRITICAL
								50%[5]		116 fewer per 1000 (from 212 fewer to 3 more)		
Overall Survival - Gemcitabine vs Chemoradiotherapy												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3,6]	none	26/45 (57.8%)	25/45 (55.6%)	HR 1.02 (0.61 to 1.72)[4]	7 more per 1000 (from	VERY LOW	CRITICAL

										165 fewer to 197 more)		
								50%[5]		7 more per 1000 (from 155 fewer to 196 more)		
Disease-free survival - Gemcitabine vs Chemoradiotherapy												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3,6]	none	37/45 (82.2%)	34/45 (75.6%)	HR 0.97 (0.62 to 1.52)[4]	11 fewer per 1000 (from 173 fewer to 127 more)	VERY LOW	CRITICAL
								50%[5]		11 fewer per 1000 (from 151 fewer to 151 more)		
# patients with any Grade 3 or 4 haematological toxicities - 5FU+FA vs Chemoradiotherapy (assessed with: UICC Common Toxicity Criteria)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[7]	none	2/75 (2.7%)	0/73 (0%)	RR 4.87 (0.24 to 99.7)	-	VERY LOW	CRITICAL
# patients with any Grade 3 or 4 non-haematological toxicities - 5FU+FA vs Chemoradiotherapy (assessed with: UICC Common Toxicity Criteria)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[8]	none	9/75 (12%)	2/73 (2.7%)	RR 4.38 (0.98 to 19.59)	93 more per 1000 (from 1	VERY LOW	CRITICAL

										fewer to 509 more)		
# patients with Grade 3 or 4 Anorexia - Gemcitabine vs Chemoradiotherapy (assessed with: NCI Common Terminology Criteria for Adverse Events)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[7]	none	0/42 (0%)	2/43 (4.7%)	RR 0.2 (0.01 to 4.14)	37 fewer per 1000 (from 46 fewer to 146 more)	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Diarrhoea - Chemotherapy vs Chemoradiotherapy (assessed with: NCI Common Terminology Criteria for Adverse Events; UCCI Common Toxicity Criteria)												
2	randomised trials	very serious[1, 2]	no serious inconsistency	no serious indirectness	very serious[7]	none	2/117 (1.7%)	1/116 (0.86%)	RR 1.49 (0.25 to 8.95)	4 more per 1000 (from 6 fewer to 69 more)	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Diarrhoea - Gemcitabine vs Chemoradiotherapy (assessed with: NCI Common Terminology Criteria for Adverse Events)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[7]	none	0/42 (0%)	1/43 (2.3%)	RR 0.31 (0.01 to 8.14)	16 fewer per 1000 (from 23 fewer to 166 more)	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Diarrhoea - 5FU+FA vs Chemoradiotherapy (assessed with: UICC Common Toxicity Criteria)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[7]	none	2/75 (2.7%)	0/73 (0%)	RR 4.87 (0.24 to 99.7)	-	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Fatigue - Gemcitabine vs Chemoradiotherapy (assessed with: NCI Common Terminology Criteria for Adverse Events)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[7]	none	2/42 (4.8%)	3/43 (7%)	RR 0.68 (0.12 to 3.88)	22 fewer per 1000 (from 61	VERY LOW	CRITICAL

										fewer to 201 more)		
# patients with Grade 3 or 4 Fever - Gemcitabine vs Chemoradiotherapy (assessed with: NCI Common Terminology Criteria for Adverse Events)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[7]	none	0/42 (0%)	3/43 (7%)	RR 0.15 (0.01 to 2.75)	59 fewer per 1000 (from 69 fewer to 122 more)	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Gastritis - Gemcitabine vs Chemoradiotherapy (assessed with: NCI Common Terminology Criteria for Adverse Events)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[7]	none	0/42 (0%)	2/43 (4.7%)	RR 0.2 (0.01 to 4.14)	37 fewer per 1000 (from 46 fewer to 146 more)	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Haemoglobin - Gemcitabine vs Chemoradiotherapy (assessed with: NCI Common Terminology Criteria for Adverse Events)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[7]	none	0/42 (0%)	3/43 (7%)	RR 0.15 (0.01 to 2.75)	59 fewer per 1000 (from 69 fewer to 122 more)	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Haemorrhage - Gemcitabine vs Chemoradiotherapy (assessed with: NCI Common Terminology Criteria for Adverse Events)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[7]	none	1/42 (2.4%)	1/43 (2.3%)	RR 1.02 (0.07 to 15.84)	0 more per 1000 (from 22 fewer to 345 more)	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Nausea - Gemcitabine vs Chemoradiotherapy (assessed with: NCI Common Terminology Criteria for Adverse Events)												

1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[7]	none	0/42 (0%)	1/43 (2.3%)	RR 0.34 (0.01 to 8.14)	15 fewer per 1000 (from 23 fewer to 166 more)	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Neutrophils - Gemcitabine vs Chemoradiotherapy (assessed with: NCI Common Terminology Criteria for Adverse Events)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[7]	none	18/42 (42.9%)	14/43 (32.6%)	RR 1.32 (0.76 to 2.29)	104 more per 1000 (from 78 fewer to 420 more)	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Other Gastrointestinal toxicity - Gemcitabine vs Chemoradiotherapy (assessed with: NCI Common Terminology Criteria for Adverse Events)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[7]	none	0/42 (0%)	1/43 (2.3%)	RR 0.34 (0.01 to 8.14)	15 fewer per 1000 (from 23 fewer to 166 more)	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Platelets - Gemcitabine vs Chemoradiotherapy (assessed with: NCI Common Terminology Criteria for Adverse Events)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[7]	none	0/42 (0%)	1/43 (2.3%)	RR 0.34 (0.01 to 8.14)	15 fewer per 1000 (from 23 fewer to 166 more)	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Serum Glutamicpyruvic Transaminase - Gemcitabine vs Chemoradiotherapy (assessed with: NCI Common Terminology Criteria for Adverse Events)												

1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[7]	none	5/42 (11.9%)	5/43 (11.6%)	RR 1.02 (0.32 to 3.28)	2 more per 1000 (from 79 fewer to 265 more)	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Stomatitis - 5FU+FA vs Chemoradiotherapy (assessed with: UICC Common Toxicity Criteria)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[7]	none	4/75 (5.3%)	0/73 (0%)	RR 8.76 (0.48 to 159.93)	-	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Vomiting - Gemcitabine vs Chemoradiotherapy (assessed with: NCI Common Terminology Criteria for Adverse Events)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[7]	none	0/42 (0%)	1/43 (2.3%)	RR 0.34 (0.01 to 8.14)	15 fewer per 1000 (from 23 fewer to 166 more)	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Weight Loss - Gemcitabine vs Chemoradiotherapy (assessed with: NCI Common Terminology Criteria for Adverse Events)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[7]	none	0/42 (0%)	1/43 (2.3%)	RR 0.34 (0.01 to 8.14)	15 fewer per 1000 (from 23 fewer to 166 more)	VERY LOW	CRITICAL
# patients with Grade 3 or 4 White Blood Cell count - Gemcitabine vs Chemoradiotherapy ((assessed with: NCI Common Terminology Criteria for Adverse Events)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[7]	none	6/42 (14.3%)	7/43 (16.3%)	RR 0.88 (0.32 to 2.4)	20 fewer per 1000 (from 111 fewer to	VERY LOW	CRITICAL

										228 more)		

1 Overall high risk of bias (Neoptolemos et al. 2004). Main reasons include: unclear risk randomisation method; selective reporting (one or more outcomes of interest reported incompletely); other sources of bias (clinicians chose which ESPAC-1 trial patients were randomised to [ESPAC-1 2x2, ESPAC-1+ chemotherapy only trial, ESPAC-1+ chemoradiotherapy only trials]; Kaplan-Meier curves for separate groups not provided, unclear whether proportional hazards satisfied).
2 Overall high risk of risk (van Laethem et al. 2010). Main reasons include: unclear risk randomisation method/allocation concealment; high risk selective reporting (one or more outcomes of interest not fully reported); other sources of bias (Kaplan-Meier curve cross, proportional hazards not satisfied).
3 Not clinically important (p>0.5).
4 Hazard ratio for van Laethem et al. 2010 estimated using Kaplan-Meier curve and method 10 in Tierney et al. 2010.
5 Fifty percent 2-year overall survival and disease-free survival rate assumed for chemoradiotherapy control group.
6 The committee decided to consider all survival outcomes that were clinically important, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not clinically important.
7 Crosses 2 default MIDs (0.8 and 1.25).
8 Crosses 1 default MID (0.8 or 1.25).

I.14.43 Adjuvant chemotherapy versus adjuvant chemoimmunotherapy

Table 48: Full GRADE profile for adjuvant chemotherapy versus adjuvant chemoimmunotherapy in resected pancreatic cancer patients

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Chemotherapy**	**Chemoimmunotherapy**	**Relative (95% CI)**	**Absolute**		
Overall Survival - Gemcitabine, Carboplatin, Mitomycin C, 5FU+FA vs CT+Interleukin-2												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	22/45 (48.9%)	20/43 (46.5%)	HR 2.05 (1.12 to 3.76)[3]	258 more per 1000 (from 39 more to 440 more)	□□□□ LOW	CRITICAL
								40%[4]		249 more		

										per 1000 (from 36 more to 453 more)		
Disease-free Survival - Gemcitabine, Carboplatin, Mitomycin C, 5FU+FA vs CT+Interleukin-2												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision [2]	none	19/45 (42.2%)	21/43 (48.8%)	HR 1.99 (1.07 to 3.7)[3]	248 more per 1000 (from 23 more to 428 more)	LOW	CRITICAL
								40%[4]		238 more per 1000 (from 21 more to 449 more)		
# patients with Grade 3 or 4 Nausea - Gemcitabine, Carboplatin, mitoxantrone, mitomycin C, 5FU+FA vs CT+Interleukin-2 (assessed with: Not stated in study)												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious[5]	none	1/45 (2.2%)	0/43 (0%)	RR 2.87 (0.12 to 68.58)	-	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Vomiting - Gemcitabine, Carboplatin, mitoxantrone, mitomycin C, 5FU+FA vs CT+Interleukin-2 (assessed with: Not stated in study)												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious[5]	none	0/45 (0%)	2/43 (4.7%)	RR 0.19 (0.01 to 3.87)	38 fewer per 1000 (from 46 fewer to 133 more)	VERY LOW	CRITICAL

1 Overall high risk of bias for Lygidakis et al. 2002. Main reasons include unclear risk randomisation method/allocation method; high risk selective reporting (fails to report survival results in expected manner); other sources of bias (power calculation not reported; Kaplan-Meier curves for disease-free survival cross, proportional hazards not satisfied).
2 The committee decided to consider all survival outcomes that were clinically important, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not clinically important.
3 Forty percent 2-year overall and disease-free survival rate assumed for chemoimmunotherapy control group.
4 Hazard ratio estimated from Kaplan-Meier curve and summary statistics using method 7 in Tierney et al. (2007).
5 Crosses 2 default MIDs (0.8 and 1.25).

I.14.59 Adjuvant chemotherapy versus adjuvant chemoradioimmunotherapy

Table 49: Full GRADE profile for adjuvant chemotherapy versus adjuvant chemoradioimmunotherapy in resected pancreatic cancer patients

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemotherapy	Chemoradioimmunotherapy	Relative (95% CI)	Absolute		
Overall Survival - 5FU vs 5FU, Cisplatin + Interferon alpha-2b												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2,3]	none	0/68 (0%)[4]	0/64 (0%)[4] 40%[5]	HR 0.96 (0.63 to 1.48)	- 12 fewer per 1000 (from 125 fewer to 130 more)	VERY LOW	CRITICAL
Disease-free Survival - 5FU vs 5FU, Cisplatin + Interferon alpha-2b (Copy)												
1	randomised trials		no serious inconsistency	no serious indirectness	serious[2,3]	none	0/68 (0%)[4]	0/64 (0%)[4]	HR 1.02	-		CRITICAL

		very serious [1]						40%[5]	(0.64 to 1.65)[6]	6 more per 1000 (from 121 fewer to 170 more)	VERY LOW	
# patients with any Grade 3 or 4 toxicities - 5FU vs 5FU, Cisplatin + Inteferon alpha-2b (assessed with: Common Toxicity Criteria)												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[7]	none	9/53 (17%)	45/57 (78.9%)	RR 0.22 (0.12 to 0.4)	616 fewer per 1000 (from 474 fewer to 695 fewer)	VERY LOW	CRITICAL
EORTC QLQ-30 Quality of Life - Global Health Status (Better indicated by higher values)												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[8]	none	36	50	-	MD 7 higher (0.41 to 13.59 higher)	VERY LOW	CRITICAL
EORTC QLQ-30 Quality of Life - Nausea/Vomiting (Better indicated by higher values)												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[8]	none	36	50	-	MD 7.7 higher (1.67 to 13.73 higher)	VERY LOW	CRITICAL
EORTC QLQ-30 Quality of Life - Role functioning (Better indicated by higher values)												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[8]	none	35	50	-	MD 13.9 higher (4.16 to 23.64 higher)	VERY LOW	CRITICAL
EORTC QLQ-30 Quality of Life - Social functioning (Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[8]	none	35	50	-	MD 10 higher (0.75 to 19.25 higher)	VERY LOW	CRITICAL

1 Overall high risk of bias (Schmidt et al. 2012). Main reasons include: selective reporting (one or more outcomes of interest not fully reported); hiigh risk blinding of participants and personnel (participants not blinded, quality of life outcomes likely to be influenced by this); high risk other sources of bias (Kaplan-Meier curves for overall and disease-free survival cross, proportional hazards not satisfied).
2 The committee decided to consider all survival outcomes that were clinically important, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not clinically important.
3 Not clinically important (p>0.5).
4 The number of observed deaths in each group was not provided in the study (Schmidt et al. 2012).
5 Forty percent 2-year overall survival rate assumed for chemoradioimmunotherapy control group.
6 Hazard ratio estimated using Kaplan-Meier curve and method 10 of Tierney et al. 2007.
7 Small sample size (<300 events).
8 Crosses 1 MID (+5 or -5, from Osoba et al. 1998).

I.14.6.2 Adjuvant chemoradiotherapy followed by chemotherapy versus no adjuvant therapy

Table 50: Full GRADE profile for adjuvant chemoradiotherapy followed by chemotherapy versus no adjuvant therapy in resected pancreatic cancer patients

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemoradiotherapy ->Chemotherapy	No adjuvant therapy	Relative (95% CI)	Absolute		
# patients with any Grade 3 or 4 haematological toxicities - Chemoradiotherapy->5FU+FA vs No adjuvant therapy (assessed with: UICC Common Toxicity Criteria)												

1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/72 (6.9%)	0/69 (0%)	RR 10.55 (0.59 to 187.23)	-	VERY LOW	CRITICAL
# patients with any Grade 3 or 4 non-haematological toxicities - Chemoradiotherapy->5FU+FA vs No adjuvant therapy (assessed with: UICC Common Toxicity Criteria)												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[3]	none	11/72 (15.3%)	0/69 (0%)	RR 22.05 (1.32 to 367.2)	-	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Stomatitis - Chemoradiotherapy->5FU+FA vs No adjuvant therapy (assessed with: UICC Common Toxicity Criteria)												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/75 (5.3%)	0/69 (0%)	RR 8.29 (0.45 to 151.2)	-	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Diarrhoea - Chemoradiotherapy->5FU+FA vs No adjuvant therapy (assessed with: UICC Common Toxicity Criteria)												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/75 (2.7%)	0/69 (0%)	RR 4.61 (0.22 to 94.27)	-	VERY LOW	CRITICAL

1 Overall high risk of bias (Neoptolemos et al. 2004). Main reasons include: unclear risk randomisation method; selective reporting (one or more outcomes of interest reported incompletely); other sources of bias (clinicians chose which ESPAC-1 trial patients were randomised to [ESPAC-1 2x2, ESPAC-1+ chemotherapy only trial, ESPAC-1+ chemoradiotherapy only trials]; Kaplan-Meier overall survival curves for separate groups not provided, unclear whether proportional hazards satisfied).
2 Crosses 2 default MIDs (0.8 and 1.25).
3 Small sample size (<300 events).

I.14.7 Adjuvant chemoradiotherapy followed by chemotherapy versus adjuvant chemotherapy

Table 51: Full GRADE profile for any adjuvant chemoradiotherapy followed by chemotherapy versus any adjuvant chemotherapy in resected pancreatic cancer patients

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemoradiotherapy->Chemotherapy	Chemotherapy	Relative (95% CI)	Absolute		
Overall Survival - Chemoradiotherapy->5FU+FA vs 5FU+FA												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2,3]	none	60/72 (83.3%)	65/75 (86.7%)	HR 1.32 (0.9 to 1.92)	63 more per 1000 (from 30 fewer to 112 more)	VERY LOW	CRITICAL
								40%[4]		90 more per 1000 (from 31 fewer to 225 more)		
# patients with any Grade 3 or 4 haematological toxicities - Chemoradiotherapy->5FU+FA vs 5FU+FA (assessed with: UICC Common Toxicity Criteria)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	5/72 (6.9%)	2/75 (2.7%)	RR 2.6 (0.52 to 13)	43 more per 1000 (from 13 fewer to 320 more)	VERY LOW	CRITICAL
# patients with any Grade 3 or 4 non-haematological toxicities - Chemoradiotherapy->5FU+FA vs 5FU+FA (assessed with: UICC Common Toxicity Criteria)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	11/72 (15.3%)	9/75 (12%)	RR 1.27 (0.56 to 2.89)	32 more per 1000 (from 53 fewer to 227 more)	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Stomatitis - Chemoradiotherapy->5FU+FA vs 5FU+FA (assessed with: UICC Common Toxicity Criteria)												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	4/75 (5.3%)	0/69 (0%)	RR 8.29 (0.45 to 151.2)	-	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Diarrhoea - Chemoradiotherapy->5FU+FA vs 5FU+FA (assessed with: UICC Common Toxicity Criteria)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	2/75 (2.7%)	0/75 (0%)	RR 5 (0.24 to 102.42)	-	VERY LOW	CRITICAL

1 Overall high risk of bias (Neoptolemos et al. 2004). Main reasons include: unclear risk randomisation method; selective reporting (one or more outcomes of interest reported incompletely); other sources of bias (clinicians chose which ESPAC-1 trial patients were randomised to [ESPAC-1 2x2, ESPAC-1+ chemotherapy only trial, ESPAC-1+ chemoradiotherapy only trials]; Kaplan-Meier overall survival curves for separate groups not provided, unclear whether proportional hazards satisfied).
2 The committee decided to consider all survival outcomes that were clinically important, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not clinically important.
3 Not clinically important (p>0.5).
4 Forty percent 2-year overall survival assumed for chemotherapy control group.
5 Crosses 2 default MIDs (0.8 and 1.25).

I.14.89 Adjuvant chemoradiotherapy followed by chemotherapy versus adjuvant chemoradiotherapy

Table 52: Full GRADE profile for adjuvant chemoradiotherapy followed by chemotherapy versus adjuvant chemoradiotherapy in resected pancreatic cancer patients

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Chemoradiotherapy->Chemotherapy**	**Chemoradiotherapy**	**Relative (95% CI)**	**Absolute**		
Overall Survival - Chemoradiotherapy->5FU+FA vs Chemoradiotherapy												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	60/72 (83.3%)	65/73 (89%)	HR 0.67 (0.47 to 0.96)	118 fewer per 1000 (from 10 fewer to	LOW	CRITICAL

										244 fewer)		
								50%[3]		129 fewer per 1000 (from 14 fewer to 222 fewer)		
# patients with any Grade 3 or 4 haematological toxicities - Chemoradiotherapy->5FU+FA vs Chemoradiotherapy (assessed with: UICC Common Toxicity Criteria)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	5/72 (6.9%)	0/73 (0%)	RR 11.15 (0.63 to 198.04)	-	VERY LOW	CRITICAL
# patients with any Grade 3 or 4 non-haematological toxicities - Chemoradiotherapy->5FU+FA vs Chemoradiotherapy (assessed with: UICC Common Toxicity Criteria)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	11/72 (15.3%)	2/73 (2.7%)	RR 5.58 (1.28 to 24.28)	125 more per 1000 (from 8 more to 638 more)	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Stomatitis - Chemoradiotherapy->5FU+FA vs Chemoradiotherapy (assessed with: UICC Common Toxicity Criteria)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	4/75 (5.3%)	0/73 (0%)	RR 8.76 (0.48 to 159.93)	-	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Diarrhoea - Chemoradiotherapy->5FU+FA vs Chemoradiotherapy (assessed with: UICC Common Toxicity Criteria)												

1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious[4]	none	2/75 (2.7%)	0/69 (0%)	RR 4.61 (0.22 to 94.27)	-	VERY LOW	CRITICAL

1 Overall high risk of bias (Neoptolemos et al. 2004). Main reasons include: unclear risk randomisation method; selective reporting (one or more outcomes of interest reported incompletely); other sources of bias (clinicians chose which ESPAC-1 trial patients were randomised to [ESPAC-1 2x2, ESPAC-1+ chemotherapy only trial, ESPAC-1+ chemoradiotherapy only trials]; Kaplan-Meier overall survival curves for separate groups not provided, unclear whether proportional hazards satisfied).
2 The committee decided to consider all survival outcomes that were clinically important, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not clinically important.
3 Fifty percent 2-year overall survival assumed for chemoradiotherapy control group.
4 Crosses 2 default MIDs (0.8 and 1.25).

I.14.9 Adjuvant chemotherapy-1 (gemcitabine) followed by chemoradiotherapy versus adjuvant chemotherapy-2 (other) followed by chemoradiotherapy

Table 53: GRADE profile for adjuvant chemotherapy-1 (gemcitabine) followed by chemoradiotherapy versus adjuvant chemotherapy-2 (other) followed by chemoradiotherapy in resected pancreatic cancer patients

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Chemotherapy-1 (gemcitabine)->Chemoradiotherapy**	**Chemotherapy-2 (other)->Chemoradiotherapy**	**Relative (95% CI)**	**Absolute**		
Overall Survival - Gemcitabine->CRT->Gemcitabine vs 5-FU->CRT->5FU												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	serious[2,3]	none	180/221 (81.4%)	188/230 (81.7%)	HR 0.93 (0.76 to 1.15)	23 fewer per 1000 (from 92 fewer to 41 more)	LOW	CRITICAL
Disease-free Survival - Gemcitabine->CRT vs PEFG->CRT												

1	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	serious[2,3]	none	0/51 (0%)[5]	0/49 (0%)[5] 40%[7]	HR 1.33 (0.86 to 2.06)[6]	- 93 more per 1000 (from 44 fewer to 251 more)	VERY LOW	CRITICAL
# patients with any Grade 4 toxicity - Gemcitabine->CRT->gemcitabine vs 5FU->CRT->5FU (assessed with: Monitored by RTOG Data Monitoring Committee)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	32/221 (14.5%)	3/230 (1.3%)	RR 11.1 (3.45 to 35.73)	132 more per 1000 (from 32 more to 453 more)	MODERATE	CRITICAL
# patients with Grade 3 or 4 Diarrhoea - Gemcitabine->CRT->gemcitabine vs 5FU->CRT->5FU (assessed with: Monitored by RTOG Data Monitoring Committee)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[8]	none	33/221 (14.9%)	44/230 (19.1%)	RR 0.78 (0.52 to 1.18)	42 fewer per 1000 (from 92 fewer to 34 more)	LOW	CRITICAL
# patients with Grade 3 or 4 Neutropenia - Gemcitabine->CRT vs PEFG->CRT (measured with: NCI Common Terminology Criteria for Adverse Events; Better indicated by lower values)												

1	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	serious[8]	none	51	51	-	SMD 0.8 lower (1.21 to 0.4 lower)	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Stomatitis - Gemcitabine->CRT->gemcitabine vs 5FU->CRT->5FU (assessed with: Monitored by RTOG Data Monitoring Committee)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[8]	none	22/221 (10%)	35/230 (15.2%)	RR 0.65 (0.4 to 1.08)	53 fewer per 1000 (from 91 fewer to 12 more)	LOW	CRITICAL
# patients with Grade 3 or 4 Thrombocytopenia - Gemcitabine->CRT vs PEFG->CRT (measured with: NCI Common Terminology Criteria for Adverse Events; Better indicated by lower values)												
1	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	serious[8]	none	51	51	-	SMD 0.8 lower (1.21 to 0.4 lower)	VERY LOW	CRITICAL
# patients with Grade 3 or 4 Worst haematological AEs - Gemcitabine->CRT->gemcitabine vs 5FU->CRT->5FU (assessed with: Monitored by RTOG Data Monitoring Committee)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	129/221 (58.4%)	22/230 (9.6%)	RR 6.1 (4.04 to 9.22)	488 more per 1000 (from 291 more to	MODERATE	CRITICAL

										786 more)		
# patients with Grade 3 or 4 Worst non-haematological AEs - Gemcitabine->CRT->gemcitabine vs 5FU->CRT->5FU (assessed with: Monitored by RTOG Data Monitoring Committee)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	129/221 (58.4%)	137/230 (59.6%)	RR 0.98 (0.84 to 1.14)	12 fewer per 1000 (from 95 fewer to 83 more)	MODERATE	CRITICAL
# patients with Grade 3 or 4 Worst overall AEs - Gemcitabine->CRT->gemcitabine vs 5FU->CRT->5FU (assessed with: Monitored by RTOG Data Monitoring Committee)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[8]	none	175/221 (79.2%)	143/230 (62.2%)	RR 1.27 (1.13 to 1.44)	168 more per 1000 (from 81 more to 274 more)	LOW	CRITICAL

1 Overall unclear risk of bias (Regine et al. 2008/2011). Main reasons include: unclear risk randomisation method/allocation concealment (insufficient information).
2 The committee decided to consider all survival outcomes that were clinically important, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not clinically important.
3 Not clinically important (p>0.5).
4 Overall high risk of bias (Reni et al. 2012) due to high risk selective reporting (primary outcomes not fully reported).
5 Observed disease-free events not provided by authors (Reni et al. 2012).
6 Hazard ratio estimated from Kaplan-Meier survival curve using method 11 in Tierney et al. (2007).
7 Forty percent 2-year overall survival and disease-free survival assumed for chemotherapy then chemoradiotherapy group.
8 Crosses 1 default MID (dichotomous outcomes: 0.8 or 1.25; continuous outcomes: 0.5 or -0.5).

I.14.10 Immunotherapy versus no adjuvant therapy

Table 54: Full GRADE profile for any adjuvant immunotherapy versus no adjuvant therapy in resected pancreatic cancer patients

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immunotherapy	No adjuvant therapy	Relative (95% CI)	Absolute		
Overall Survival - IgG1 murine Monoclonal Antibody 494/32 vs Observation												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2,3]	none	19/29 (65.5%)	17/32 (53.1%)	HR 1.12 (0.21 to 6.03)[4]	41 more per 1000 (from 384 fewer to 458 more)	VERY LOW	CRITICAL
								30%[5]		29 more per 1000 (from 228 fewer to 584 more)		
# patients with Grade 3 or 4 Abdominal Pain - IgG1 murine Monoclonal Antibody 494/32 vs No adjuvant therapy												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[6]	none	1/29 (3.4%)	0/32 (0%)	RR 3.3 (0.14 to 77.95)	-	VERY LOW	CRITICAL

1 Overall high risk of bias (Büchler 1991). Main reasons include: unclear randomisation method/allocation concealment (insufficient information); selective reporting (primary outcome not fully reported); other sources of bias (Kaplan-Meier curve crosses, proportional hazards not satisfied).
2 The committee decided to consider all survival outcomes that were clinically important, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not clinically important.
3 Not clinically important (p>0.5).
4 Hazard ratio estimated from Kaplan-Meier curve using method 10 in Tierney et al. (2007).
5 Thirty percent 2-year overall survival rate and 20% 2-year disease-free survival rate assumed for no adjuvant therapy control group.
6 Crosses 2 default MIDs (0.8 and 1.25).

I.14.11 Chemoimmunotherapy versus no adjuvant therapy

Table 55: Full GRADE profile for any adjuvant chemoimmunotherapy versus no adjuvant therapy in resected pancreatic cancer patients

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemoimmunotherapy	No adjuvant therapy	Relative (95% CI)	Absolute		
Overall Survival - Gemcitabine, Carboplatin, Mitomycin C, 5FU+FA+Interleukin-2 vs No adjuvant therapy												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	20/43 (46.5%)	15/40 (37.5%)	HR 0.45 (0.23 to 0.88)[3]	184 fewer per 1000 (from 36 fewer to 273 fewer)	LOW	CRITICAL
								30%[4]		152 fewer per 1000 (from 31 fewer to 221 fewer)		
Disease-free Survival - Gemcitabine, Carboplatin, Mitomycin C, 5FU+FA+Interleukin-2 vs No adjuvant therapy												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	21/43 (48.8%)	15/40 (37.5%)	HR 0.33 (0.17 to 0.64)[3]	231 fewer per 1000 (from 115 fewer to	LOW	CRITICAL

										298 fewer)		
								20%[4]		129 fewer per 1000 (from 67 fewer to 163 fewer)		
# patients with Grade 3 or 4 Vomiting - Gemcitabine, Carboplatin, mitoxantrone, mitomycin C, 5FU+FA+Interleukin-2 vs No adjuvant therapy (assessed with: Not stated in study)												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious[5]	none	2/43 (4.7%)	0/40 (0%)	RR 4.66 (0.23 to 94.18)	-	VERY LOW	CRITICAL

1 Overall high risk of bias for Lygidakis et al. 2002. Main reasons include unclear risk randomisation method/allocation method; high risk selective reporting (fails to report survival results in expected manner); other sources of bias (power calculation not reported).

2 The committee decided to consider all survival outcomes that were clinically important, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not clinically important.

3 Hazard ratio estimated from Kaplan-Meier curve and summary statistics using method 7 in Tierney et al. (2007).

4 Thirty percent 2-year overall survival rate and 20% 2-year disease-free survival rate assumed for no adjuvant therapy control group.

5 Crosses 2 default MIDs (0.8 and 1.25).

I.15 Follow-up for people with resected pancreatic cancer

I.15.1 CT/MRI versus PET (time-varying exposure model)

Table 56: Full GRADE profile for follow-up imaging with CT/MRI versus PET for people with resected pancreatic adenocarcinoma

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PET	CT/MRI on Mortality (time-varying exposure model)	Relative (95% CI)	Absolute		
Mortality in Surgical Group (assessed with: Time-varying exposure model)												
1	observational studies	serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision2	none	-	-	HR 0.66 (0.52 to 0.83)	-	VERY LOW	CRITICAL
Mortality in Borderline Group (assessed with: Time-varying exposure model)												
1	observational studies	serious [1]	no serious inconsistency	serious[3]	very serious[2]	none	-	-	HR 0.95 (0.81 to 1.13)	-	VERY LOW	CRITICAL

[1] Unclear if confounders between cohorts were accounted for in the analyses. 31% drop out in the analyses.

[2] The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant

[3] Unclear if participants in the borderline population underwent surgical resection

I.15.21 No follow-up imaging versus PET (time-varying exposure model)

2 **Table 57: Full GRADE profile for no follow up imaging versus PET for people with resected pancreatic adenocarcinoma**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PET	No follow-up on mortality (time-varying exposure model)	Relative (95% CI)	Absolute		
Mortality in Surgical Group (assessed with: Time-varying exposure model)												
1	observational studies	serious	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.17 (0.1 to 0.28)	-	VERY LOW	CRITICAL
Mortality in Borderline Group (assessed with: Time-varying exposure model)												
1	observational studies	serious [1]	no serious inconsistency	serious[2]	serious[3]	none	-	-	HR 1.02 (0.84 to 1.24)	-	VERY LOW	CRITICAL

3 *[1] Unclear if population confounders between cohorts were accounted for in the analyses. High drop-out rate 31% in the analyses*
4 *[2] Unclear if participants in the borderline population underwent resection*
5 *[3] The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs.*
6 *Survival*
7 *outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant*

I.15.31 CT/MRI versus PET (early-exposure model)

Table 58: Full GRADE profile for follow-up imaging with CT/MRI versus PET (early-exposure model) for people with resected pancreatic adenocarcinoma

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PET	CT/MRI on Survival Beyond 180 days	Relative (95% CI)	Absolute		
Mortality in Surgical Group (follow-up 180 days)												
1	observational studies	serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.8 (0.57 to 1.14)	-	VERY LOW	
Mortality in Borderline Group (follow-up 180 days)												
1	observational studies	serious [1]	no serious inconsistency	serious[3]	serious[2]	none	-	-	HR 1.04 (0.82 to 1.33)	-	VERY LOW	CRITICAL

[1] Unclear if population confounders were accounted for in the analyses. High drop out rate 57%

[2] The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant.

[3] Unclear if participants in the borderline population underwent resection

I.15.4 No follow-up imaging versus PET on survival beyond 180 days (early-exposure model)

Table 59: Full GRADE profile for no follow-up imaging versus PET (early-exposure model) for people with resected pancreatic adenocarcinoma

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PET	No follow-up on Survival Beyond 180 days	Relative (95% CI)	Absolute	Quality	Importance
Surgical Group (follow-up 180 days)												
1	observational studies	serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.56 (0.37 to 0.85)	-	VERY LOW	CRITICAL
Borderline group (follow-up 180 days)												
1	observational studies	serious [1]	no serious inconsistency	serious[2]	serious[3]	none	-	-	HR 0.9 (0.69 to 1.19)	-	VERY LOW	CRITICAL

[1] Unclear if confounders in the population were accounted for in the analyses. High drop out rate 57%.
[2] The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant
[3] Unclear if participants in the borderline population underwent resection

I.15.5 CT versus clinical symptoms and CA 19-9 on proportion of asymptomatic recurrence

GRADE quality assessment was not conducted as estimations around inconsistency, indirectness, and imprecisions were not calculable due to the paucity of data in the study abstract

I.16 Management of locally advanced pancreatic cancer

I.16.1 Different chemoradiotherapy regimens

Table 60: Full GRADE profile for gemcitabine-based chemoradiotherapy versus paclitaxel-based chemoradiotherapy in adults with unresectable non-metastatic locally advanced pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GEM-CRT	Paclitaxel-CRT	Relative (95% CI)	Absolute		
Overall response rates (CR+PR) - 1 month follow-up												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/22 (13.6%)	6/24 (25%)	RR 0.55 (0.15 to 1.92)	112 fewer per 1000 (from 213 fewer to 230 more)	VERY LOW	CRITICIAL
Overall response rates (CR+PR) - 1 year follow-up												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/22 (18.2%)	4/24 (16.7%)	RR 1.09 (0.31 to 3.84)	15 more per 1000 (from 115 fewer to 473 more)	VERY LOW	CRITICIAL
Overall survival[4]												
1[1]	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	serious[6]	none	22	24	HR 0.98 (0.52 to 1.85)[4]		VERY LOW	CRITICIAL
Adverse effects - Grade 3/4 toxicities - Haematological												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/22 (22.7%)	5/24 (20.8%)	RR 1.09 (0.36 to 3.27)	19 more per 1000 (from 133 fewer to 473 more)	VERY LOW	CRITICIAL

Adverse effects - Grade 3/4 toxicities - Non-haematological											
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/22 (81.8%)	10/24 (41.7%)	RR 1.96 (1.18 to 3.28)	400 more per 1000 (from 75 more to 950 more)	LOW	CRITICIAL

[1] *Chung et al. 2004*
[2] *The quality of the evidence was downgraded because of the unclear risk of selection bias (no details given about the allocation method), the unclear risk of performance and detection bias (no details given in the text). Furthermore no research protocol was published for this trial*
[3] *Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs*
[4] *The median survival was 12 months in the gemcitabine group vs. 14 months in the paclitaxel group. There was no statistically significant difference in survival between the 2 groups (p= 0.951, log–rank test). Relative effect was calculated by the NGA staff by means of the Tieney 2007 methods.*
[5] *The quality of the evidence was downgraded of one because the unclear risk of selection bias (no details given about the randomisation and allocation methods). Furthermore no research protocol was published for this trial and no sample size calculations were provided.*
[6] *The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant*

Table 61: Full GRADE profile for gemcitabine-based chemoradiotherapy versus 5FU-based chemoradiotherapy in adults with unresectable non-metastatic locally advanced pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**GEM-CRT**	**5FU-CRT**	**Relative (95% CI)**	**Absolute**		
Overall pain control - follow-up not reported												
1[1]	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	serious[3]	none	7/18 (38.9%)	1/16 (6.3%)	RR 6.22 (0.86 to 45.25)	326 more per 1000 (from 9 fewer to 1000 more)	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Neutropenia												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	6/18 (33.3%)	3/16 (18.8%)	RR 1.78 (0.53 to 5.97)	146 more per 1000 (from 88 fewer to 932 more)	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Thrombocytopenia												

1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	0/18 (0%)	1/16 (6.3%)	RR 0.3 (0.01 to 6.84)	44 fewer per 1000 (from 62 fewer to 365 more)	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Anaemia												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	4/18 (22.2%)	3/16 (18.8%)	RR 1.19 (0.31 to 4.51)	36 more per 1000 (from 129 fewer to 658 more)	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Anorexia												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	6/18 (33.3%)	5/16 (31.3%)	RR 1.07 (0.4 to 2.83)	22 more per 1000 (from 188 fewer to 572 more)	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Nausea												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	6/18 (33.3%)	5/16 (31.3%)	RR 1.07 (0.4 to 2.83)	22 more per 1000 (from 188 fewer to 572 more)	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Vomiting												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	3/18 (16.7%)	3/16 (18.8%)	RR 0.89 (0.21 to 3.8)	21 fewer per 1000 (from 148 fewer to 525 more)	LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - GI bleeding												
1[1]	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	1/18 (5.6%)	1/16 (6.3%)	RR 0.89 (0.06 to 13.08)	7 fewer per 1000 (from 59 fewer to 755 more)	VERY LOW	CRITICAL
HQRL: Average monthly Karnofsky performance score - follow-up not reported (Better indicated by lower values)												

1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	18	16	-	MD 9 higher (6.98 to 11.02 higher)	LOW	CRITICAL

[1] *Li et al. 2003*
[2] *The quality of the evidence was downgraded because of the unclear risk of selection bias (no details given about the allocation method), the unclear risk of performance and detection bias (no details given in the text). Furthermore no research protocol was published for this trial*
[3] *Evidence was further downgraded by 1 due to serious imprecision as 95%CI crossed one default MID*
[4] *Evidence was further downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs*

Table 62: Full GRADE profile for gemcitabine/Cisplatin-based chemoradiotherapy versus 5FU-based chemoradiotherapy in adults with unresectable non-metastatic locally advanced pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**GEM/Cisplatin-CRT**	**5FU-CRT**	**Relative (95% CI)**	**Absolute**		
Adverse effects - Grade 3/4 toxicities - Leukocytopenia												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	16/31 (51.6%)	1/29 (3.4%)	RR 14.97 (2.12 to 105.82)	482 more per 1000 (from 39 more to 1000 more)	LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Thrombocytopenia												
1[1]	randomised trials	very serious	no serious inconsistency	no serious indirectness	no serious imprecision	none	16/31 (51.6%)	1/29 (3.4%)	RR 14.97 (2.12 to 105.82)	482 more per 1000 (from 39 more to 1000 more)	LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Anaemia												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/31 (6.5%)	0/29 (0%)	RR 4.69 (0.23 to 93.7)	-	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Lower GI tract												

1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/31 (9.7%)	1/29 (3.4%)	RR 2.81 (0.31 to 25.48)	62 more per 1000 (from 24 fewer to 844 more)	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Upper GI tract												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	6/31 (19.4%)	0/29 (0%)	RR 12.19 (0.72 to 207.14)	-	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Non-haematological[4]												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	11/31 (35.5%)	8/29 (27.6%)	RR 1.29 (0.6 to 2.74)	80 more per 1000 (from 110 fewer to 480 more)	VERY LOW	CRITICAL

[1] Wilkowski et al. 2009
[2] The quality of the evidence was downgraded because of the unclear risk of selection bias (no details given about the allocation method) , the unclear risk of performance and detection bias (no details given in the text). Furthermore no research protocol was published for this trial and no sample size calculations were provided.
[3] Evidence was further downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs
[4] 1- Fatigue; 2-Weight loss; 3- Diarrhoea; 4- Nausea; 5-Febrile neutropenia; 6-Infection without neutropenia.

I.16.2 Different chemoradiotherapy regimens after induction chemotherapy

Table 63: Full GRADE profile for gemcitabine-chemoradiotherapy after induction chemotherapy versus capecitabine-chemoradiotherapy after induction chemotherapy in adults with unresectable non-metastatic locally advanced pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GEM-CRT	Capecitabine-CRT	Relative (95% CI)	Absolute		
Overall response rates (CR+PR)[1]												

1[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	7/36 (19.4%)	8/35 (22.9%)	RR 0.85 (0.35 to 2.1)	34 fewer per 1000 (from 149 fewer to 251 more)	VERY LOW	CRITICAL
Progression Free Survival[5]												
1[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	38	35	HR 0.6 (0.32 to 1.12)	[5]	MODERATE	CRITICAL
Overall Survival												
1[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	38	35	HR 0.39 (0.18 to 0.85)	[4]	HIGH	CRITICAL
Adverse effects - Grade 3/4 toxicities - Haematological												
1[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[7]	none	7/38 (18.4%)	0/34 (0%)	RR 13.46 (0.8 to 227.22)	-	LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Non-haematological												
1[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[8]	none	10/38 (26.3%)	4/34 (11.8%)	RR 2.24 (0.77 to 6.48)	146 more per 1000 (from 27 fewer to 645 more)	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Other												
1[2]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[8]	none	3/38 (7.9%)	2/34 (5.9%)	RR 1.34 (0.24 to 7.56)	20 more per 1000 (from 45	VERY LOW	CRITICAL

										fewer to 386 more)		
HQRL - 23 -26 -39 - 52 weeks follow-up[9] (Better indicated by lower values)												
1[2]	randomised trials	very serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	none	26	22	-[9]	not pooled[9]	LOW	CRITICAL

[1] *GEM-CRT group: no complete responses; CAP-CRT group: 2 complete responses*
[2] *Mukherjee et al. 2013*
[3] *The quality of the evidence was downgraded of one point because the high risk of performance bias (no blinding of patients/ care providers delivering the interventions) and the high risk of detention bias (no masking of outcome assessors)*
[4] *Evidence was further downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs*
[5] *Median progression-free survival was 12·0 months (95% CI 10·2–14·6) in the Capecitabine group and 10·4 months (95% CI 8·9–12·5) in the gemcitabine group*
[6] *Quality of evidence was further downgraded due to imprecision in the effect estimates (the 95% confidence interval around best estimate of effect included the no effect line)*
[7] *Evidence was further downgraded by 1 due to serious imprecision as 95%CI crossed one default MID*
[8] *The quality of the evidence was downgraded of two points because the high risk of performance bias and the high risk of detention bias*
[9] *Differences in changes in HQRL scores between trial arms rarely reached statistical significance; however, where they did, they favoured capecitabine therapy.*

Table 64: Full GRADE profile for capecitabine-chemoradiotherapy + cetuximab versus capecitabine-chemoradiotherapy alone after induction chemotherapy in adults with unresectable non-metastatic locally advanced pancreatic cancer

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Capecitabine-CRT + cetuximab**	**Capecitabine-CRT alone**	**Relative (95% CI)**	**Absolute**		
Objective response rate												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/6 (16.7%)	2/6 (33.3%)	RR 0.5 (0.04 to 2.27)	167 fewer per 1000 (from 320 fewer to 423 more)	VERY LOW	CRITICAL
Overall survival[4]												

1[1]	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	6	6	[4]	[4]	LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Hyponatraemia[6]												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/6 (0%)	1/6 (16.7%)	RR 0.33 (0.02 to 6.86)	112 fewer per 1000 (from 163 fewer to 977 more)	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Fatigue[6]												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/6 (0%)	1/6 (16.7%)	RR 0.33 (0.02 to 6.86)	112 fewer per 1000 (from 163 fewer to 977 more)	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Abdominal pain[6]												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	0/6 (0%)	1/6 (16.7%)	RR 0.33 (0.02 to 6.86)	112 fewer per 1000 (from 163 fewer to 977 more)	LOW	CRITICAL

[1] Khan et al. 2016

[2] The quality of the evidence was downgraded because of the unclear risk of selection bias (no details given about the allocation method) , the unclear risk of performance and detection bias (no details given in the text). Furthermore sample size not achieved as the trial was closed pre-maturely -following emergent data from LAP-07

[3] Evidence was further downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs

[4] median OS was 15.8 months and 22.0 months in arms capecitabine-CRT alone and Capecitabine-CRT + cetuximab respectively (p > 0.05)

[5] The quality of the evidence was downgraded because of the unclear risk of selection bias. Furthermore sample size not achieved as the trial was closed pre-maturely - following emergent data from LAP-07

[6] no grade 3-4 toxicity was registered

I.16.3 Chemoradiotherapy versus best supportive care

Table 65: Full GRADE profile for chemoradiotherapy versus best supportive care in adults with unresectable non-metastatic locally advanced pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CRT	Best supportive care	Relative (95% CI)	Absolute		
Average of monthly Karnofsky scores (Better indicated by lower values)												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	16	15	-	MD 11.6 higher (6.61 to 16.59 higher)	LOW	CRITICAL

[1] *Shinchi et al. 2002*

[2] *The quality of the evidence was downgraded because of the unclear risk of selection bias (no details given about the allocation method) , the unclear risk of performance and detection bias (no details given in the text). Furthermore no research protocol was published for this trial and no sample size calculations were provided.*

I.16.4 Chemoradiotherapy followed by chemotherapy versus chemoradiotherapy alone

Table 66: Full GRADE profile for chemoradiotherapy followed by chemotherapy versus chemoradiotherapy alone in adults with unresectable non-metastatic locally advanced pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CRT followed by CT	CRT	Relative (95% CI)	Absolute		
Adverse effects - Grade 3/4 toxicities - Leukocytopenia												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	17/27 (63%)	1/29 (3.4%)	RR 18.26 (2.6 to 128.02)	595 more per 1000 (from 55 more to 1000 more)	LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Thrombocytopenia												

1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious	none	10/27 (37%)	1/29 (3.4%)	RR 10.74 (1.47 to 78.39)	336 more per 1000 (from 16 more to 1000 more)	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Anaemia												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/27 (3.7%)	0/29 (0%)	RR 3.21 (0.14 to 75.68)	-	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Upper GI tract												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/27 (7.4%)	0/29 (0%)	RR 5.36 (0.27 to 106.78)	-	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Lower GI tract												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/27 (0%)	1/29 (3.4%)	RR 0.36 (0.02 to 8.41)	22 fewer per 1000 (from 34 fewer to 256 more)	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Non-haematological[4]												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[5]	none	2/27 (7.4%)	8/29 (27.6%)	RR 0.27 (0.06 to 1.15)	201 fewer per 1000 (from 259 fewer to 41 more)	VERY LOW	CRITICAL

1 *[1] Wilkowski et al. 2009*
2 *[2] The quality of the evidence was downgraded because of the unclear risk of selection bias (no details given about the allocation method) , the unclear risk of performance and*
3 *detection bias (no details given in the text). Furthermore no research protocol was published for this trial and no sample size calculations were provided.*
4 *[3] Evidence was further downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs*
5 *[4] 1- Fatigue; 2-Weight loss; 3- Diarrhoea; 4- Nausea; 5-Febrile neutropenia; 6-Infection without neutropenia.*
6 *[5] Evidence was further downgraded by 1 due to serious imprecision as 95%CI crossed one default MID*

I.16.5 Chemoradiotherapy + R115777 versus chemoradiotherapy

Table 67: Full GRADE profile for chemoradiotherapy + R115777 versus chemoradiotherapy alone in adults with unresectable non-metastatic locally advanced pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CRT + R115777	CRT	Relative (95% CI)	Absolute		
Overall survival[1]												
1[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	94	91	1	1	MODERATE	CRITICAL
Adverse effects - Grade 3/4 toxicities - Allergy/immunology[4]												
1[2]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	2/94 (2.1%)	3/91 (3.3%)	RR 0.65 (0.11 to 3.77)	12 fewer per 1000 (from 29 fewer to 91 more)	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Blood/bone marrow[4]												
1[2]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[7]	none	43/94 (45.7%)	30/91 (33%)	RR 1.39 (0.96 to 2)	129 more per 1000 (from 13 fewer to 330 more)	LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Cardiovascular (general)[4]												
1[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[6]	none	7/94 (7.4%)	3/91 (3.3%)	RR 2.26 (0.6 to 8.47)	42 more per 1000 (from 13 fewer to 246 more)	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Coagulation[4]												
1[2]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	0/94 (0%)	1/91 (1.1%)	RR 0.32 (0.01 to 7.82)	7 fewer per 1000 (from 11 fewer to 75 more)	VERY LOW	CRITICAL

Adverse effects - Grade 3/4 toxicities - Constitutional symptoms[4]												
1[2]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	14/94 (14.9%)	8/91 (8.8%)	RR 1.69 (0.75 to 3.84)	61 more per 1000 (from 22 fewer to 250 more)	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Endocrine[4]												
1[2]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	0/94 (0%)	1/91 (1.1%)	RR 0.32 (0.01 to 7.82)	7 fewer per 1000 (from 11 fewer to 75 more)	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Hemorrhage												
1[2]	randomised trials[4]	serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	2/94 (2.1%)	30/91 (33%)	RR 0.06 (0.02 to 0.26)	310 fewer per 1000 (from 244 fewer to 323 fewer)	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Gastrointestinal												
1[2]	randomised trials[4]	serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	37/94 (39.4%)	32/91 (35.2%)	RR 1.12 (0.77 to 1.63)	42 more per 1000 (from 81 fewer to 222 more)	VERY LOW	CRITICAL

[1] All patients included in this analysis have died, the median survival time was 11.5 months (95% CI: 8.2–12.6) for the CXRT arm and 8.9 months (95% CI: 7.3–10.4) for the CXRT+R115777 arm (non significant difference: p value not reported)

[2] Rich et al. 2012

[3] The quality of the evidence was downgraded of one point because of the unclear risk of selection bias (no details given about the randomisation and allocation methods)

[4] No 3-4 grade toxicities were reported for the following outcomes in both intervention groups: Auditory/hearing; Cardiovascular (arrhythmia); Dermatology/skin; Ocular/visual/renal/genitourinary

[5] The quality of the evidence was downgraded of one point because of the unclear risk of selection bias (no details given about the randomisation and allocation methods), the unclear risk of performance and detection bias (no details given in the text)

[6] Evidence was further downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs

[7] Evidence was further downgraded by 1 due to serious imprecision as 95%CI crossed one default MID

I.16.6 Chemoradiotherapy + TNFerade versus chemoradiotherapy

Table 68: Full GRADE profile for chemoradiotherapy + TNFerade versus chemoradiotherapy alone in adults with unresectable non-metastatic locally advanced pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CRT + TNFerade	CRT	Relative (95% CI)	Absolute		
Adverse effects - Grade 3/4 toxicities - Gatrointestinal[1]												
1[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	34/187 (18.2%)	10/90 (11.1%)	RR 1.64 (0.85 to 3.16)	71 more per 1000 (from 17 fewer to 240 more)	LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Haematological[5]												
1[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[5]	none	60/187 (32.1%)	32/90 (35.6%)	RR 0.9 (0.64 to 1.28)	36 fewer per 1000 (from 128 fewer to 100 more)	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Non-gastrointestinal/non-haematologic[6]												
1[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[5]	none	22/187 (11.8%)	7/90 (7.8%)	RR 1.51 (0.67 to 3.41)	40 more per 1000 (from 26 fewer to 187 more)	VERY LOW	CRITICAL

[1] In descending order of frequency, the most commonly occurring GI toxicities were nausea/vomiting, abdominal pain, and anorexia in the SOC TNFerade arm versus nausea/vomiting, diarrhoea and anorexia in the SOC arm.
[2] Herman et al. 2013
[3] The quality of the evidence was downgraded of one point because of the unclear risk of selection bias (no details given about the randomisation and allocation methods) and the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions)
[4] Evidence was further downgraded by 1 due to serious imprecision as 95%CI crossed one default MID
[5] Evidence was further downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs
[6] In both arms, the majority of hematologic toxicities (85%) took place during gemcitabine-maintenance therapy following chemoradiotherapy.
[7] In descending order of frequency, the most commonly occurring non-GI/ nonhematologic toxicities were fatigue, chills/rigors/sweats, pyrexia, and dehydration in the SOC TNFerade arm versus fatigue, dehydration, dermatitis, and hypokalemia in the SOC arm.

I.16.7 Chemoradiotherapy versus chemotherapy

Table 69: Full GRADE profile for chemoradiotherapy versus chemotherapy in adults with unresectable non-metastatic locally advanced pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CRT	CT	Relative (95% CI)	Absolute		
Adverse effects - Grade 3/4 toxicities - Hemoglobin												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	6/34 (17.6%)	2/35 (5.7%)	RR 3.09 (0.67 to 14.25)	119 more per 1000 (from 19 fewer to 757 more)	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Leukocytes												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	11/34 (32.4%)	5/35 (14.3%)	RR 2.26 (0.88 to 5.83)	180 more per 1000 (from 17 fewer to 690 more)	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Neutrophils												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	13/34 (38.2%)	12/35 (34.3%)	RR 1.12 (0.6 to 2.09)	41 more per 1000 (from 137 fewer to 374 more)	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Nausea												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	Serious[4]	none	10/34 (29.4%)	3/35 (8.6%)	RR 3.43 (1.03 to 11.4)	208 more per 1000 (from 3 more to 891 more)	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Vomiting												

1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	Serious[4]	none	9/34 (26.5%)	3/35 (8.6%)	RR 3.09 (0.91 to 10.44)	179 more per 1000 (from 8 fewer to 809 more)	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Hypokalemia												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/34 (11.8%)	2/35 (5.7%)	RR 2.06 (0.4 to 10.51)	61 more per 1000 (from 34 fewer to 543 more)	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Fatigue												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	11/34 (32.4%)	2/35 (5.7%)	RR 5.66 (1.35 to 23.68)	266 more per 1000 (from 20 more to 1000 more)	LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Anorexia												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	6/34 (17.6%)	1/35 (2.9%)	RR 6.18 (0.78 to 48.64)	148 more per 1000 (from 6 fewer to 1000 more)	VERY LOW	CRITICAL
HQRL - Trial outcome index [mean difference of change from baseline] - Change at week 6 (Better indicated by lower values)												
1[1]	randomised trials	very serious[2,5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	34	37	-	MD 12.2 lower (17.98 to 6.42 lower)	LOW	CRITICAL
HQRL - Trial outcome index [mean difference of change from baseline] - Change at week 15/16 (Better indicated by lower values)												
1[1]	randomised trials	very serious[2,5]	no serious inconsistency	no serious indirectness	Serious[4]	none	34	37	-	MD 3.3 lower (9.08 lower to 2.48 higher)	VERY LOW	CRITICAL
HQRL - Trial outcome index [mean difference of change from baseline] - Change at 9 months (Better indicated by lower values)												
1[1]	randomised trials	very serious[2,5]	no serious inconsistency	no serious indirectness	Serious[4]	none	34	37	-	MD 2.7 higher (3.08 lower to 8.48 higher)	VERY LOW	CRITICAL

[1] *Loehrer et al. 2011*
[2] *The quality of the evidence was downgraded of two points point because the high risk of bias: 1)Sample size calculation required a sample size of 316 patients however recruitment was stopped early due to poor accrual rates; 2) 46% of patients in Arm A and 21% of patients in Arm B did not have CT scans performed at adequate intervals to appropriately assess duration of treatment response; and 3) Comparison of progression was compromised as precise tumour measurement was difficult in many patients due to margins being obscured by local inflammatory processes. Additionally quality of the evidence was downgraded because of the unclear risk of selection bias (no details given about the allocation method) , the unclear risk of performance and detection bias (no details given in the text).*
[3] *Evidence was further downgraded by 2 due to serious imprecision as 95%CI crossed 2 default MIDs*
[4] *Evidence was further downgraded by 1 due to serious imprecision as 95%CI crossed one default MID*
[5] *Quality of life data should be taken with caution due to high rate of attrition from baseline (high risk of attrition bias)*

Table 70: Full GRADE profile chemoradiotherapy versus chemotherapy followed by maintenance chemotherapy in adults with unresectable non-metastatic locally advanced pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CRT followed by maintenance GEM- CT	GEM-CT	Relative (95% CI)	Absolute		
Adverse effects - Grade 3/4 hematological toxicities - Induction phase												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	17/59 (28.8%)	15/60 (25%)	RR 1.15 (0.64 to 2.09)	37 more per 1000 (from 90 fewer to 272 more)	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 hematological toxicities - Maintenance phase												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	29/59 (49.2%)	12/60 (20%)	RR 2.46 (1.39 to 4.34)	292 more per 1000 (from 78 more to 668 more)	LOW	CRITICAL
Adverse effects - Grade 3/4 non-hematological toxicities - Induction phase												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	24/59 (40.7%)	10/60 (16.7%)	RR 2.44 (1.28 to 4.65)	240 more per 1000 (from 47	LOW	CRITICAL

										more to 608 more)		
Adverse effects - Grade 3/4 non-hematological toxicities - Maintenance phase												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	12/59 (20.3%)	11/60 (18.3%)	RR 1.11 (0.53 to 2.31)	20 more per 1000 (from 86 fewer to 240 more)	VERY LOW	CRITICAL

1 Chauffert et al. 2008
2 The quality of the evidence was downgraded because of the unclear risk of performance bias (no blinding of patients/ care providers delivering the interventions), the potential risk of detection bias (no details about the blinding of outcome assessors) and unclear risk of selection bias (no details given about the cocealment allocation methods). Furthermore no research protocol was published for this trial, no sample size calculations were provided. and the trial was stopped before completion of recruitment
3 Evidence was further downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs

Table 71: Full GRADE profile for chemoradiotherapy versus chemotherapy after chemotherapy induction therapy in adults with unresectable non-metastatic locally advanced pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CRT**	**CT**	**Relative (95% CI)**	**Absolute**		
Overall survival[1]												
1[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	136	133	HR 1.03 (0.79 to 1.14)	[1]	MODERATE	CRITICAL
Progression-free survival[4]												
1[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	136	133	HR 0.78 (0.61 to 1)	[4]	MODERATE	CRITICAL
Adverse effects - Grade 3/4 toxicities - Hematological[5]												

1[2]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[7]	none	12/136 (8.8%)	4/133 (3%)	RR 2.93 (0.97 to 8.87)	58 more per 1000 (from 1 fewer to 237 more)	LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Non-hematological[8]												
1[2]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	very serious[9]	none	23/136 (16.9%)	24/133 (18%)	RR 0.94 (0.56 to 1.58)	11 fewer per 1000 (from 79 fewer to 105 more)	VERY LOW	CRITICAL

[1] no difference in survival with median overall survival from the date of the first randomization of 15.2months (95%CI, 13.9-17.3months) in the CRT group vs 16.5 months (95%CI, 14.5-18.5 months) in the CT group (HR, 1.03; 95% CI, 0.79-1.34; P = 0.83)
[2] Hammel et al. 2016 -2nd randomisation
[3] Quality of evidence was further downgraded due to imprecision in the effect estimates (the 95% confidence interval around best estimate of effect included the no effect line)
[4] no difference in progression-free survival from the date of the first randomization between CT group (median, 8.4 months; 95% CI, 7.8-9.4 months) and the CRT group (median, 9.9months; 95%CI, 8.8-10.4months)
[5] Including neutrophils, platelets, hemoglobin, and febrile neutropenia
[6] The quality of the evidence was downgraded of one point because the high risk of performance bias (no blinding of patients/ care providers delivering the interventions) and the high risk of detention bias (no masking of outcome assessors)
[7] Evidence was further downgraded by 1 due to serious imprecision as 95%CI crossed one default MID
[8] Including Nausea, vomiting, diarrhoea , mucotitis, acne, rash, dyspnea, allergic reaction, fever, aspartate transaminase, bilirubin, and γ-glutamyl transpeptidase and creatinine. Nausea 3-4 grade toxicity differed : N/n= 133/6; N/n=136/0; p=0.008
[9] Evidence was further downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs

I.16.8.4 Chemoradiotherapy versus radiotherapy

Table 72: Full GRADE profile for chemoradiotherapy versus radiotherapy in adults with unresectable non-metastatic locally advanced pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CRT	Radiotherapy	Relative (95% CI)	Absolute		
Adverse effects - Grade 3/4 toxicities - Gastrointestinal												

1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/55 (0%)	1/53 (1.9%)	RR 0.32 (0.01 to 7.72)	13 fewer per 1000 (from 19 fewer to 127 more)	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Vomiting												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/55 (5.5%)	4/53 (7.5%)	RR 0.72 (0.17 to 3.08)	21 fewer per 1000 (from 63 fewer to 157 more)	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Diarrhoea												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	0/55 (0%)	0/53 (0%)	-	-	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Infection												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/55 (1.8%)	0/53 (0%)	RR 2.89 (0.12 to 69.47)	-	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Hemorrhage												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/55 (0%)	0/53 (0%)	-	-	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Skin, mucous membrane												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/55 (3.6%)	0/53 (0%)	RR 4.82 (0.24 to 98.13)	-	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Neurologic												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/55 (7.3%)	1/53 (1.9%)	RR 3.85 (0.45 to 33.38)	54 more per 1000 (from 10 fewer to 611 more)	VERY LOW	CRITICAL

Adverse effects - Grade 3/4 toxicities - Respiratory												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/55 (0%)	0/53 (0%)	-	-	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Genitourinary												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/55 (1.8%)	1/53 (1.9%)	RR 0.96 (0.06 to 15.01)	1 fewer per 1000 (from 18 fewer to 264 more)	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Hematologic												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	14/55 (25.5%)	5/53 (9.4%)	RR 2.7 (1.04 to 6.97)	160 more per 1000 (from 4 more to 563 more)	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Liver												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/55 (3.6%)	5/53 (9.4%)	RR 0.39 (0.08 to 1.9)	58 fewer per 1000 (from 87 fewer to 85 more)	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Other[4]												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/55 (3.6%)	1/53 (1.9%)	RR 1.93 (0.18 to 20.63)	18 more per 1000 (from 15 fewer to 370 more)	VERY LOW	CRITICAL

[1] Cohen et al. 2005

[2] The quality of the evidence was downgraded orf two points because of the unclear risk of selection bias (no sufficient details given about the randomisation method), the high of performance and detection bias (no blinding of patients/ care providers delivering the interventions; and no masking of outcome assessors). Furthermore no research protocol was published for this trial and no sample size calculations were provided.

[3] Evidence was further downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs

[4] Includes constipation, cardiac, fever.

I.16.9 Different chemotherapy regimens

Table 73: Full GRADE profile for gemcitabine+erlonitib-based chemotherapy versus gemcitabine-based chemotherapy in adults with unresectable non-metastatic locally advanced pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GEM+erlonitib-CT	GEM-CT	Relative (95% CI)	Absolute		
Adverse effects - Grade 3/4 toxicities - Hematological[1]												
1[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	85/219 (38.8%)	74/223 (33.2%)	RR 1.17 (0.91 to 1.5)	56 more per 1000 (from 30 fewer to 166 more)	LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Non-hematological[1]												
1[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[5]	none	87/219 (39.7%)	88/223 (39.5%)	RR 1.01 (0.8 to 1.27)	4 more per 1000 (from 79 fewer to 107 more)	VERY LOW	CRITICAL

[1] *Including neutrophils, platelets, hemoglobin, and febrile neutropenia*
[2] *Hammel et al. 2016 -1st randomisation*
[3] *The quality of the evidence was downgraded of one point because the high risk of performance bias (no blinding of patients/ care providers delivering the interventions) and the high risk of detention bias (no masking of outcome assessors)*
[4] *Evidence was further downgraded by 1 due to serious imprecision as 95%CI crossed one default MID*
[5] *Evidence was further downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs*

Table 74: Full GRADE profile for FLEC-based chemotherapy versus gemcitabine-based chemotherapy in adults with unresectable non-metastatic locally advanced pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FLEC-CT	GEM-CT	Relative (95% CI)	Absolute		

Adverse effects - Grade 3/4 toxicities[1]												
1[2]	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	34/71 (47.9%)	15/67 (22.4%)	RR 2.14 (1.29 to 3.55)	255 more per 1000 (from 65 more to 571 more)	LOW	CRITICAL

[1] Any 3-4 grade toxicity including: leukopenia, vomiting, diarrhoea , anemia, thrombocytopenia, fever, mucositis, and gastrointestinal bleeding.
[2] Cantore et al. 2005
[3] The quality of the evidence was downgraded because of the unclear risk of selection bias (no details given about the allocation method) , the unclear risk of performance and detection bias (no details given in the text). Furthermore no research protocol was published for this trial and the required sample size (103 patients per) was not achieved

I.16.105 Gemcitabine-based chemotherapy + upmostat versus Gemcitabine-based chemotherapy

Table 75: Full GRADE profile for gemcitabine-based chemotherapy + upmostat versus gemcitabine-based chemotherapy alone in adults with unresectable non-metastatic locally advanced pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**GEM-CT + upmostat**	**GEM-CT**	**Relative (95% CI)**	**Absolute**		
Adverse effects - Grade 3/4 toxicities - Patients with any grade 3/4 toxicity - GEM + 200mg upmostat												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	17/30 (56.7%)	13/30 (43.3%)	RR 1.31 (0.78 to 2.19)	134 more per 1000 (from 95 fewer to 516 more)	VERY LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities - Patients with any grade 3/4 toxicity - GEM + 400mg upmostat												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	22/33 (66.7%)	13/30 (43.3%)	RR 1.54 (0.96 to 2.47)	234 more per 1000 (from 17 fewer to 637 more)	LOW	CRITICAL

[1] Heinemann et al. 2013
[2] The quality of the evidence was downgraded because of the high risk of performance bias (no blinding of patients/ care providers delivering the interventions) and the high risk of detention bias (no masking of outcome assessors)
[3] Evidence was further downgraded by 2 due to serious imprecision as 95%CI crossed two default MIDs
[4] Evidence was further downgraded by 1 due to serious imprecision as 95%CI crossed one default MID

I.16.11 Radiotherapy + PR-350 Radiosensitizer versus Radiotherapy

Table 76: Full GRADE profile for radiotherapy + PR-350 radiosensitizer versus radiotherapy + placebo in adults with unresectable non-metastatic locally advanced pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Radiotherapy + PR-350	Radiotherapy + Placebo	Relative (95% CI)	Absolute		
Objective Response - Effective response												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	9/19 (47.4%)	5/23 (21.7%)	RR 2.18 (0.88 to 5.41)	257 more per 1000 (from 26 fewer to 959 more)	VERY LOW	CRITICAL
Overall survival[4]												
1[1]	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	22	25	[4]	[4]	LOW	CRITICAL
Adverse effects - Grade 3/4 toxicities[6]												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[7]	none	0/22 (0%)	1/25 (4%)	RR 0.38 (0.02 to 8.8)	25 fewer per 1000 (from 39 fewer to 312 more)	VERY LOW	CRITICAL

[1] Sunamura et al. 2004
[2] The quality of the evidence was downgraded of two points because the potential risk of performance bias (no details about blinding of patients/ care providers delivering the interventions), the unclear risk of detention bias (no information provided in the text) and the unclear risk of selection bias (no details given about the randomisation and allocation methods). Furthermore no research protocol was published for this trial and no sample size calculations were provided.
[3] Evidence was further downgraded by 1 due to serious imprecision as 95%CI crossed one default MID
[4] The median survival period of the PR-350 group was 318.5 days and that of control group was 303.0 days (no difference between the 2 groups, p value not reported)
[5] The quality of the evidence was downgraded of one because the unclear risk of selection bias (no details given about the randomisation and allocation methods). Furthermore

no research protocol was published for this trial and no sample size calculations were provided.
[6] All patients, except 1 from the control group, were determined to be negative for toxicity, and the PR-350 compound was considered to be safe
[7] Evidence was further downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs

I.16.12 RFA as primary treatment versus RFA after other primary treatments

Table 77: Full GRADE profile for radiofrequency ablation as primary treatment versus radiofrequency ablation after other primary treatments in adults with unresectable non-metastatic locally advanced pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RFA as primary treatment	RFA after other primary treatments	Relative (95% CI)	Absolute		
Overall Survival[1]												
1[2]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	-[1]	-[1]	LOW	CRITICAL

[1] Median overall survival was shorter in the primary RFA group than in control group -RFA following any other primary treatment (14·7 versus 25·6 months; P = 0·004)
[2] Cantore et al. 2012

I.17 Management of metastatic pancreatic cancer

I.17.1 Chemotherapy versus chemoimmunotherapy

Table 78: Full GRADE profile for first-line chemotherapy with sequential or concurrent immunotherapy versus chemotherapy in adults with locally advanced or metastatic pancreatic cancer

Quality assessment	No of patients	Effect	Quality	

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	1st-line chemotherapy + sequential/concurrent immunotherapy *versus* chemotherapy alone	Control	Relative (95% CI)	Absolute		Importance
Overall response rate (CR + PR) at 8 weeks - Sequential ICT												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	25/350 (7.1%)	26/358 (7.3%)	RR 0.98 (0.58 to 1.67)	1 fewer per 1000 (from 31 fewer to 49 more)	VERY LOW	CRITICAL
Overall response rate (CR + PR) at 8 weeks - Concurrent ICT												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	29/354 (8.2%)	26/358 (7.3%)	RR 1.13 (0.68 to 1.88)	9 more per 1000 (from 23 fewer to 64 more)	VERY LOW	CRITICAL
Time to progression - Sequential ICT												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 1.5 (1.26 to 1.79)	-	MODERATE	CRITICAL
Time to progression - Concurrent ICT												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	-	-	HR 1 (0.84 to 1.19)	-	LOW	CRITICAL
Overall Survival - Sequential ICT												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	-	-	HR 1.19 (0.97 to 1.48)	-	LOW	CRITICAL

Overall Survival - Concurrent ICT												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	-	-	HR 1.05 (0.85 to 1.29)	-	LOW	CRITICAL
Grade 3/4/5 toxicities: Nausea - Sequential ICT												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	15/350 (4.3%)	13/358 (3.6%)	RR 1.18 (0.57 to 2.44)	7 more per 1000 (from 16 fewer to 52 more)	VERY LOW	CRITICAL
Grade 3/4/5 toxicities: Nausea - Concurrent ICT												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	20/354 (5.6%)	13/358 (3.6%)	RR 1.56 (0.79 to 3.08)	20 more per 1000 (from 8 fewer to 76 more)	VERY LOW	CRITICAL
Grade 3/4/5 toxicities: Vomiting - Sequential ICT												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	18/350 (5.1%)	17/358 (4.7%)	RR 1.08 (0.57 to 2.07)	4 more per 1000 (from 20 fewer to 51 more)	VERY LOW	CRITICAL
Grade 3/4/5 toxicities: Vomiting - Concurrent ICT												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	22/354 (6.2%)	17/358 (4.7%)	RR 1.31 (0.71 to 2.42)	15 more per 1000 (from 14 fewer to 67 more)	VERY LOW	CRITICAL
Grade 3/4/5 toxicities: Diarrhoea - Sequential ICT												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	11/350 (3.1%)	17/358 (4.7%)	RR 0.66 (0.31 to 1.39)	16 fewer per 1000 (from 33	LOW	CRITICAL

										fewer to 19 more)		
Grade 3/4/5 toxicities: Diarrhoea - Concurrent ICT												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	11/354 (3.1%)	17/358 (4.7%)	RR 0.65 (0.31 to 1.38)	17 fewer per 1000 (from 33 fewer to 18 more)	VERY LOW	CRITICAL
Grade 3/4/5 toxicities: Fatigue - Sequential ICT												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	36/350 (10.3%)	27/358 (7.5%)	RR 1.36 (0.85 to 2.2)	27 more per 1000 (from 11 fewer to 91 more)	VERY LOW	CRITICAL
Grade 3/4/5 toxicities: Fatigue - Concurrent ICT												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	44/354 (12.4%)	27/358 (7.5%)	RR 1.65 (1.04 to 2.6)	49 more per 1000 (from 3 more to 121 more)	VERY LOW	CRITICAL
Grade 3/4/5 toxicities: Neutropenia - Sequential ICT												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	58/350 (16.6%)	68/358 (19%)	RR 0.87 (0.63 to 1.2)	25 fewer per 1000 (from 70 fewer to 38 more)	LOW	CRITICAL
Grade 3/4/5 toxicities: Neutropenia - Concurrent ICT												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	79/354 (22.3%)	68/358 (19%)	RR 1.17 (0.88 to 1.57)	32 more per 1000 (from 23 fewer to	LOW	CRITICAL

										108 more)		
Grade 3/4/5 toxicities: Pain - Sequential ICT												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	39/350 (11.1%)	34/358 (9.5%)	RR 1.17 (0.76 to 1.81)	16 more per 1000 (from 23 fewer to 77 more)	LOW	CRITICAL
Grade 3/4/5 toxicities: Pain - Concurrent ICT												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	42/354 (11.9%)	34/358 (9.5%)	RR 1.25 (0.81 to 1.92)	24 more per 1000 (from 18 fewer to 87 more)	LOW	CRITICAL
Health Related Quality of Life at 20 weeks (EORTC QLQ-C30) - Sequential ICT (Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	358	350	-	MD 11.1 lower (24.28 lower to 2.08 higher)	LOW	CRITICAL
Health Related Quality of Life at 20 weeks (EORTC QLQ-C30) - Concurrent ICT (Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	354	350	-	MD 1.7 higher (10.46 lower to 13.86 higher)	LOW	CRITICAL

[1] *Middleton et al., 2014*
[2] *The quality of the evidence was downgraded because of the high risk of performance bias (no blinding of patients/ care providers delivering the interventions)*
[3] *Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs*
[4] *The quality of the evidence was further downgraded from moderate to low due to serious imprecision as 95%CI crossed one default MID*

Table 79: Full GRADE profile for second-line chemoimmunotherapy versus chemotherapy in adults with locally advanced or metastatic pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	2nd-line chemotherapy + concurrent immunotherapy *versus* chemotherapy alone	Control	Relative (95% CI)	Absolute		
Overall response rate (CR + PR) -unclear follow-up												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/28 (7.1%)	2/30 (6.7%)	RR 1.07 (0.16 to 7.1)	5 more per 1000 (from 56 fewer to 407 more)	VERY LOW	CRITICAL
Progression Free Survival												
1[1]	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	-[5]	-	LOW	CRITICAL
Overall Survival												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	-[5]	-	LOW	CRITICAL
Grade 3/4 toxicities - Neutropenia												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/28 (3.6%)	1/30 (3.3%)	RR 1.07 (0.07 to 16.32)	2 more per 1000 (from 31 fewer to 511 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities - Nausea/vomiting												

1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/28 (0%)	1/30 (3.3%)	RR 0.36 (0.02 to 8.4)	21 fewer per 1000 (from 33 fewer to 247 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities - Diarrhoea												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/28 (7.1%)	2/30 (6.7%)	RR 1.07 (0.16 to 7.1)	5 more per 1000 (from 56 fewer to 407 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities - Fatigue												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/28 (0%)	1/30 (3.3%)	RR 0.36 (0.02 to 8.4)	21 fewer per 1000 (from 33 fewer to 247 more)	VERY LOW	CRITICAL

[1] Wang et al., 2013
[2] The quality of the evidence was downgraded of two points because of the unclear risk of selection bias, the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions) and the unclear risk of detention bias (no masking of outcome assessors)
[3] The quality of the evidence was further downgraded from low to very low due to serious imprecision as 95%CI crossed two default MIDs
[4] The quality of the evidence was downgraded because of the unclear risk of selection bias and the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions). Furthermore, for this outcome the findings were reported only narratively (potential bias due to selective reporting)
[5] The median time to progression was 2.5 (95 % CI 2.3–2.8) and 2.9 (95 % CI 2.6–3.2) months (p = 0.037) for CT group and ICT group, respectively. The median overall survival was 6.1 (95 % CI 5.7–6.5) and 6.6 (95 % CI 6.1–7.1) months (p = 0.09) for CT group and ICT group, respectively.

I.17.2 Gemcitabine versus other chemotherapy

I.17.2.1 In adults with metastatic pancreatic cancer

Table 80: Full GRADE profile for gemcitabine versus other chemotherapy (Response rate, overall survival, progression-free survival) in adults with metastatic pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GEM alone	Exp. Chemotherapy (pure metastatic pop.)	Relative (95% CI)	Absolute		
Overall response rate (CR + PR) - FOLFIRINOX												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	54/171 (31.6%)	16/171 (9.4%)	RR 3.38 (2.01 to 5.65)	223 more per 1000 (from 95 more to 435 more)	HIGH	CRITICAL
Overall response rate (CR + PR) - GEM + Cisplatin												
2[2,3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[5]	none	27/220 (12.3%)	22/225 (9.8%)	RR 1.25 (0.73 to 2.12)	24 more per 1000 (from 26 fewer to 110 more)	VERY LOW	CRITICAL
Overall response rate (CR + PR) - GEM + Ganitumab 12 mg/kg												
1[6]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	none	49/305 (16.1%)	32/314 (10.2%)	RR 1.58 (1.04 to 2.39)	59 more per 1000 (from 4 more to 142 more)	MODERATE	CRITICAL
Overall response rate (CR + PR) - GEM + Ganitumab 20 mg/kg												
1[6]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	none	22/150 (14.7%)	32/314 (10.2%)	RR 1.44 (0.87 to 2.39)	45 more per 1000 (from 13 fewer to	MODERATE	CRITICAL

										142 more)		
Progression Free Survival - FOLFIRINOX												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.47 (0.32 to 0.69)	-	HIGH	CRITICAL
Progression Free Survival - GEM + Aflibercept												
1[8]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[9]	none	-	-	HR 1.02 (0.83 to 1.25)	-	MODERATE	CRITICAL
Progression Free Survival - GEM + Cisplatin												
1[3]	randomised trials	serious[10]	no serious inconsistency	no serious indirectness	serious[9]	none	-	-	HR 0.97 (0.8 to 1.18)	-	LOW	CRITICAL
Progression Free Survival - GEM + Ganitumab - 12 mg/kg												
1[6]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[9]	none	-	-	HR 1 (0.84 to 1.19)	-	MODERATE	CRITICAL
Progression Free Survival - GEM + Ganitumab - 20 mg/kg												
1[6]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[9]	none	-	-	HR 0.97 (0.77 to 1.22)	-	MODERATE	CRITICAL
Overall Survival - GEM + Aflibercept												
1[8]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[9]	none	-	-	HR 1.17 (0.92 to 1.49)	-	MODERATE	CRITICAL

Overall Survival - GEM + Cisplatin												
2[2,3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[9]	none	-	-	HR 0.92 (0.76 to 1.11)	-	LOW	CRITICAL
Overall Survival - GEM + Ganitumab - 12 mg/kg												
1[6]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[9]	none	-	-	HR 1 (0.82 to 1.22)	-	MODERATE	CRITICAL
Overall Survival - GEM + Ganitumab - 20 mg/kg												
1[6]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[9]	none	-	-	HR 0.97 (0.76 to 1.24)	-	MODERATE	CRITICAL

[1] Conroy et al., 2011
[2] Chao et al., 2013
[3] Colucci et al., 2010
[4] The quality of the evidence was downgraded because of the unclear risk of selection bias (no details provided in the text) in one study (Chao et al., 2013), besides the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions), and detection bias in both pooled studies
[5] Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs
[6] Fuchs et al., 2015
[7] Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID
[8] Rougier et al., 2013
[9] The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant.
[10] The quality of the evidence was downgraded because of the unclear risk of performance bias (no blinding of patients/ care providers delivering the interventions) and the potential risk of detection bias (no details about the blinding of outcome assessors)

Table 81: Full GRADE profile for gemcitabine versus other chemotherapy (Adverse events) in adults with metastatic pancreatic cancer

Quality assessment									No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GEM alone	Exp. Chemotherapy (pure metastatic pop.)	Relative (95% CI)	Absolute		
Grade 3/4 toxicities: Diarrhea - FOLFIRINOX												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	21/165 (12.7%)	3/169 (1.8%)	RR 7.17 (2.18 to 23.58)	110 more per 1000 (from 21 more to 401 more)	HIGH	CRITICAL
Grade 3/4 toxicities: Diarrhea - GEM + Aflibercept												
1[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	3/270 (1.1%)	3/271 (1.1%)	RR 1 (0.2 to 4.93)	0 fewer per 1000 (from 9 fewer to 44 more)	LOW	CRITICAL
Grade 3/4 toxicities: Diarrhea - GEM + Cisplatin												
2[4,5]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/207 (0.48%)	3/214 (1.4%)	RR 0.34 (0.04 to 3.23)	9 fewer per 1000 (from 13 fewer to 31 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities: Diarrhea - GEM + Ganitumab 12 mg/kg												
1[7]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	3/315 (0.95%)	1/317 (0.32%)	RR 3.02 (0.32 to 28.87)	6 more per 1000 (from 2 fewer to 88 more)	LOW	CRITICAL
Grade 3/4 toxicities: Diarrhea - GEM + Ganitumab 20 mg/kg												

1[7]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	2/160 (1.3%)	1/317 (0.32%)	RR 3.96 (0.36 to 43.37)	9 more per 1000 (from 2 fewer to 134 more)	LOW	CRITICAL
Grade 3/4 toxicities: Fatigue - FOLFIRINOX												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[8]	none	39/165 (23.6%)	30/169 (17.8%)	RR 1.33 (0.87 to 2.04)	59 more per 1000 (from 23 fewer to 185 more)	MODERATE	CRITICAL
Grade 3/4 toxicities: Fatigue - GEM + Cisplatin												
1[5]	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	very serious[3]	none	10/186 (5.4%)	6/189 (3.2%)	RR 1.69 (0.63 to 4.57)	22 more per 1000 (from 12 fewer to 113 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities: Fatigue - GEM + Ganitumab 12 mg/kg												
1[7]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	19/315 (6%)	12/317 (3.8%)	RR 1.59 (0.79 to 3.23)	22 more per 1000 (from 8 fewer to 84 more)	LOW	CRITICAL
Grade 3/4 toxicities: Fatigue - GEM + Ganitumab 20 mg/kg												
1[7]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	8/160 (5%)	12/317 (3.8%)	RR 1.32 (0.55 to 3.17)	12 more per 1000 (from 17 fewer to 82 more)	LOW	CRITICAL
Grade 3/4 toxicities: Neutropenia - FOLFIRINOX												

1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	75/164 (45.7%)	35/167 (21%)	RR 2.18 (1.56 to 3.06)	247 more per 1000 (from 117 more to 432 more)	HIGH	CRITICAL
Grade 3/4 toxicities: Neutropenia - GEM + Aflibercept												
1[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[8]	none	82/270 (30.4%)	65/271 (24%)	RR 1.27 (0.96 to 1.67)	65 more per 1000 (from 10 fewer to 161 more)	MODERATE	CRITICAL
Grade 3/4 toxicities: Neutropenia - GEM + Cisplatin												
2[4,5]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[8]	none	50/207 (24.2%)	28/214 (13.1%)	RR 1.84 (1.21 to 2.8)	110 more per 1000 (from 27 more to 236 more)	LOW	CRITICAL
Grade 3/4 toxicities: Neutropenia - GEM + Ganitumab 20 mg/kg												
1[7]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	74/160 (46.3%)	65/317 (20.5%)	RR 2.26 (1.72 to 2.97)	258 more per 1000 (from 148 more to 404 more)	HIGH	CRITICAL
Grade 3/4 toxicities: Neutropenia - GEM + Ganitumab 12 mg/kg												
1[7]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	31/315 (9.8%)	65/317 (20.5%)	RR 0.48 (0.32 to 0.71)	107 fewer per 1000 (from 59 fewer to	HIGH	CRITICAL

										139 fewer)		
Grade 3/4 toxicities: Nausea/Vomiting - FOLFIRINOX												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[8]	none	24/166 (14.5%)	14/169 (8.3%)	RR 1.75 (0.94 to 3.26)	62 more per 1000 (from 5 fewer to 187 more)	MODERATE	CRITICAL
Grade 3/4 toxicities: Nausea/Vomiting - GEM + Aflibercept												
1[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[8]	none	21/270 (7.8%)	10/271 (3.7%)	RR 2.11 (1.01 to 4.39)	41 more per 1000 (from 0 more to 125 more)	MODERATE	CRITICAL
Grade 3/4 toxicities: Nausea/Vomiting - GEM + Cisplatin												
2[4,5]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	very serious[3]	none	7/207 (3.4%)	4/214 (1.9%)	RR 1.83 (0.54 to 6.2)	16 more per 1000 (from 9 fewer to 97 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities: Nausea/Vomiting - GEM + Ganitumab 12 mg/kg												
1[7]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	19/315 (6%)	20/317 (6.3%)	RR 0.96 (0.52 to 1.76)	3 fewer per 1000 (from 30 fewer to 48 more)	LOW	CRITICAL
Grade 3/4 toxicities: Nausea/Vomiting - GEM + Ganitumab 20 mg/kg												
1[7]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	5/160 (3.1%)	20/317 (6.3%)	RR 0.5 (0.19 to 1.3)	32 fewer per 1000 (from 51	LOW	CRITICAL

										fewer to 19 more)		
Grade 3/4 toxicities: Thrombocytopenia - FOLFIRINOX												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[8]	none	15/165 (9.1%)	6/168 (3.6%)	RR 2.55 (1.01 to 6.4)	55 more per 1000 (from 0 more to 193 more)	MODERATE	CRITICAL
Grade 3/4 toxicities: Thrombocytopenia - GEM + Aflibercept												
1[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[8]	none	30/270 (11.1%)	17/271 (6.3%)	RR 1.77 (1 to 3.13)	48 more per 1000 (from 0 more to 134 more)	MODERATE	CRITICAL
Grade 3/4 toxicities: Thrombocytopenia - GEM + Cisplatin												
2[4,5]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	34/207 (16.4%)	11/214 (5.1%)	RR 3.2 (1.67 to 6.14)	113 more per 1000 (from 34 more to 264 more)	MODERATE	CRITICAL
Grade 3/4 toxicities: Thrombocytopenia - GEM + Ganitumab 12 mg/kg												
1[7]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	27/315 (8.6%)	21/317 (6.6%)	RR 1.29 (0.75 to 2.24)	19 more per 1000 (from 17 fewer to 82 more)	LOW	CRITICAL
Grade 3/4 toxicities: Thrombocytopenia - GEM + Ganitumab 20 mg/kg												
1[7]	randomised trials	no serious	no serious inconsistency	no serious indirectness	very serious[3]	none	12/160 (7.5%)	21/317 (6.6%)	RR 1.13 (0.57 to 2.24)	9 more per 1000 (from 28	LOW	CRITICAL

		risk of bias								fewer to 82 more)		
Grade 3/4 toxicities: Leukopoenia - GEM + Cisplatin												
2[4,5]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[8]	none	18/207 (8.7%)	10/214 (4.7%)	RR 1.89 (0.9 to 3.98)	42 more per 1000 (from 5 fewer to 139 more)	LOW	CRITICAL
Grade 3/4 toxicities: Leukopoenia - GEM + Ganitumab 12 mg/kg												
1[7]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	15/315 (4.8%)	9/317 (2.8%)	RR 1.68 (0.74 to 3.78)	19 more per 1000 (from 7 fewer to 79 more)	LOW	CRITICAL
Grade 3/4 toxicities: Leukopoenia - GEM + Ganitumab 20 mg/kg												
1[7]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	4/160 (2.5%)	9/317 (2.8%)	RR 0.88 (0.28 to 2.82)	3 fewer per 1000 (from 20 fewer to 52 more)	LOW	CRITICAL

[1] *Conroy et al., 2011*
[2] *Rougier et al., 2013*
[3] *Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs*
[4] *Chao et al., 2013*
[5] *Colucci et al., 2010*
[6] *The quality of the evidence was downgraded because of the unclear risk of selection bias (no details provided in the text) in one study (Chao et al., 2013), besides the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions), and detection bias in both pooled studies*
[7] *Fuchs et al., 2015*
[8] *Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID*
[9] *The quality of the evidence was downgraded because of the unclear risk of performance bias (no blinding of patients/ care providers delivering the interventions) and the potential risk of detection bias (no details about the blinding of outcome assessors)*

Table 82: Full GRADE profile for gemcitabine versus other chemotherapy (Health-related quality of life) in adults with metastatic pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GEM alone	Exp. Chemotherapy (pure metastatic pop.)	Relative (95% CI)	Absolute		
HRQL - Number of patients with a clinically significant (10 point) deterioration QLQ-C30 - Global health status												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	13/163 (8%)	32/157 (20.4%)	RR 0.39 (0.21 to 0.72)	124 fewer per 1000 (from 57 fewer to 161 fewer)	HIGH	CRITICAL
HRQL - Number of patients with a clinically significant (10 point) deterioration QLQ-C30 - Physical functioning												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	27/163 (16.6%)	37/157 (23.6%)	RR 0.7 (0.45 to 1.1)	71 fewer per 1000 (from 130 fewer to 24 more)	MODERATE	CRITICAL
HRQL - Number of patients with a clinically significant (10 point) deterioration QLQ-C30 - Role functioning												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	27/163 (16.6%)	43/157 (27.4%)	RR 0.6 (0.39 to 0.93)	110 fewer per 1000 (from 19 fewer to 167 fewer)	MODERATE	CRITICAL
HRQL - Number of patients with a clinically significant (10 point) deterioration QLQ-C30 - Emotional functioning												

1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	14/163 (8.6%)	14/157 (8.9%)	RR 0.96 (0.47 to 1.95)	4 fewer per 1000 (from 47 fewer to 85 more)	LOW	CRITICAL
HRQL - Number of patients with a clinically significant (10 point) deterioration QLQ-C30 - Cognitive functioning												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	11/163 (6.7%)	16/157 (10.2%)	RR 0.66 (0.32 to 1.38)	35 fewer per 1000 (from 69 fewer to 39 more)	LOW	CRITICAL
HRQL - Number of patients with a clinically significant (10 point) deterioration QLQ-C30 - Social functioning												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	23/163 (14.1%)	40/157 (25.5%)	RR 0.55 (0.35 to 0.88)	115 fewer per 1000 (from 31 fewer to 166 fewer)	HIGH	CRITICAL
HRQL - Number of patients with a clinically significant (10 point) deterioration QLQ-C30 - Fatigue												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	36/163 (22.1%)	49/157 (31.2%)	RR 0.71 (0.49 to 1.02)	91 fewer per 1000 (from 159 fewer to 6 more)	MODERATE	CRITICAL
HRQL - Number of patients with a clinically significant (10 point) deterioration QLQ-C30 - Nausea/vomiting												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	19/163 (11.7%)	30/157 (19.1%)	RR 0.61 (0.36 to 1.04)	75 fewer per 1000 (from 122 fewer to 8 more)	MODERATE	CRITICAL
HRQL - Number of patients with a clinically significant (10 point) deterioration QLQ-C30 - Pain												

1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	12/163 (7.4%)	22/157 (14%)	RR 0.53 (0.27 to 1.03)	66 fewer per 1000 (from 102 fewer to 4 more)	MODERATE	CRITICAL
HRQL - Number of patients with a clinically significant (10 point) deterioration QLQ-C30 - Dyspnea												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	32/163 (19.6%)	38/157 (24.2%)	RR 0.81 (0.54 to 1.23)	46 fewer per 1000 (from 111 fewer to 56 more)	MODERATE	CRITICAL
HRQL - Number of patients with a clinically significant (10 point) deterioration QLQ-C30 - Insomnia												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	20/163 (12.3%)	15/157 (9.6%)	RR 1.28 (0.68 to 2.42)	27 more per 1000 (from 31 fewer to 136 more)	MODERATE	CRITICAL
HRQL - Number of patients with a clinically significant (10 point) deterioration QLQ-C30 - Loss of appetite												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	24/163 (14.7%)	28/157 (17.8%)	RR 0.83 (0.5 to 1.36)	30 fewer per 1000 (from 89 fewer to 64 more)	LOW	CRITICAL
HRQL - Number of patients with a clinically significant (10 point) deterioration QLQ-C30 - Constipation												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	18/163 (11%)	21/157 (13.4%)	RR 0.83 (0.46 to 1.49)	23 fewer per 1000 (from 72 fewer to 66 more)	LOW	CRITICAL
HRQL - Number of patients with a clinically significant (10 point) deterioration QLQ-C30 - Diarrhea												

1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	37/163 (22.7%)	32/157 (20.4%)	RR 1.11 (0.73 to 1.69)	22 more per 1000 (from 55 fewer to 141 more)	LOW	CRITICAL
HRQL - Number of patients with a clinically significant (10 point) deterioration QLQ-C30 - Financial difficulties (follow-up - between baseline and the end of treatment (6 months).[3])												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	22/163 (13.5%)	8/157 (5.1%)	RR 2.65 (1.22 to 5.77)	84 more per 1000 (from 11 more to 243 more)	LOW	CRITICAL

[1] *Gourgou-Bourgade et al., 2013*
[2] *Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID*
[3] *Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs*
[4] *between baseline and the end of treatment (6 months).*

Table 83: Full GRADE profile for gemcitabine and erlotinib versus gemcitabine, erlotinib and capecatibine in adults with metastatic pancreatic cancer

Quality assessment						**No of patients**		**Effect**			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Gemcitabine + erlotinib**	**Exp. Chemotherapy (Gemcitabine + erlotinib + capecitabine) (pure metastatic)**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Overall response rate (CR + PR)												

1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	13/60 (21.7%)	11/60 (18.3%)	RR 1.18 (0.58 to 2.43)	33 more per 1000 (from 77 fewer to 262 more)	VERY LOW	CRITICAL
Progression Free Survival												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	-	-	HR 0.88 (0.58 to 1.34)	-	MODERATE	CRITICAL
Overall survival												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	-	-	HR 1.09 (0.72 to 1.65)	-	MODERATE	CRITICAL
Grade 3/4 toxicities: any[5]												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	42/58 (72.4%)	34/60 (56.7%)	RR 1.28 (0.97 to 1.68)	159 more per 1000 (from 17 fewer to 385 more)	LOW	CRITICAL

[1] Irigoyen et al., 2017
[2] The quality of the evidence was downgraded because of the unclear risk of selection bias and potential risk of performance bias (open-label trial)
[3] Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs
[4] Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID
[5] inluding asthenia, diarrhoea, neutropenia, reduced appetite, thrombocytopenia, nausea, anaemia, rash, constipation, mucositis, vomiting, pyrexia, elevated GGT, hand - foot syndrome, and peripheral oedema)

I.17.2.2 **In adults with locally advanced or metastatic pancreatic cancer**

Table 84: Full GRADE profile for gemcitabine versus other chemotherapy (Response rate) in adults with locally advanced or metastatic pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GEM alone	Exp. Chemotherapy	Relative (95% CI)	Absolute		
Overall response rate (CR + PR) - 5-FU single-agent												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	0/63 (0%)	3/63 (4.8%)	RR 0.14 (0.01 to 2.71)	41 fewer per 1000 (from 47 fewer to 81 more)	LOW	CRITICAL
Overall response rate (CR + PR) - S-1 single-agent												
1[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	52/248 (21%)	32/241 (13.3%)	RR 1.58 (1.06 to 2.36)	77 more per 1000 (from 8 more to 181 more)	MODERATE	CRITICAL
Overall response rate (CR + PR) - GEM + 5-FU												
1[5]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/160 (6.9%)	9/162 (5.6%)	RR 1.24 (0.53 to 2.91)	13 more per 1000 (from 26 fewer to 106 more)	VERY LOW	CRITICAL
Overall response rate (CR + PR) - GEM + Axitinib												

1[7]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	12/305 (3.9%)	4/308 (1.3%)	RR 3.03 (0.99 to 9.29)	26 more per 1000 (from 0 fewer to 108 more)	MODERATE	CRITICAL
Overall response rate (CR + PR) - GEM + Bevacizumab												
1[8]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	39/302 (12.9%)	30/300 (10%)	RR 1.29 (0.82 to 2.02)	29 more per 1000 (from 18 fewer to 102 more)	LOW	CRITICAL
Overall response rate (CR + PR) - GEM + Capecitabine												
2[9,10,25]	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	serious[4]	none	104/525 (19.8%)	61/525 (11.6%)	RR 1.70 (1.27 to 2.27)	81 more per 1000 (from 31 more to 148 more)	LOW	CRITICAL
Overall response rate (CR + PR) - GEM + Cetuximab												
1[12]	randomised trials	serious[13]	no serious inconsistency	no serious indirectness	very serious[2]	none	28/329 (8.5%)	23/331 (6.9%)	RR 1.22 (0.72 to 2.08)	15 more per 1000 (from 19 fewer to 75 more)	VERY LOW	CRITICAL
Overall response rate (CR + PR) - GEM + Cisplatin												
1[14]	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/98 (10.2%)	8/97 (8.2%)	RR 1.24 (0.51 to 3)	20 more per 1000 (from 40 fewer to 165 more)	VERY LOW	CRITICAL

Overall response rate (CR + PR) - PEFG												
1[15]	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	no serious imprecision	none	20/52 (38.5%)	4/47 (8.5%)	RR 4.52 (1.67 to 12.27)	300 more per 1000 (from 57 more to 959 more)	MODERATE	CRITICAL
Overall response rate (CR + PR) - GEM + Exatecan												
1	randomised trials	very serious[6]	no serious inconsistency	no serious indirectness	very serious[2]	none	12/175 (6.9%)	9/174 (5.2%)	RR 1.33 (0.57 to 3.07)	17 more per 1000 (from 22 fewer to 107 more)	VERY LOW	CRITICAL
Overall response rate (CR + PR) - GEM + Irinotecan												
2[16,17]	randomised trials	serious[11]	serious[18]	no serious indirectness	no serious imprecision	none	38/240 (15.8%)	16/250 (6.4%)	RR 2.5 (1.43 to 4.39)	96 more per 1000 (from 28 more to 217 more)	LOW	CRITICAL
Overall response rate (CR + PR) - GEM + Marimastat												
1[19]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[19]	none	11/120 (9.2%)	14/119 (11.8%)	RR 0.78 (0.37 to 1.65)	26 fewer per 1000 (from 74 fewer to 76 more)	LOW	CRITICAL
Overall response rate (CR + PR) - GEM + Oxaliplatin												
1	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	serious[4]	none	42/157 (26.8%)	27/156 (17.3%)	RR 1.55 (1.01 to 2.38)	95 more per 1000 (from 2 more to	LOW	CRITICAL

										239 more)		
Overall response rate (CR + PR) - GEM + Pemetrexed												
1[20]	randomised trials	serious[21]	no serious inconsistency	no serious indirectness	no serious imprecision	none	42/283 (14.8%)	20/282 (7.1%)	RR 2.09 (1.26 to 3.47)	77 more per 1000 (from 18 more to 175 more)	MODERATE	CRITICAL
Overall response rate (CR + PR) - GEM + Sorafenib												
1[22]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	6/48 (12.5%)	12/52 (23.1%)	RR 0.54 (0.22 to 1.33)	106 fewer per 1000 (from 180 fewer to 76 more)	LOW	CRITICAL
Overall response rate (CR + PR) - GEM + Tipifarnib												
1[23]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	20/341 (5.9%)	28/347 (8.1%)	RR 0.73 (0.42 to 1.26)	22 fewer per 1000 (from 47 fewer to 21 more)	LOW	CRITICAL
Overall response rate (CR + PR) - GEM + S-1												
2[3,24]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	82/293 (28%)	35/291 (12%)	RR 2.33 (1.62 to 3.34)	160 more per 1000 (from 75 more to 281 more)	HIGH	CRITICAL

[1] Burris et al., 1997
[2] Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs
[3] Ueno et al., 2013
[4] Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID
[5] Berlin et al., 2002
[6] The quality of the evidence was downgraded because of the unclear risk of selection bias (no details provided in the text), the potential risk of performance bias (no blinding of

patients/ care providers delivering the interventions), besides the unclear risk of detection bias
[7] Kindler et al., 2011
[8] Kindler et al., 2010
[9] Cunningham et al., 2009
[10] Herrmann et al., 2007
[11] The quality of the evidence was downgraded because of the unclear risk of performance bias (no blinding of patients/ care providers delivering the interventions) and detection bias
[12] Philip et al., 2010
[13] The quality of the evidence was downgraded because of the unclear risk of detection bias and the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions)
[14] Heinemann et al., 2006
[15] Reni et al., 2005
[16] Rocha Lima et al., 2004
[17] Stathopoulos et al., 2006
[18] Serious heterogeneity. I-squared = 39%
[19] Bramhall et al., 2002
[20] Oettle et al., 2005
[21] The quality of the evidence was downgraded because of the high risk of detection bias (no blinding of outcome assessors) and the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions)
[22] Gonçalves et al., 2012
[23] Van-Cutsem et al., 2004
[24] Sudo et al., 2014
[25] Lee et al., 2017

Table 85: Full GRADE profile for gemcitabine versus other chemotherapy (Overall survival and progression-free survival) in adults with locally advanced or metastatic pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GEM alone	Exp. Chemotherapy	Relative (95% CI)	Absolute		
Progression Free Survival - S-1 single-agent												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	-	-	HR 1.09 (0.9 to 1.32)	-	MODERATE	CRITICAL
Progression Free Survival - GEM + 5-FU												

1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.77 (0.62 to 0.96)	-	MODERATE	CRITICAL
Progression Free Survival - GEM + Axitinib												
1[5]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	-	-	HR 1.01 (0.78 to 1.3)	-	MODERATE	CRITICAL
Progression Free Survival - GEM + Capecitabine												
2[7,8]	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.80 (0.72 to 0.90)	-	MODERATE	CRITICAL
Progression Free Survival - GEM + Bevacizumab												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	-	-	HR 0.96 (0.81 to 1.15)[10]	-	MODERATE	CRITICAL
Progression Free Survival - GEM + Cetuximab												
1[11]	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	serious[6]	none	-	-	HR 1.07 (0.93 to 1.23)	-	LOW	CRITICAL
Progression Free Survival - GEM + Cisplatin												
1[12]	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.69 (0.5 to 0.95)	-	MODERATE	CRITICAL
Progression Free Survival - PEFG												
1[13]	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.51 (0.33 to 0.78)	-	MODERATE	CRITICAL

Progression Free Survival - GEM + Elpamotide[14]												
1[15]	randomised trials	serious[14]	no serious inconsistency	no serious indirectness	no serious imprecision[16,17]	none	-	-	not estimated[14]	not estimated[14]	MODERATE	CRITICAL
Progression Free Survival - GEM + Erlotinib												
1[18]	randomised trials	no serious risk of bias[14]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.77 (0.65 to 0.92)	-	HIGH	CRITICAL
Progression Free Survival - GEM + Irinotecan												
1[19]	randomised trials	serious[20]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.98 (0.77 to 1.25)	-	MODERATE	CRITICAL
Progression Free Survival - GEM + Marimastat												
1[21]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	-	-	HR 0.95 (0.73 to 1.23)	-	MODERATE	CRITICAL
Progression Free Survival - GEM + Oxaliplatin												
2[22,23]	randomised trials	serious[20]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.83 (0.72 to 0.97)	-	MODERATE	CRITICAL
Progression Free Survival - GEM + Sorafenib												
1[24]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 1.04 (0.7 to 1.55)	-	MODERATE	CRITICAL
Progression Free Survival - GEM + Tipifarnib												

1[25]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	-	-	HR 1.03 (0.87 to 1.22)	-	MODERATE	CRITICAL
Progression Free Survival - GEM + S-1												
2[1,26]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.65 (0.57 to 0.75)	-	HIGH	CRITICAL
Overall Survival - [29]												
23[30]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	9989[31]		FOLFIRINOX, PEFG, GEM/erlotinib+/-bevacizumab, GEM/capecitabine, and GEM/oxaliplatin were associated with significant improvements in overall survival[32]		HIGH	CRITICAL
Overall Survival - 5-FU single-agent												
1[27]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR1.75 (1.21-2.54)	-	HIGH	CRITICAL
Overall Survival - S-1 single-agent												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	-	-	HR 0.96 (0.71 to 1.3)	-	MODERATE	CRITICAL
Overall Survival - GEM + Bevacizumab												

1[28]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	-	-	HR 0.96 (0.81 to 1.15)	-	MODERATE	CRITICAL
Overall Survival - GEM + Elpamotide												
1[15]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	-	-	HR 0.87 (0.49 to 1.56)	-	MODERATE	CRITICAL
Overall Survival - GEM + Masitinib												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	-	-	HR 0.89 (0.7 to 1.13)	-	MODERATE	CRITICAL
Overall Survival - GEM + S-1												
2[1,26]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	-	-	HR 0.89 (0.74 to 1.08)	-	MODERATE	CRITICAL

[1] Ueno et al., 2013
[2] No explanation was provided
[3] Berlin et al., 2002
[4] The quality of the evidence was downgraded because of the unclear risk of selection bias (no details given about the allocation method), besides the unclear risk of performance bias (no details given in the text)
[5] Kindler et al., 2011
[6] The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant.
[7] Cunningham et al., 2009
[8] Herrmann et al., 2007
[9] The quality of the evidence was downgraded because of the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions) and detection bias (not masking of outcome assessors)
[10] The median PFS was 3.8 months (95% CI, 3.4 to 4.0 months) and 2.9 months (95% CI, 2.4 to 3.7 months) for the bevacizumab and placebo arms, respectively (P .075).
[11] Philip et al., 2010
[12] Heinemann et al., 2006
[13] Reni et al., 2005
[14] The quality of the evidence was downgraded because of the potential risk of selective findings reporting for this outcome.
[15] Yamaue et al., 2015

[16] *The median PFS length was 3.71 months (95% CI, 2.10 – 3.98) in the Active group and3.75 months (95% CI, 2.27 – 5.59) in the Placebo group. There were no significant differences found between the two groups (log – rank P-value, 0.332).*
[17] *From data provided by the authors about this outcome, is not possible estimate the precision in the effect size estimates.*
[18] *Moore et al., 2007*
[19] *Rocha Lima et al., 2004*
[20] *The quality of the evidence was downgraded because of the unclear risk of performance bias (no information on blinding of patients/ care providers delivering the interventions) and unclear risk of detection bias*
[21] *Bramhall et al., 2002*
[22] *Louvet et al., 2005*
[23] *Poplin et al., 2006 (2009)*
[24] *Gonçalves et al., 2012*
[25] *Van-Cutsem et al., 2004*
[26] *Sudo et al., 2014*
[27] *Burris et al., 1997*
[28] *Kindler et al., 2010*
[29] *FOLFIRINOX; Gemcitabine + 5-FU; Gemcitabine + Axitinib; Gemcitabine + Capecitabine; Gemcitabine + Capecitabine; Gemcitabine + Cetuximab; Gemcitabine + Cisplatin; Gemcitabine + Cisplatin; Gemcitabine + Erlotinib; Gemcitabine + Erlotinib; Gemcitabine + Erlotinib then Capecitabine; Gemcitabine + Exatecan; Gemcitabine + Irinotecan; Gemcitabine + Irinotecan; Gemcitabine + Marimastat; Gemcitabine + Nab-paclitaxel; Gemcitabine + Oxaliplatin; Gemcitabine + oxaliplatin; Gemcitabine + Pemetrexed; Gemcitabine + Sorafenib; Gemcitabine + Tipifarnib; Gemcitabine, 5-FU + Folinic Acid; and PEFG*
[30] *Abou-Alfa et al. 2006; Berlin et al. 2002; Bramhall et al. 2002; Colucci et al. 2010; Conroy et al. 2011; Cunningham et al. 2009; Gonçalves et al. 2012; Heinemann et al. 2006; Heinemann et al. 2012; Herrmann et al. 2007; Kindler et al. 2011; Louvet et al. 2005; Moore et al. 2007; Oettle et al. 2005; Philip et al. 2010; Poplin et al. 2006 (2009) ; Reni et al. 2005; Riess et al. 2005; Rocha Lima et al. 2004; Stathopoulos et al. 2006; Van-Cutsem et al. 2004; Van-Cutsem et al. 2009; Von-Hoff et al. 2013*
[31] *The majority of the trials compared Gemcitabine single-agent to an experimental treatment.*
[32] *Please use the following hyperlinks for details on the findings:*
** http://media.springernature.com/full/springer-static/image/art%3A10.1186%2F1471-2407-14-471/MediaObjects/12885_2013_Article_4675_Fig2_HTML.jpg: Figure 2-Network of eligible trials where center node represents the reference comparator: Gemcitabine.*
** http://media.springernature.com/full/springer-static/image/art%3A10.1186%2F1471-2407-14-471/MediaObjects/12885_2013_Article_4675_Fig3_HTML.jpg: Figure 3-Indirect comparisons for overall survival: HRs and 95% CIs for various treatment comparisons.*

Table 86: Full GRADE profile for gemcitabine versus other chemotherapy (Adverse events - Nausea/Vomiting) in adults with locally advanced or metastatic pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GEM alone	Exp. Chemotherapy	Relative (95% CI)	Absolute		
Grade 3/4 toxicities: Nausea/Vomiting - 5-FU single-agent												

1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	3/63 (4.8%)	8/63 (12.7%)	RR 0.38 (0.1 to 1.35)	79 fewer per 1000 (from 114 fewer to 44 more)	LOW	CRITICAL
Grade 3/4 toxicities: Nausea/Vomiting - S-1 single-agent												
1[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[2]	none	9/272 (3.3%)	7/273 (2.6%)	RR 1.29 (0.49 to 3.42)	7 more per 1000 (from 13 fewer to 62 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities: Nausea/Vomiting - GEM + 5-FU												
1[5]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[2]	none	15/158 (9.5%)	19/158 (12%)	RR 0.79 (0.42 to 1.5)	25 fewer per 1000 (from 70 fewer to 60 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities: Nausea/Vomiting - GEM + Axitinib												
1[6]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	25/305 (8.2%)	18/308 (5.8%)	RR 1.4 (0.78 to 2.52)	23 more per 1000 (from 13 fewer to 89 more)	LOW	CRITICAL
Grade 3/4 toxicities: Nausea/Vomiting - GEM + Capecitabine												
2[7,8,29]	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	very serious[2]	none	55/513 (10.7%)	45/504 (8.9%)	RR 1.20 (0.83 to 1.74)	18 more per 1000 (from 15 fewer to 66 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities: Nausea/Vomiting - GEM + Cetuximab												

1[10]	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	serious[11]	none	33/361 (9.1%)	19/355 (5.4%)	RR 1.71 (0.99 to 2.95)	38 more per 1000 (from 1 fewer to 104 more)	LOW	CRITICAL
Grade 3/4 toxicities: Nausea/Vomiting - GEM + Cisplatin												
1[12]	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	22/98 (22.4%)	6/97 (6.2%)	RR 3.63 (1.54 to 8.56)	163 more per 1000 (from 33 more to 468 more)	MODERATE	CRITICAL
Grade 3/4 toxicities: Nausea/Vomiting - GEM + Elpamotide												
1[15]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[11]	none	2/100 (2%)	2/53 (3.8%)	RR 0.53 (0.08 to 3.66)	18 fewer per 1000 (from 35 fewer to 100 more)	LOW	CRITICAL
Grade 3/4 toxicities: Nausea/Vomiting - GEM + Exatecan												
1[16]	randomised trials	very serious[17]	no serious inconsistency	no serious indirectness	very serious[2]	none	15/168 (8.9%)	9/157 (5.7%)	RR 1.56 (0.7 to 3.46)	32 more per 1000 (from 17 fewer to 141 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities: Nausea/Vomiting - GEM + Irinotecan												
2[18,19]	randomised trials	serious[20]	no serious inconsistency	no serious indirectness	serious[11]	none	55/233 (23.6%)	34/239 (14.2%)	RR 1.6 (1.09 to 2.33)	85 more per 1000 (from 13 more to	LOW	CRITICAL

										189 more)		
Grade 3/4 toxicities: Nausea/Vomiting - GEM + Marimastat												
1[21]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[11]	none	13/120 (10.8%)	26/119 (21.8%)	RR 0.5 (0.27 to 0.92)	109 fewer per 1000 (from 17 fewer to 159 fewer)	MODERATE	CRITICAL
Grade 3/4 toxicities: Nausea/Vomiting - GEM + Oxaliplatin												
2[22,23]	randomised trials	serious[20]	no serious inconsistency	no serious indirectness	no serious imprecision	none	72/420 (17.1%)	26/420 (6.2%)	RR 2.77 (1.81 to 4.25)	110 more per 1000 (from 50 more to 201 more)	MODERATE	CRITICAL
Grade 3/4 toxicities: Nausea/Vomiting - GEM + Pemetrexed												
1[24]	randomised trials	serious[25]	no serious inconsistency	no serious indirectness	very serious[2]	none	18/273 (6.6%)	18/273 (6.6%)	RR 1 (0.53 to 1.88)	0 fewer per 1000 (from 31 fewer to 58 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities: Nausea/Vomiting - GEM + Tipifarnib												
2[26,27]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[11]	none	62/455 (13.6%)	84/460 (18.3%)	RR 0.75 (0.55 to 1.01)	46 fewer per 1000 (from 82 fewer to 2 more)	MODERATE	CRITICAL
Grade 3/4 toxicities: Nausea/Vomiting - GEM + S-1												
2[3,28]	randomised trials	no serious	no serious inconsistency	no serious indirectness	no serious imprecision	none	30/317 (9.5%)	10/319 (3.1%)	RR 2.99 (1.49 to 5.99)	62 more per 1000 (from 15	HIGH	CRITICAL

		risk of bias								more to 156 more)		

[1] *Burris et al., 1997*
[2] *Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs*
[3] *Ueno et al., 2013*
[4] *The quality of the evidence was downgraded because of the unclear risk of selection bias (no details given about the allocation method), besides the unclear risk of performance bias (no details given in the text)*
[5] *Berlin et al., 2002*
[6] *Kindler et al., 2011*
[7] *Cunningham et al., 2009*
[8] *Herrmann et al., 2007*
[9] *The quality of the evidence was downgraded because of the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions) and detection bias (not masking of outcome assessors)*
[10] *Philip et al., 2010*
[11] *Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID*
[12] *Heinemann et al., 2006*
[14] *The quality of the evidence was downgraded because of the potential risk of performance bias (no detail on blinding of patients/ care providers delivering the interventions) and the high detection bias (not masking of outcome assessors)*
[15] *Yamaue et al., 2015*
[16] *Abou-Alfa et al., 2006*
[17] *The quality of the evidence was downgraded because of the unclear risk of selection bias (no details provided in the text), the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions), besides the unclear risk of detection bias*
[18] *Rocha Lima et al., 2004*
[19] *Stathopoulos et al., 2006*
[20] *The quality of the evidence was downgraded because of the unclear risk of performance bias (no information on blinding of patients/ care providers delivering the interventions) and unclear risk of detection bias*
[21] *Bramhall et al., 2002*
[22] *Louvet et al., 2005*
[23] *Poplin et al., 2006 (2009)*
[24] *Oettle et al., 2005*
[25] *The quality of the evidence was downgraded because of the unclear risk of performance bias (no information on blinding of patients/ care providers delivering the interventions) and high risk of detection bias*
[26] *Eckhardt et al., 2009*
[27] *Van-Cutsem et al., 2004*
[28] *Sudo et al., 2014*
[29] *Lee et al., 2017*

Table 87: Full GRADE profile for gemcitabine versus other chemotherapy (Adverse events – Diarrhoea) in adults with locally advanced or metastatic pancreatic cancer

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GEM alone	Exp. Chemotherapy	Relative (95% CI)	Absolute		
Grade 3/4 toxicities: Diarrhoea - 5-FU single-agent												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	3/63 (4.8%)	1/63 (1.6%)	RR 3 (0.32 to 28.07)	32 more per 1000 (from 11 fewer to 430 more)	LOW	CRITICAL
Grade 3/4 toxicities: Diarrhoea - S-1 single-agent												
1[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	15/272 (5.5%)	3/273 (1.1%)	RR 5.02 (1.47 to 17.14)	44 more per 1000 (from 5 more to 177 more)	HIGH	CRITICAL
Grade 3/4 toxicities: Diarrhoea - GEM + 5-FU												
1[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/158 (6.3%)	4/158 (2.5%)	RR 2.5 (0.8 to 7.8)	38 more per 1000 (from 5 fewer to 172 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities: Diarrhoea - GEM + Axitinib												
1[7]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	4/305 (1.3%)	5/308 (1.6%)	RR 0.81 (0.22 to 2.98)	3 fewer per 1000 (from 13 fewer to 32 more)	LOW	CRITICAL
Grade 3/4 toxicities: Diarrhoea - GEM + Capecitabine												

2[8]	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	very serious[2]	none	22/513 (4.3%)	14/504 (2.8%)	RR 1.53 (0.80 to 2.91)	15 more per 1000 (from 6 fewer to 53 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities: Diarrhoea - GEM + Cetuximab												
1[10]	randomised trials	serious	no serious inconsistency	no serious indirectness	very serious[2]	none	10/361 (2.8%)	9/355 (2.5%)	RR 1.09 (0.45 to 2.66)	2 more per 1000 (from 14 fewer to 42 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities: Diarrhoea - GEM + Cisplatin												
1[11]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/98 (3.1%)	5/97 (5.2%)	RR 0.59 (0.15 to 2.42)	21 fewer per 1000 (from 44 fewer to 73 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities: Diarrhoea - GEM + Erlotinib												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	6/282 (2.1%)	2/280 (0.71%)	RR 2.98 (0.61 to 14.63)	14 more per 1000 (from 3 fewer to 97 more)	LOW	CRITICAL
Grade 3/4 toxicities: Diarrhoea - GEM + Exatecan												
1[13]	randomised trials	very serious[14]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/168 (1.2%)	1/157 (0.64%)	RR 1.87 (0.17 to 20.41)	6 more per 1000 (from 5 fewer to 124 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities: Diarrhoea - GEM + Irinotecan												

2[15,16]	randomised trials	serious[17]	serious[18]	no serious indirectness	no serious imprecision	none	34/233 (14.6%)	5/239 (2.1%)	RR 6.92 (2.71 to 17.67)	124 more per 1000 (from 36 more to 349 more)	LOW	CRITICAL
Grade 3/4 toxicities: Diarrhoea - GEM + Oxaliplatin												
2[19,20]	randomised trials	serious[17]	no serious inconsistency	no serious indirectness	serious[6]	none	25/420 (6%)	10/420 (2.4%)	RR 2.5 (1.22 to 5.15)	36 more per 1000 (from 5 more to 99 more)	LOW	CRITICAL
Grade 3/4 toxicities: Diarrhoea - GEM + Pemetrexed												
1[21]	randomised trials	serious[17]	no serious inconsistency	no serious indirectness	serious[6]	none	8/273 (2.9%)	2/273 (0.73%)	RR 4 (0.86 to 18.67)	22 more per 1000 (from 1 fewer to 129 more)	LOW	CRITICAL
Grade 3/4 toxicities: Diarrhoea - GEM + Sorafenib												
1[22]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	2/50 (4%)	3/52 (5.8%)	RR 0.69 (0.12 to 3.98)	18 fewer per 1000 (from 51 fewer to 172 more)	LOW	CRITICAL
Grade 3/4 toxicities: Diarrhoea - GEM + Tipifarnib												
2[23,24]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	13/455 (2.9%)	10/460 (2.2%)	RR 1.34 (0.6 to 3.02)	7 more per 1000 (from 9 fewer to 44 more)	LOW	CRITICAL
Grade 3/4 toxicities: Diarrhoea - GEM + S-1												

2[3,25]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	13/317 (4.1%)	5/319 (1.6%)	RR 2.59 (0.94 to 7.14)	25 more per 1000 (from 1 fewer to 96 more)	MODERATE	CRITICAL

[1] *Burris et al., 1997*
[2] *Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs*
[3] *Ueno et al., 2013*
[4] *Berlin et al., 2002*
[5] *The quality of the evidence was downgraded because of the unclear risk of selection bias (no details given about the allocation method), besides the unclear risk of performance bias (no details given in the text)*
[6] *Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID*
[7] *Kindler et al., 2011*
[8] *Herrmann et al., 2007, Cunningham et l., 2009 and Lee et al., 2017*
[9] *The quality of the evidence was downgraded because of the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions) and detection bias (not masking of outcome assessors)*
[10] *Philip et al., 2010*
[11] *Heinemann et al., 2006*
[13] *Abou-Alfa et al., 2006*
[14] *The quality of the evidence was downgraded because of the unclear risk of selection bias (no details provided in the text), the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions), besides the unclear risk of detection bias*
[15] *Rocha Lima et al., 2004*
[16] *Stathopoulos et al., 2006*
[17] *The quality of the evidence was downgraded because of the unclear risk of performance bias (no information on blinding of patients/ care providers delivering the interventions) and unclear risk of detection bias*
[18] *Serious heterogeneity. I-squared = 73%*
[19] *Louvet et al., 2005*
[20] *Poplin et al., 2006 (2009)*
[21] *Oettle et al., 2005*
[22] *Gonçalves et al., 2012*
[23] *Eckhardt et al., 2009*
[24] *Van-Cutsem et al., 2004*
[25] *Sudo et al., 2014*

Table 88: Full GRADE profile for gemcitabine versus other chemotherapy – (Adverse events -Fatigue) in adults with locally advanced or metastatic pancreatic cancer

Quality assessment							No of patients		Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GEM alone	Exp. Chemotherapy	Relative (95% CI)	Absolute		
Grade 3/4 toxicities: Fatigue - S-1 single-agent												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	18/272 (6.6%)	10/273 (3.7%)	RR 1.81 (0.85 to 3.84)	30 more per 1000 (from 5 fewer to 104 more)	MODERATE	CRITICAL
Grade 3/4 toxicities: Fatigue - GEM + Axitinib												
1[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	27/305 (8.9%)	21/308 (6.8%)	RR 1.3 (0.75 to 2.25)	20 more per 1000 (from 17 fewer to 85 more)	LOW	CRITICAL
Grade 3/4 toxicities: Fatigue - GEM + Cetuximab												
1[5]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[2]	none	72/361 (19.9%)	64/355 (18%)	RR 1.11 (0.82 to 1.5)	20 more per 1000 (from 32 fewer to 90 more)	LOW	CRITICAL
Grade 3/4 toxicities: Fatigue - GEM + Erlotinib												
1[7]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	15/282 (5.3%)	15/280 (5.4%)	RR 0.99 (0.49 to 1.99)	1 fewer per 1000 (from 27 fewer to 53 more)	LOW	CRITICAL
Grade 3/4 toxicities: Fatigue - GEM + Exatecan												
1[8]	randomised trials	very serious[9]	no serious inconsistency	no serious indirectness	serious[2]	none	14/168 (8.3%)	5/157 (3.2%)	RR 2.62 (0.96 to 7.1)	52 more per 1000 (from 1	VERY LOW	CRITICAL

										fewer to 194 more)		
Grade 3/4 toxicities: Fatigue - GEM + Irinotecan												
1[10]	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	very serious[10]	none	29/173 (16.8%)	26/169 (15.4%)	RR 1.09 (0.67 to 1.77)	14 more per 1000 (from 51 fewer to 118 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities: Fatigue - GEM + Marimastat												
1[12]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	14/120 (11.7%)	7/119 (5.9%)	RR 1.98 (0.83 to 4.74)	58 more per 1000 (from 10 fewer to 220 more)	LOW	CRITICAL
Grade 3/4 toxicities: Fatigue - GEM + Oxaliplatin												
1[13]	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	serious[2]	none	45/263 (17.1%)	50/264 (18.9%)	RR 0.9 (0.63 to 1.3)	19 fewer per 1000 (from 70 fewer to 57 more)	LOW	CRITICAL
Grade 3/4 toxicities: Fatigue - GEM + Pemetrexed												
1[14]	randomised trials	serious[15]	no serious inconsistency	no serious indirectness	no serious imprecision	none	41/273 (15%)	18/273 (6.6%)	RR 2.28 (1.34 to 3.86)	84 more per 1000 (from 22 more to 189 more)	MODERATE	CRITICAL
Grade 3/4 toxicities: Fatigue - GEM + Tipifarnib												

2[16,17]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	55/455 (12.1%)	61/460 (13.3%)	RR 0.91 (0.65 to 1.27)	12 fewer per 1000 (from 46 fewer to 36 more)	LOW	CRITICAL
Grade 3/4 toxicities: Fatigue - GEM + S-1												
2[1,18]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	13/317 (4.1%)	11/319 (3.4%)	RR 1.19 (0.55 to 2.57)	7 more per 1000 (from 16 fewer to 54 more)	LOW	CRITICAL

[1] *Ueno et al., 2013*
[2] *Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID*
[3] *Kindler et al., 2011*
[4] *Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs*
[5] *Philip et al., 2010*
[6] *The quality of the evidence was downgraded because of the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions) and detection bias (not masking of outcome assessors)*
[7] *Moore et al., 2007*
[8] *Abou-Alfa et al., 2006*
[9] *The quality of the evidence was downgraded because of the unclear risk of selection bias (no details provided in the text), the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions), besides the unclear risk of detection bias*
[10] *Rocha Lima et al., 2004*
[11] *The quality of the evidence was downgraded because of the unclear risk of performance bias (no information on blinding of patients/ care providers delivering the interventions) and unclear risk of detection bias*
[12] *Bramhall et al., 2002*
[13] *Poplin et al., 2006 (2009)*
[14] *Oettle et al., 2005*
[15] *No explanation was provided*
[16] *Eckhardt et al., 2009*
[17] *Van-Cutsem et al., 2004*
[18] *Sudo et al., 2014*

Table 89: Full GRADE profile for gemcitabine versus other chemotherapy (Adverse events -Neutropenia) in adults with locally advanced or metastatic pancreatic cancer

Quality assessment							No of patients		Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GEM alone	Exp. Chemotherapy	Relative (95% CI)	Absolute		
Grade 3/4 toxicities: Neutropenia - 5-FU single-agent												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	3/63 (4.8%)	16/63 (25.4%)	RR 0.19 (0.06 to 0.61)	206 fewer per 1000 (from 99 fewer to 239 fewer)	HIGH	CRITICAL
Grade 3/4 toxicities: Neutropenia - S-1 single-agent												
1[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	24/272 (8.8%)	112/273 (41%)	RR 0.22 (0.14 to 0.32)	320 fewer per 1000 (from 279 fewer to 353 fewer)	HIGH	CRITICAL
Grade 3/4 toxicities: Neutropenia - GEM + Axitinib												
1[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	0/305 (0%)	1/308 (0.32%)	RR 0.34 (0.01 to 8.23)	2 fewer per 1000 (from 3 fewer to 23 more)	LOW	CRITICAL
Grade 3/4 toxicities: Neutropenia - GEM + Bevacizumab												
1[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	33/277 (11.9%)	29/263 (11%)	RR 1.08 (0.68 to 1.73)	9 more per 1000 (from 35 fewer to 80 more)	LOW	CRITICAL

Grade 3/4 toxicities: Neutropenia - GEM + Capecitabine												
2[5,6,25]	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	serious[8]	none	141/513 (27.5%)	96/504 (19%)	RR 1.44 (1.15 to 1.81)	84 more per 1000 (from 29 more to 154 more)	LOW	CRITICAL
Grade 3/4 toxicities: Neutropenia - GEM + Cetuximab												
1[9]	randomised trials	serious[10]	no serious inconsistency	no serious indirectness	very serious[4]	none	84/361 (23.3%)	85/355 (23.9%)	RR 0.97 (0.75 to 1.26)	7 fewer per 1000 (from 60 fewer to 62 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities: Neutropenia - GEM + Elpamotide												
1[11]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[8]	none	48/100 (48%)	30/53 (56.6%)	RR 0.85 (0.62 to 1.16)	85 fewer per 1000 (from 215 fewer to 91 more)	MODERATE	CRITICAL
Grade 3/4 toxicities: Neutropenia - GEM + Exatecan												
1[12]	randomised trials	very serious[13]	no serious inconsistency	no serious indirectness	no serious imprecision	none	51/168 (30.4%)	23/157 (14.6%)	RR 2.07 (1.33 to 3.22)	157 more per 1000 (from 48 more to 325 more)	LOW	CRITICAL
Grade 3/4 toxicities: Neutropenia - GEM + Irinotecan												
1[14]	randomised trials	serious[15]	no serious inconsistency	no serious indirectness	serious[8]	none	16/60 (26.7%)	11/70 (15.7%)	RR 1.7 (0.85 to 3.37)	110 more per 1000 (from 24 fewer to 372 more)	LOW	CRITICAL

Grade 3/4 toxicities: Neutropenia - GEM + Oxaliplatin												
2[16,17]	randomised trials	serious[18]	very serious[19]	no serious indirectness	serious[8]	none	102/420 (24.3%)	118/420 (28.1%)	RR 0.86 (0.69 to 1.09)	39 fewer per 1000 (from 87 fewer to 25 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities: Neutropenia - GEM + Pemetrexed												
1[20]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	123/273 (45.1%)	35/273 (12.8%)	RR 3.51 (2.51 to 4.92)	322 more per 1000 (from 194 more to 503 more)	HIGH	CRITICAL
Grade 3/4 toxicities: Neutropenia - GEM + Sorafenib												
1[21]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	13/50 (26%)	15/52 (28.8%)	RR 0.9 (0.48 to 1.7)	29 fewer per 1000 (from 150 fewer to 202 more)	LOW	CRITICAL
Grade 3/4 toxicities: Neutropenia - GEM + Tipifarnib												
2[22,23]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[8]	none	187/455 (41.1%)	149/460 (32.4%)	RR 1.26 (1.07 to 1.5)	84 more per 1000 (from 23 more to 162 more)	MODERATE	CRITICAL
Grade 3/4 toxicities: Neutropenia - GEM + S-1												
2[2,24]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	188/317 (59.3%)	121/319 (37.9%)	RR 1.57 (1.33 to 1.86)	216 more per 1000 (from 125 more to	HIGH	CRITICAL

										326 more)		

[1] *Burris et al., 1997*
[2] *Ueno et al., 2013*
[3] *Kindler et al., 2010*
[4] *Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs*
[5] *Cunningham et al., 2009*
[6] *Herrmann et al., 2007*
[7] *The quality of the evidence was downgraded because of the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions) and detection bias (not masking of outcome assessors) in Cunningham et al., 2009, and the unclear risk of selection bias in Herrmann et al., 2007.*
[8] *Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID*
[9] *Philip et al., 2010*
[10] *The quality of the evidence was downgraded because of the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions) and detection bias (not masking of outcome assessors)*
[11] *Yamaue et al., 2015*
[12] *Abou-Alfa et al., 2006*
[13] *The quality of the evidence was downgraded because of the unclear risk of selection bias (no details provided in the text), the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions), besides the unclear risk of detection bias*
[14] *Stathopoulos et al., 2006#*
[15] *The quality of the evidence was downgraded because of the unclear risk of performance bias (no information on blinding of patients/ care providers delivering the interventions) and unclear risk of detection bias and the potential risk of attrition bias*
[16] *Louvet et al., 2005*
[17] *Poplin et al., 2006 (2009)*
[18] *The quality of the evidence was downgraded because of the unclear risk of performance bias (no information on blinding of patients/ care providers delivering the interventions) and unclear risk of detection bias*
[19] *Serious heterogeneity. I-squared = 89%*
[20] *Oettle et al., 2005*
[21] *Gonçalves et al., 2012*
[22] *Eckhardt et al., 2009*
[23] *Van-Cutsem et al., 2004*
[24] *Sudo et al., 2014*
[25] *Lee et al., 2017*

Table 90: Full GRADE profile for gemcitabine versus other chemotherapy (Adverse events -Thrombocytopenia) in adults with locally advanced or metastatic pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GEM alone	Exp. Chemotherapy	Relative (95% CI)	Absolute		

Grade 3/4 toxicities: Thrombocytopenia - GEM + 5-FU												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	30/158 (19%)	17/162 (10.5%)	RR 1.81 (1.04 to 3.15)	85 more per 1000 (from 4 more to 226 more)	LOW	CRITICAL
Grade 3/4 toxicities: Thrombocytopenia - GEM + Axitinib												
1[4]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	0/305 (0%)	1/308 (0.32%)	RR 0.34 (0.01 to 8.23)	2 fewer per 1000 (from 3 fewer to 23 more)	LOW	CRITICAL
Grade 3/4 toxicities: Thrombocytopenia - GEM + Bevacizumab												
1[6]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	12/277 (4.3%)	12/263 (4.6%)	RR 0.95 (0.43 to 2.08)	2 fewer per 1000 (from 26 fewer to 49 more)	LOW	CRITICAL
Grade 3/4 toxicities: Thrombocytopenia - GEM + Capecitabine												
2[7,8,24]	randomised trials	serious[9]	serious[10]	no serious indirectness	serious[3]	none	36/513 (7%)	31/504 (6.2%)	RR 1.14 (0.72 to 1.82)	9 more per 1000 (from 17 fewer to 50 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities: Thrombocytopenia - GEM + Cisplatin												
1[11]	randomised trials	serious	no serious inconsistency	no serious indirectness	serious[3]	none	4/98 (4.1%)	10/97 (10.3%)	RR 0.4 (0.13 to 1.22)	62 fewer per 1000 (from 90 fewer to 23 more)	LOW	CRITICAL
Grade 3/4 toxicities: Thrombocytopenia - GEM + Elpamotide												

1[12]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	15/100 (15%)	8/53 (15.1%)	RR 0.99 (0.45 to 2.19)	2 fewer per 1000 (from 83 fewer to 180 more)	LOW	CRITICAL
Grade 3/4 toxicities: Thrombocytopenia - GEM + Exatecan												
1[13]	randomised trials	very serious[14]	no serious inconsistency	no serious indirectness	no serious imprecision	none	26/168 (15.5%)	7/157 (4.5%)	RR 3.47 (1.55 to 7.77)	110 more per 1000 (from 25 more to 302 more)	LOW	CRITICAL
Grade 3/4 toxicities: Thrombocytopenia - GEM + Irinotecan												
1[15]	randomised trials	serious	no serious inconsistency	no serious indirectness	very serious[5]	none	3/60 (5%)	0/70 (0%)	RR 8.15 (0.43 to 154.64)	-	VERY LOW	CRITICAL
Grade 3/4 toxicities: Thrombocytopenia - GEM + Oxaliplatin												
1[16]	randomised trials	serious[17]	no serious inconsistency	no serious indirectness	no serious imprecision	none	22/157 (14%)	5/156 (3.2%)	RR 4.37 (1.7 to 11.25)	108 more per 1000 (from 22 more to 329 more)	MODERATE	CRITICAL
Grade 3/4 toxicities: Thrombocytopenia - GEM + Pemetrexed												
1[18]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	49/273 (17.9%)	17/273 (6.2%)	RR 2.88 (1.7 to 4.88)	117 more per 1000 (from 44 more to 242 more)	HIGH	CRITICAL
Grade 3/4 toxicities: Thrombocytopenia - GEM + Sorafenib												

1[19]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	3/50 (6%)	6/52 (11.5%)	RR 0.52 (0.14 to 1.97)	55 fewer per 1000 (from 99 fewer to 112 more)	LOW	CRITICAL
Grade 3/4 toxicities: Thrombocytopenia - GEM + Tipifarnib												
2[20,21]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[10]	none	75/455 (16.5%)	62/460 (13.5%)	RR 1.22 (0.89 to 1.66)	30 more per 1000 (from 15 fewer to 89 more)	MODERATE	CRITICAL
Grade 3/4 toxicities: Thrombocytopenia - GEM + S-1												
2[22,23]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/317 (5.7%)	5/319 (1.6%)	RR 3.4 (1.33 to 8.7)	38 more per 1000 (from 5 more to 121 more)	HIGH	CRITICAL

[1] *Berlin et al., 2002*
[2] *The quality of the evidence was downgraded because of the unclear risk of selection bias (no details given about the allocation method), besides the unclear risk of performance bias (no details given in the text)*
[3] *Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID*
[4] *Kindler et al., 2011*
[5] *Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs*
[6] *Kindler et al., 2010*
[7] *Cunningham et al., 2009*
[8] *Herrmann et al., 2007*
[9] *The quality of the evidence was downgraded because of the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions) and detection bias (not masking of outcome assessors) in Cunningham et al., 2009, and the unclear risk of selection bias in Herrmann et al., 2007.*
[10] *Serious heterogeneity. I-squared = 80%*
[11] *Heinemann et al., 2006*
[12] *Yamaue et al., 2015*
[13] *Abou-Alfa et al., 2006*
[14] *The quality of the evidence was downgraded because of the unclear risk of selection bias (no details provided in the text), the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions), besides the unclear risk of detection bias*
[15] *Stathopoulos et al., 2006*
[16] *Louvet et al., 2005*

[17] *The quality of the evidence was downgraded because of the unclear risk of performance bias (no information on blinding of patients/ care providers delivering the interventions) and unclear risk of detection bias*
[18] *Oettle et al., 2005*
[19] *Gonçalves et al., 2012*
[20] *Eckhardt et al., 2009*
[21] *Van-Cutsem et al., 2004*
[22] *Sudo et al., 2014*
[23] *Ueno et al., 2013*
[24] *Lee et al., 2017*

Table 91: Full GRADE profile for gemcitabine versus other chemotherapy (Adverse events - Leukopoenia) in adults with locally advanced or metastatic pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GEM alone	Exp. Chemotherapy	Relative (95% CI)	Absolute		
Grade 3/4 toxicities: Leukopoenia - S-1 single-agent												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	10/272 (3.7%)	51/273 (18.7%)	RR 0.2 (0.1 to 0.38)	149 fewer per 1000 (from 116 fewer to 168 fewer)	HIGH	CRITICAL
Grade 3/4 toxicities: Leukopoenia - GEM + 5-FU												
1[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	29/158 (18.4%)	16/158 (10.1%)	RR 1.81 (1.03 to 3.2)	82 more per 1000 (from 3 more to 223 more)	LOW	CRITICAL
Grade 3/4 toxicities: Leukopoenia - GEM + Axitinib												
1[5]	randomised trials	no serious	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/305 (0%)	0/308 (0%)	-	-	HIGH	CRITICAL

		risk of bias										
Grade 3/4 toxicities: Leukopoenia - GEM + Cetuximab												
1[6]	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	serious[4]	none	40/361 (11.1%)	52/355 (14.6%)	RR 0.76 (0.51 to 1.11)	35 fewer per 1000 (from 72 fewer to 16 more)	LOW	CRITICAL
Grade 3/4 toxicities: Leukopoenia - GEM + Cisplatin												
1[8]	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	very serious[9]	none	10/98 (10.2%)	8/97 (8.2%)	RR 1.24 (0.51 to 3)	20 more per 1000 (from 40 fewer to 165 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities: Leukopoenia - GEM + Elpamotide												
1[10]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	31/100 (31%)	23/53 (43.4%)	RR 0.71 (0.47 to 1.09)	126 fewer per 1000 (from 230 fewer to 39 more)	MODERATE	CRITICAL
Grade 3/4 toxicities: Leukopoenia - GEM + Oxaliplatin												
1[11]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	32/263 (12.2%)	42/264 (15.9%)	RR 0.76 (0.5 to 1.17)	38 fewer per 1000 (from 80 fewer to 27 more)	MODERATE	CRITICAL
Grade 3/4 toxicities: Leukopoenia - GEM + S-1												
2[1,12]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[13]	none	111/317 (35%)	59/319 (18.5%)	RR 1.76 (1.09 to 2.84)	141 more per 1000 (from 17 more to	MODERATE	CRITICAL

										340 more)		

[1] *Ueno et al., 2013*
[2] *Berlin et al., 2002*
[3] *The quality of the evidence was downgraded because of the unclear risk of selection bias (no details given about the allocation method), besides the unclear risk of performance bias (no details given in the text)*
[4] *Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID*
[5] *Kindler et al., 2011*
[6] *Philip et al., 2010*
[7] *The quality of the evidence was downgraded because of the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions) and detection bias (not masking of outcome assessors)*
[8] *Heinemann et al., 2006*
[9] *Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs*
[10] *Yamaue et al., 2015*
[11] *Poplin et al., 2006 (2009)*
[12] *Sudo et al., 2014*
[13] *Serious heterogeneity. I-squared = 36%*

Table 92: Full GRADE profile for gemcitabine versus other chemotherapy (Health-related Quality of Life) in adults with locally advanced or metastatic pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**GEM alone**	**Exp. Chemotherapy (mix pop.)**	**Relative (95% CI)**	**Absolute**		
HRQL: GEM + Capecitabine *versus* GEM - mean score difference at 6 months (linear-analogue self-assessment [LASA] indicators - Physical well-being (Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	160	159	-	MD 5 higher (4.8 lower to 14.8 higher)	LOW	CRITICAL
HRQL: GEM + Capecitabine *versus* GEM - mean score difference at 6 months (linear-analogue self-assessment [LASA] indicators - Mood (Better indicated by lower values)												

1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	160	159	-	MD 6 higher (3.8 lower to 15.8 higher)	LOW	CRITICAL
HRQL: GEM + Capecitabine *versus* GEM - mean score difference at 6 months (linear-analogue self-assessment [LASA] indicators - Pain (Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	160	159	-	MD 8 higher (1.8 lower to 17.8 higher)	LOW	CRITICAL
HRQL: GEM + Capecitabine *versus* GEM - mean score difference at 6 months (linear-analogue self-assessment [LASA] indicators - Tiredness (Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	160	159	-	MD 2 higher (7.8 lower to 11.8 higher)	LOW	CRITICAL
HRQL: GEM + Capecitabine *versus* GEM - mean score difference at 6 months (linear-analogue self-assessment [LASA] indicators - Functional performance (Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	160	159	-	MD 8 higher (1.8 lower to 17.8 higher)	LOW	CRITICAL
HRQL: GEM + Capecitabine *versus* GEM - mean score difference at 6 months (linear-analogue self-assessment [LASA] indicators - Coping effort (Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	160	159	-	MD 4 higher (5.8 lower to 13.8 higher)	LOW	CRITICAL

HRQL: GEM + Capecitabine *versus* GEM - mean score difference at 6 months (linear-analogue self-assessment [LASA] indicators - Treatment burden (Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	160	159	-	MD 4 higher (5.8 lower to 13.8 higher)	LOW	CRITICAL
HQRL: GEM + Cetuximab *versus* alone - Emotional Well-Being Score at 5, 13, and 17 weeks follow-up - 5 weeks follow-up (Better indicated by lower values)												
1[5]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[3]	none	262	278	-	MD 0.3 lower (0.69 lower to 0.09 higher)	LOW	CRITICAL
HQRL: GEM + Cetuximab *versus* alone - Emotional Well-Being Score at 5, 13, and 17 weeks follow-up - 13 weeks follow-up (Better indicated by lower values)												
1[5]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[3]	none	157	183	-	MD 0.2 higher (0.34 lower to 0.74 higher)	LOW	CRITICAL
HQRL: GEM + Cetuximab *versus* alone - Emotional Well-Being Score at 5, 13, and 17 weeks follow-up - 17 weeks follow-up (Better indicated by lower values)												
1[5]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[3]	none	130	158	-	MD 0.5 higher (0.01 lower to 1.01 higher)	LOW	CRITICAL
HRQL: GEM + cisplatin *versus* GEM alone at 6 treatment cycles (Spitzer 5-Item Index) (Better indicated by lower values)												

1[7]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	98	97	-	MD 0.4 lower (0.66 to 0.14 lower)	MODERATE	CRITICAL
HQRL: PEFG *versus* GEM - Number of patients with a clinically significant improvement QLQ-C30 - Global health status												
1[8]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	11/20 (55%)	6/21 (28.6%)	RR 1.93 (0.88 to 4.22)	266 more per 1000 (from 34 fewer to 920 more)	LOW	CRITICAL
HQRL: PEFG *versus* GEM - Number of patients with a clinically significant improvement QLQ-C30 - Physical functioning												
1[8]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[9]	none	6/23 (26.1%)	2/23 (8.7%)	RR 3 (0.67 to 13.34)	174 more per 1000 (from 29 fewer to 1000 more)	VERY LOW	CRITICAL
HQRL: PEFG *versus* GEM - Number of patients with a clinically significant improvement QLQ-C30 - Role functioning												
1[8]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[9]	none	5/23 (21.7%)	7/22 (31.8%)	RR 0.68 (0.25 to 1.83)	102 fewer per 1000 (from 239 fewer to 264 more)	VERY LOW	CRITICAL
HQRL: PEFG *versus* GEM - Number of patients with a clinically significant improvement QLQ-C30 - Emotional functioning												
1[8]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	9/21 (42.9%)	4/22 (18.2%)	RR 2.36 (0.85 to 6.5)	247 more per 1000 (from 27 fewer to 1000 more)	LOW	CRITICAL

HQRL: PEFG *versus* GEM - Number of patients with a clinically significant improvement QLQ-C30 - Cognitive functioning												
1[8]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[9]	none	5/23 (21.7%)	5/24 (20.8%)	RR 1.04 (0.35 to 3.13)	8 more per 1000 (from 135 fewer to 444 more)	VERY LOW	CRITICAL
HQRL: PEFG *versus* GEM - Number of patients with a clinically significant improvement QLQ-C30 - Social functioning												
1[8]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[9]	none	7/21 (33.3%)	5/17 (29.4%)	RR 1.13 (0.44 to 2.94)	38 more per 1000 (from 165 fewer to 571 more)	VERY LOW	CRITICAL
HQRL: PEFG *versus* GEM - Number of patients with a clinically significant improvement QLQ-C30 - Fatigue												
1[8]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[9]	none	9/22 (40.9%)	6/24 (25%)	RR 1.64 (0.7 to 3.85)	160 more per 1000 (from 75 fewer to 712 more)	VERY LOW	CRITICAL
HQRL: PEFG *versus* GEM - Number of patients with a clinically significant improvement QLQ-C30 - Nausea/vomiting												
1[8]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[9]	none	2/21 (9.5%)	1/19 (5.3%)	RR 1.81 (0.18 to 18.39)	43 more per 1000 (from 43 fewer to 915 more)	VERY LOW	CRITICAL
HQRL: PEFG *versus* GEM - Number of patients with a clinically significant improvement QLQ-C30 - Pain												
1[8]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	14/22 (63.6%)	9/22 (40.9%)	RR 1.56 (0.86 to 2.82)	229 more per 1000 (from 57 fewer to	LOW	CRITICAL

										745 more)		
HQRL: PEFG *versus* GEM - Number of patients with a clinically significant improvement QLQ-C30 - Dyspnea												
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	very serious[9]	none	4/23 (17.4%)	3/23 (13%)	RR 1.33 (0.34 to 5.3)	43 more per 1000 (from 86 fewer to 561 more)	VERY LOW	CRITICAL
HQRL: PEFG *versus* GEM - Number of patients with a clinically significant improvement QLQ-C30 - Insomnia												
1[8]	randomised trials	serious	no serious inconsistency	no serious indirectness	very serious[9]	none	8/23 (34.8%)	8/24 (33.3%)	RR 1.04 (0.47 to 2.31)	13 more per 1000 (from 177 fewer to 437 more)	VERY LOW	CRITICAL
HQRL: PEFG *versus* GEM - Number of patients with a clinically significant improvement QLQ-C30 - Loss of appetite												
1[8]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[9]	none	6/23 (26.1%)	7/24 (29.2%)	RR 0.89 (0.35 to 2.26)	32 fewer per 1000 (from 190 fewer to 368 more)	VERY LOW	CRITICAL
HQRL: PEFG *versus* GEM - Number of patients with a clinically significant improvement QLQ-C30 - Constipation												
1[8]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[9]	none	7/23 (30.4%)	7/23 (30.4%)	RR 1 (0.42 to 2.4)	0 fewer per 1000 (from 177 fewer to 426 more)	VERY LOW	CRITICAL
HQRL: PEFG *versus* GEM - Number of patients with a clinically significant improvement QLQ-C30 - Diarrhea												

1[8]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[9]	none	4/21 (19%)	2/23 (8.7%)	RR 2.19 (0.45 to 10.75)	103 more per 1000 (from 48 fewer to 848 more)	VERY LOW	CRITICAL
HQRL: PEFG *versus* GEM - Number of patients with a clinically significant improvement QLQ-C30 - Financial difficulties												
1[8]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[9]	none	2/22 (9.1%)	2/21 (9.5%)	RR 0.95 (0.15 to 6.17)	5 fewer per 1000 (from 81 fewer to 492 more)	VERY LOW	CRITICAL

[1] *Bernhard et al., 2008*
[2] *The quality of the evidence was downgraded because of the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions) and unclear risk of detection bias (no details on allocation concealment and randomization)*
[3] *Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID*
[4] *The quality of the evidence was downgraded because of the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions) and unclear risk of detection bias (not infpormation given on masking of outcome assessors)*
[5] *Moinpour et al., 2010*
[6] *The quality of the evidence was downgraded because of the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions) and detection bias (not masking of outcome assessors)*
[7] *Heinemann et al., 2006*
[8] *Reni et al., 2005 (2006)*
[9] *Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs*

Table 93: Full GRADE profile for gemcitabine + erlotinib versus gemcitabine, erlotinib + bevacizumab in adults with locally advanced or metastatic pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GEM + erlotinib	Exp. Chemotherapy (GEM + erlotinib + bevacizumab)	Relative (95% CI)	Absolute		

							(pure metastatic)					
Overall response rate (CR + PR) - GEM + erlotinib + bevacizumab												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	40/306 (13.1%)	25/301 (8.3%)	RR 1.57 (0.98 to 2.53)	47 more per 1000 (from 2 fewer to 127 more)	MODERATE	CRITICAL
Progression Free Survival - GEM + erlotinib + bevacizumab												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	-	-	HR 0.73 (0.61 to 0.87)	-	MODERATE	CRITICAL
Grade 3/4 toxicities - Thrombocytopenia												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	23/296 (7.8%)	17/287 (5.9%)	RR 1.31 (0.72 to 2.4)	18 more per 1000 (from 17 fewer to 83 more)	LOW	CRITICAL
Grade 3/4 toxicities - Neutropenia												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	49/296 (16.6%)	49/287 (17.1%)	RR 0.97 (0.68 to 1.39)	5 fewer per 1000 (from 55 fewer to 67 more)	LOW	CRITICAL
Grade 3/4 toxicities - Diarrhoea												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	12/296 (4.1%)	17/287 (5.9%)	RR 0.68 (0.33 to 1.41)	19 fewer per 1000 (from 40 fewer to 24 more)	LOW	CRITICAL

Grade 3/4 toxicities - Nausea/Vomiting												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	27/296 (9.1%)	17/287 (5.9%)	RR 1.54 (0.86 to 2.76)	32 more per 1000 (from 8 fewer to 104 more)	LOW	CRITICAL

[1] *Van-Cutsem et al., 2009*
[2] *Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID*
[3] *The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant.*
[4] *Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs*

Table 94: Full GRADE profile for gemcitabine + erlotinib versus capecitabine + erlotinib in adults with locally advanced or metastatic pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**GEM + erlotinib**	**Exp. Chemotherapy (capecitabine + erlotinib) (mix pop.)**	**Relative (95% CI)**	**Absolute**		
Overall response rate (CR + PR) - Capecitabine + erlotinib												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	22/143 (15.4%)	7/131 (5.3%)	RR 2.88 (1.27 to 6.52)	100 more per 1000 (from 14 more to 295 more)	MODERATE	CRITICAL
Grade 3/4 toxicities - Leucocytopenia												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	8/132 (6.1%)	0/124 (0%)	RR 15.98	-	LOW	CRITICAL

									(0.93 to 273.93)			
Grade 3/4 toxicities - Thrombocytopenia												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	11/132 (8.3%)	2/124 (1.6%)	RR 5.17 (1.17 to 22.85)	67 more per 1000 (from 3 more to 352 more)	LOW	CRITICAL
Grade 3/4 toxicities - Diarrhoea												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	7/132 (5.3%)	12/124 (9.7%)	RR 0.55 (0.22 to 1.35)	44 fewer per 1000 (from 75 fewer to 34 more)	LOW	CRITICAL
Grade 3/4 toxicities - Nausea/Vomiting												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	13/132 (9.8%)	9/124 (7.3%)	RR 1.36 (0.6 to 3.06)	26 more per 1000 (from 29 fewer to 150 more)	LOW	CRITICAL

[1] *Heinemann et al., 2012*
[2] *The quality of the evidence was downgraded because of the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions) and detection bias (not masking of outcome assessors)*
[3] *Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID*
[4] *Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs*

I.17.36 Gemcitabine versus novel agents

Table 95: Full GRADE profile for gemcitabine versus BAY 12-9566/ ZD9331 in adults with locally advanced or metastatic pancreatic cancer

Quality assessment							No of patients		Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GEM alone chemotherapy	Novel agent	Relative (95% CI)	Absolute		
Overall response rate (CR + PR) at 8 weeks of therapy - BAY 12-9566												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/108 (0.93%)	6/115 (5.2%)	RR 0.18 (0.02 to 1.45)	43 fewer per 1000 (from 51 fewer to 23 more)	VERY LOW	CRITICAL
Overall response rate (CR + PR) at 8 weeks of therapy - ZD9331												
1[5]	randomised trials	very serious[6]	no serious inconsistency	no serious indirectness	serious[4]	none	1/30 (3.3%)	2/25 (8%)	RR 0.42 (0.04 to 4.33)	46 fewer per 1000 (from 77 fewer to 266 more)	VERY LOW	CRITICAL
Progression Free Survival - BAY 12-9566												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.53 (0.41 to 0.68)	-	MODERATE	CRITICAL
Overall Survival - BAY 12-9566												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.57 (0.44 to 0.74)	-	MODERATE	CRITICAL
Grade 3/4 toxicities: Nausea - BAY 12-9566												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	11/138 (8%)	5/139 (3.6%)	RR 2.22 (0.79 to 6.21)	44 more per 1000 (from 8 fewer to 187 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities: Nausea - ZD9331												

1[5]	randomised trials	very serious[6]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/30 (6.7%)	1/25 (4%)	RR 1.67 (0.16 to 17.32)	27 more per 1000 (from 34 fewer to 653 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities: Vomiting - BAY 12-9566												
1[5]	randomised trials	very serious[6]	no serious inconsistency	no serious indirectness	very serious[6]	none	4/138 (2.9%)	7/139 (5%)	RR 0.58 (0.17 to 1.92)	21 fewer per 1000 (from 42 fewer to 46 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities: Vomiting - ZD9331												
1[5]	randomised trials	very serious[6]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/30 (6.7%)	0/25 (0%)	RR 4.19 (0.21 to 83.5)	-	VERY LOW	CRITICAL
Grade 3/4 toxicities: Diarrhoea - BAY 12-9566												
1[5]	randomised trials	very serious[6]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/138 (1.4%)	3/139 (2.2%)	RR 0.67 (0.11 to 3.96)	7 fewer per 1000 (from 19 fewer to 64 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities: Diarrhoea - ZD9331												
1[5]	randomised trials	very serious[6]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/30 (6.7%)	1/25 (4%)	RR 1.67 (0.16 to 17.32)	27 more per 1000 (from 34 fewer to 653 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities: Fatigue - ZD9331												
1[5]	randomised trials	very serious[6]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/30 (10%)	0/25 (0%)	RR 5.87 (0.32 to 108.53)	-	VERY LOW	CRITICAL

Grade 3/4 toxicities: Neutropenia - ZD9331												
1[5]	randomised trials	very serious[6]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/30 (16.7%)	1/25 (4%)	RR 4.17 (0.52 to 33.37)	127 more per 1000 (from 19 fewer to 1000 more)	VERY LOW	CRITICAL
Health Related Quality of Life (EORTC C30,Domains) - Mean change From Baseline at 8 weeks follow-up - Physical (Better indicated by higher values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	41	70	-	MD 13.2 lower (24.46 to 1.94 lower)	MODERATE	CRITICAL
Health Related Quality of Life (EORTC C30,Domains) - Mean change From Baseline at 8 weeks follow-up - Role (Better indicated by higher values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	41	70	-	MD 20.6 lower (34.97 to 6.23 lower)	MODERATE	CRITICAL
Health Related Quality of Life (EORTC C30,Domains) - Mean change From Baseline at 8 weeks follow-up - Emotional (Better indicated by higher values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	41	70	-	MD 7 lower (14.96 lower to 0.96 higher)	LOW	CRITICAL
Health Related Quality of Life (EORTC C30,Domains) - Mean change From Baseline at 8 weeks follow-up - Cognitive (Better indicated by higher values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	41	70	-	MD 11.8 lower (20.18 to	MODERATE	CRITICAL

										3.42 lower)		
Health Related Quality of Life (EORTC C30,Domains) - Mean change From Baseline at 8 weeks follow-up - Social (Better indicated by higher values)												
1[1]	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	serious[4]	none	41	70	-	MD 11.5 lower (24.19 lower to 1.19 higher)	LOW	CRITICAL
Health Related Quality of Life (EORTC C30,Domains) - Mean change From Baseline at 8 weeks follow-up - Global (Better indicated by higher values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	41	70	-	MD 12.6 lower (20.87 to 4.33 lower)	MODERATE	CRITICAL
Health Related Quality of Life (EORTC C30,Symptoms) - Mean change From Baseline at 8 weeks follow-up - Fatigue (Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	41	70	-	MD 13.1 higher (2.32 to 23.88 higher)	MODERATE	CRITICAL
Health Related Quality of Life (EORTC C30,Symptoms) - Mean change From Baseline at 8 weeks follow-up - Nausea (Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	41	70	-	MD 6.7 higher (2.39 lower to 15.79 higher)	LOW	CRITICAL
Health Related Quality of Life (EORTC C30,Symptoms) - Mean change From Baseline at 8 weeks follow-up - Pain (Better indicated by lower values)												

1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	41	70	-	MD 14.1 higher (3.17 to 25.03 higher)	MODERATE	CRITICAL
Health Related Quality of Life (EORTC C30,Symptoms) - Mean change From Baseline at 8 weeks follow-up - Dyspnea (Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	41	70	-	MD 7.3 higher (3.47 lower to 18.07 higher)	LOW	CRITICAL
Health Related Quality of Life (EORTC C30,Symptoms) - Mean change From Baseline at 8 weeks follow-up - Insomnia (Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	41	70	-	MD 9.8 higher (3.51 lower to 23.11 higher)	LOW	CRITICAL
Health Related Quality of Life (EORTC C30,Symptoms) - Mean change From Baseline at 8 weeks follow-up - Constipation (Better indicated by lower values)												
1[1]	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	41	70	-	MD 19.3 higher (5.55 to 33.05 higher)	MODERATE	CRITICAL
Health Related Quality of Life (EORTC C30,Symptoms) - Mean change From Baseline at 8 weeks follow-up - Diarrhoea (Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	41	70	-	MD 1.4 lower (11.13	LOW	CRITICAL

										lower to 8.33 higher)		
Health Related Quality of Life (EORTC C30,Symptoms) - Mean change From Baseline at 8 weeks follow-up - Financial (Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	41	70	-	MD 0.7 lower (9.62 lower to 8.22 higher)	LOW	CRITICAL

[1] *Moore et al., 2003*
[2] *The quality of the evidence was downgraded because of the unclear risk of selection bias (no details given about randomization and allocation methods)*
[3] *Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs*
[4] *Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID*
[5] *Smith et al., 2003*
[6] *The quality of the evidence was downgraded because of the unclear risk of selection bias and the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions). Furthermore due to unclear risk of selective outcome reporting and potential risk of detection bias, the quality of the evidence was further downgraded to low*

Table 96: Full GRADE profile for gemcitabine + placebo versus gemcitabine + vandetanib in adults with locally advanced or metastatic pancreatic cancer

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**GEM + placebo**	**GEM + vandetanib**	**Relative (95% CI)**	**Absolute**		
Overall response rate (CR + PR)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	10/72 (13.9%)	9/70 (12.9%)	RR 1.08 (0.47 to 2.5)	10 more per 1000 (from 68 fewer to 193 more)	LOW	CRITICAL
Progression Free Survival												

1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	-	-	HR 1.11 (0.87 to 1.41)	-	MODERATE	CRITICAL
Overall survival												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency[1]	no serious indirectness	serious[3]	none	-	-	HR 1.21 (0.96 to 1.53)	-	MODERATE	CRITICAL
Grade 3/4 toxicities - Thrombocytopenia												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	20/72 (27.8%)	16/70 (22.9%)	RR 1.22 (0.69 to 2.15)	50 more per 1000 (from 71 fewer to 263 more)	LOW	CRITICAL
Grade 3/4 toxicities - Neutropenia												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	35/72 (48.6%)	22/70 (31.4%)	RR 1.55 (1.02 to 2.35)	173 more per 1000 (from 6 more to 424 more)	MODERATE	CRITICAL
Grade 3/4 toxicities - Fatigue												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	17/72 (23.6%)	15/70 (21.4%)	RR 1.1 (0.6 to 2.03)	21 more per 1000 (from 86 fewer to 221 more)	LOW	CRITICAL
Grade 3/4 toxicities - Leucopenia												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	12/72 (16.7%)	13/70 (18.6%)	RR 0.9 (0.44 to 1.83)	19 fewer per 1000 (from 104	LOW	CRITICAL

										fewer to 154 more)		
Grade 3/4 toxicities - Hypertension												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	9/72 (12.5%)	11/70 (15.7%)	RR 0.8 (0.35 to 1.8)	31 fewer per 1000 (from 102 fewer to 126 more)	LOW	CRITICAL
Grade 3/4 toxicities - ALT increased												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	8/72 (11.1%)	11/70 (15.7%)	RR 0.71 (0.3 to 1.65)	46 fewer per 1000 (from 110 fewer to 102 more)	LOW	CRITICAL
Grade 3/4 toxicities - Hyponatraemia												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	9/72 (12.5%)	8/70 (11.4%)	RR 1.09 (0.45 to 2.67)	10 more per 1000 (from 63 fewer to 191 more)	LOW	CRITICAL
Grade 3/4 toxicities - ALP increased												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	8/72 (11.1%)	10/70 (14.3%)	RR 0.78 (0.33 to 1.86)	31 fewer per 1000 (from 96 fewer to 123 more)	LOW	CRITICAL
Grade 3/4 toxicities - Lethargy												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	9/72 (12.5%)	7/70 (10%)	RR 1.25 (0.49 to 3.17)	25 more per 1000 (from 51 fewer to 217 more)	LOW	CRITICAL

Grade 3/4 toxicities - Lymphocyte count decreased												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	9/72 (12.5%)	6/70 (8.6%)	RR 1.46 (0.55 to 3.88)	39 more per 1000 (from 39 fewer to 247 more)	LOW	CRITICAL
Grade 3/4 toxicities - Diarrhoea												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	7/72 (9.7%)	4/70 (5.7%)	RR 1.7 (0.52 to 5.56)	40 more per 1000 (from 27 fewer to 261 more)	LOW	CRITICAL
Grade 3/4 toxicities - Blood bilirubin increased												
1[1]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	4/72 (5.6%)	2/70 (2.9%)	RR 1.94 (0.37 to 10.28)	27 more per 1000 (from 18 fewer to 265 more)	LOW	CRITICAL
Grade 3/4 toxicities - Abdominal pain												
1[1]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	2/72 (2.8%)	5/70 (7.1%)	RR 0.39 (0.08 to 1.94)	44 fewer per 1000 (from 66 fewer to 67 more)	LOW	CRITICAL

1 *[1] Middleton et al., 2017*
2 *[2] Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs*
3 *[3] Evidence was downgraded by 1 due to very serious imprecision as 95%CI crossed one default MID*

I.17.41 Standard-dose versus low-dose gemcitabine

2 **Table 97: Full GRADE profile for standard-dose versus low-dose gemcitabine in adults with locally advanced or metastatic pancreatic**
3 **cancer**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Standard-dose versus low-dose gemcitabine	Control	Relative (95% CI)	Absolute		
Overall response rate (CR + PR)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/11 (18.2%)	2/10 (20%)	RR 0.91 (0.16 to 5.3)	18 fewer per 1000 (from 168 fewer to 860 more)	VERY LOW	CRITICAL
Overall Survival												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision[5]	none	-	-	-[4]	-[4]	MODERATE	CRITICAL
Grade 3/4 toxicities. - Neutropenia												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/11 (9.1%)	3/10 (30%)	RR 0.3 (0.04 to 2.46)	210 fewer per 1000 (from 288 fewer to 438 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities. - Anaemia												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/11 (0%)	3/10 (30%)	RR 0.13 (0.01 to 2.26)	261 fewer per 1000 (from 297 fewer to 378 more)	VERY LOW	CRITICAL

Grade 3/4 toxicities. - Thrombocytopenia												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/11 (0%)	3/10 (30%)	RR 0.13 (0.01 to 2.26)	261 fewer per 1000 (from 297 fewer to 378 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities. - General fatigue												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/11 (27.3%)	5/10 (50%)	RR 0.55 (0.17 to 1.72)	225 fewer per 1000 (from 415 fewer to 360 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities. - Nausea/vomiting												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/11 (9.1%)	2/10 (20%)	RR 0.45 (0.05 to 4.28)	110 fewer per 1000 (from 190 fewer to 656 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities. - Diarrhoea												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/11 (9.1%)	4/10 (40%)	RR 0.23 (0.03 to 1.71)	308 fewer per 1000 (from 388 fewer to 284 more)	VERY LOW	CRITICAL

[1] Sakamoto et al., 2006
[2] The quality of the evidence was downgraded because of the unclear risk of performance bias (no information on blinding of patients/ care providers delivering the interventions) and detection bias.
[3] The quality of the evidence was further downgraded from moderate to very low due to very serious imprecision as 95%CI crossed two default MIDs
[4] The median survival time for all patients was 5.2 months [95% confidence interval (CI), 2 to 24.6 months] in the standard arm and 7.2 months (95% CI, 2.9 to 21.5 months) in the group receiving low-dose therapy. Survival did not differ significantly between the two groups (P = 0.47).
[5] From data provided by the authors about this outcome, is not possible estimate the precision in the effect size estimates.

I.17.5 5-FU versus combination 5-FU

Table 98: Full GRADE profile for FU versus combination 5-FU in adults with metastatic pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	5-FU alone *versus* 5-FU combination chemotherapy	Control	Relative (95% CI)	Absolute		
Overall response rate (CR + PR)												
2[1,2]	randomised trials	serious[3]	serious[4]	no serious indirectness	no serious imprecision	none	12/157 (7.6%)	1/162 (0.62%)	RR 8.62 (1.57 to 47.22)	47 more per 1000 (from 4 more to 285 more)	LOW	CRITICAL
Overall response rate (CR + PR) - 5-FU + doxorubicin + cisplatin												
1[1]	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	2/59 (3.4%)	1/64 (1.6%)	RR 2.17 (0.2 to 23.31)	18 more per 1000 (from 13 fewer to 349 more)	VERY LOW	CRITICAL
Overall response rate (CR + PR) - 5-FU + cisplatin												
1	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	very serious[6]	none	10/98 (10.2%)	0/98 (0%)	RR 21 (1.25 to 353.49)	-	VERY LOW	CRITICAL
Progression Free Survival - 5-FU + cisplatin												
1[2]	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.55 (0.41 to 0.74)	-	MODERATE	CRITICAL

Overall Survival												
2[3]	randomised trials	serious	no serious inconsistency	no serious indirectness	serious[8]	none	-	-	HR 0.97 (0.79 to 1.2)	-	LOW	CRITICAL
Grade 3/4 toxicities: Nausea - 5-FU + doxorubicin + cisplatin												
1[1]	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	13/59 (22%)	3/64 (4.7%)	RR 4.7 (1.51 to 10.91)	173 more per 1000 (from 24 more to 465 more)	LOW	CRITICAL
Grade 3/4 toxicities: Vomiting												
2[1,2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	25/156 (16%)	7/164 (4.3%)	RR 3.75 (1.73 to 7.32)	117 more per 1000 (from 31 more to 270 more)	MODERATE	CRITICAL
Grade 3/4 toxicities: Vomiting - 5-FU + doxorubicin + cisplatin												
1[1]	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	serious[13]	none	9/59 (15.3%)	3/64 (4.7%)	RR 3.25 (0.94 to 8.78)	105 more per 1000 (from 3 fewer to 365 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities: Vomiting - 5-FU + cisplatin												
1[2]	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	16/97 (16.5%)	4/100 (4%)	RR 4.12 (1.49 to 9.52)	125 more per 1000 (from 20 more to 341 more)	MODERATE	CRITICAL
Grade 3/4 toxicities: Diarrhoea - 5-FU + cisplatin												

1[2]	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	very serious[6]	none	5/97 (5.2%)	2/100 (2%)	RR 2.57 (0.51 to 11.15)	31 more per 1000 (from 10 fewer to 203 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities: Leukopoenia - 5-FU + doxorubicin + cisplatin												
1[1]	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	31/59 (52.5%)	20/64 (31.3%)	RR 1.68 (1.11 to 2.23)	212 more per 1000 (from 34 more to 384 more)	LOW	CRITICAL
Grade 3/4 toxicities: Stomatitis												
2[1,2]	randomised trials	serious[3]	very serious[9]	no serious indirectness	very serious[6]	none	16/156 (10.3%)	14/164 (8.5%)	RR 1.2 (0.6 to 2.27)	17 more per 1000 (from 34 fewer to 108 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities: Stomatitis - 5-FU + doxorubicin + cisplatin												
1[1]	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	3/59 (5.1%)	9/64 (14.1%)	RR 0.36 (0.09 to 1.22)	90 fewer per 1000 (from 128 fewer to 31 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities: Stomatitis - 5-FU + cisplatin												
1	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	serious[13]	none	13/97 (13.4%)	5/100 (5%)	RR 2.68 (1.01 to 6.23)	84 more per 1000 (from 0 more to 262 more)	LOW	CRITICAL

[1] *Cullinan et al., 1990*
[2] *Ducreux et al., 2002*
[3] *The quality of the evidence was downgraded because of the unclear risk of selection bias and performance bias in pooled studies*
[4] *Serious heterogeneity. I-squared = 40%*
[5] *The quality of the evidence was downgraded because of the unclear risk of selection bias and the high risk of performance bias (no blinding of patients/ care providers delivering the interventions).*
[6] *The quality of the evidence was downgraded due to very serious imprecision as 95%CI crossed two default MIDs*
[7] *The quality of the evidence was downgraded because of the unclear risk of selection bias and performance bias (no details given in the text to ascertain these criteria)*
[8] *The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant.*
[9] *Very serious heterogeneity. I-squared = 84%*
[10] *Spitzer's index values assessing quality of life were initially available at 1 and 2 months for 114 patients. Values was missing initially in 16% of patients. Mean index values in the FU group were 7.1 (initially), and 6.6 and 5.9 at 1 and 2 months, respectively (n = 54). For the FUP group values were 7.6, 7.4 and 7.0, respectively (n = 56).*
[11] *The quality of the evidence for this outcome was downgraded because of the high risk of selective reporting of study findings.*
[12] *From data provided by the authors about this outcome, is not possible estimate the precision in the effect size estimates*
[13] *Evidence was downgraded by 1 due to very serious imprecision as 95%CI crossed one default MID*

Table 99: Full GRADE profile for 5-FU versus combination 5-FU in adults with locally advanced or metastatic pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	5-FU alone *versus* 5-FU combination chemotherapy	Control	Relative (95% CI)	Absolute		
Overall response rate (CR + PR)												
2[1,2]	randomised trials	serious[3]	very serious[4]	no serious indirectness	serious[5]	none	19/105 (18.1%)	12/115 (10.4%)	RR 1.7 (0.88 to 3.3)	73 more per 1000 (from 13 fewer to 240 more)	VERY LOW	CRITICAL
Overall response rate (CR + PR) - 5-FU + doxorubicin + mitomycin												
1[1]	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[7]	none	1/13 (7.7%)	3/10 (30%)	RR 0.26 (0.03 to 2.11)	222 fewer per 1000 (from 291 fewer to	VERY LOW	CRITICAL

										333 more)		
Overall response rate (CR + PR) - 5-FU + mitomycin												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	18/92 (19.6%)	9/105 (8.6%)	RR 2.28 (1.08 to 4.83)	110 more per 1000 (from 7 more to 328 more)	MODERATE	CRITICAL
Progression Free Survival - 5-FU + mitomycin												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	-	-	HR 0.81 (0.62 to 1.06)	-	MODERATE	CRITICAL
Overall Survival												
2[1,2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[5]	none	-	-	HR 0.97 (0.79 to 1.20)	-	LOW	CRITICAL
Grade 3/4 toxicities: Diarrhoea - 5-FU + mitomycin												
1[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[7]	none	5/102 (4.9%)	5/107 (4.7%)	RR 1.05 (0.31 to 3.32)	2 more per 1000 (from 32 fewer to 108 more)	LOW	CRITICAL
Grade 3/4 toxicities: Neutropenia - 5-FU + mitomycin												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[7]	none	3/102 (2.9%)	0/107 (0%)	RR 7.34 (0.38 to 140.36)	-	LOW	CRITICAL
Grade 3/4 toxicities: Stomatitis - 5-FU + mitomycin												

1[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[7]	none	11/102 (10.8%)	8/107 (7.5%)	OR 1.5 (0.58 to 3.88)	33 more per 1000 (from 30 fewer to 164 more)	LOW	CRITICAL

[1] *Cullinan et al., 1985*
[2] *Maisey et al., 2002*
[3] *The quality of the evidence was downgraded because of the potential risk of selection bias and performance bias in one pooled study (Cullinan et al., 1985)*
[4] *Very serious heterogeneity. I-squared = 73%*
[5] *The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant.*
[6] *The quality of the evidence was downgraded because of the unclear risk of selection bias and performance bias (no details given in the text to ascertain these criteria)*
[7] *Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs*

I.17.6 Combination 5-FU (FSM) versus other chemotherapy

Table 100: Full GRADE profile for combination 5-FU (FSM) versus other chemotherapy regimens in adults with locally advanced or metastatic pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**5-FU combination chemotherapy (FSM)**	**Control**	**Relative (95% CI)**	**Absolute**		
Overall response rate (CR + PR) - FAM: 5-FU, Adriamycin, mitomycin												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/94 (3.2%)	9/90 (10%)	RR 0.32 (0.09 to 1.14)	68 fewer per 1000 (from 91 fewer to 14 more)	VERY LOW	CRITICAL
Overall response rate (CR + PR) - Mitomycin + 5-FU												

1[4]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	19/70 (27.1%)	5/70 (7.1%)	RR 3.8 (1.5 to 9.61)	200 more per 1000 (from 36 more to 615 more)	LOW	CRITICAL
Overall Survival - FAM: 5-FU, Adriamycin, mitomycin[5]												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision[6]	none	-	-	not estimated[5]	not estimated[5]	LOW	CRITICAL
Overall Survival - Mitomycin + 5-FU[7]												
1[4]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision[6]	none	-	-	not estimated[7]	not estimated[7]	LOW	CRITICAL
Grade 3/4 toxicities: Diarrhoea - Mitomycin + 5-FU												
1[4]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/70 (1.4%)	2/70 (2.9%)	RR 0.50 (0.05-5.39)	14 fewer per 1000 (from 27 fewer to 112 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities: Nausea/vomiting - FAM: 5-FU, Adriamycin, mitomycin												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	15/94 (16%)	12/90 (13.3%)	RR 1.2 (0.59 to 2.41)	27 more per 1000 (from 55 fewer to 188 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities: Nausea/vomiting - Mitomycin + 5-FU												
1[4]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[8]	none	29/70 (41.4%)	18/70 (25.7%)	RR 1.61 (0.99 to 2.62)	157 more per 1000 (from 3 fewer to 417 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities: Leukopenia - FAM: 5-FU, Adriamycin, mitomycin												

1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[8]	none	12/94 (12.8%)	24/90 (26.7%)	RR 0.48 (0.26 to 0.9)	139 fewer per 1000 (from 27 fewer to 197 fewer)	VERY LOW	CRITICAL
Grade 3/4 toxicities: Leukopenia - Mitomycin + 5-FU												
1[4]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	9/70 (12.9%)	11/70 (15.7%)	RR 0.82 (0.36 to 1.85)	28 fewer per 1000 (from 101 fewer to 134 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities: Thrombocytopenia - FAM: 5-FU, Adriamycin, mitomycin												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[8]	none	20/94 (21.3%)	33/90 (36.7%)	RR 0.58 (0.36 to 0.93)	154 fewer per 1000 (from 26 fewer to 235 fewer)	VERY LOW	CRITICAL
Grade 3/4 toxicities: Thrombocytopenia - Mitomycin + 5-FU												
1[4]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	10/70 (14.3%)	16/70 (22.9%)	RR 0.62 (0.31 to 1.28)	87 fewer per 1000 (from 158 fewer to 64 more)	VERY LOW	CRITICAL
Drug-related deaths - Mitomycin + 5-FU												
1[4]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/70 (1.4%)	4/70 (5.7%)	RR 0.25 (0.03 to 2.18)	43 fewer per 1000 (from 55 fewer to 67 more)	VERY LOW	CRITICAL

1 *[1] Oster et al., 1986*
2 *[2] The quality of the evidence was downgraded because of the unclear risk of selection bias and performance bias (no details given in the text to ascertain these criteria), and*
3 *likely selective reporting of study findings/outcomes*
4 *[3] The quality of the evidence was downgraded due to very serious imprecision as 95%CI crossed two default MIDs*
5 *[4] Bukowski et al., 1983*

[5] *Overall survival did not differ significantly between the treatments (median, 18.3 weeks on FSM; 26.4 weeks on FAM; P = 0.21).*
[6] *From data provided by the authors about this outcome, is not possible estimate the precision in the effect size estimates.*
[7] *no differences between groups (Median survival (wks, measurable and non measurable disease): SFM= 18-21, MF=17-18)*
[8] *The quality of the evidence was downgraded due to serious imprecision as 95%CI crossed one default MID*

I.17.75 Intra-arterial chemotherapy versus systemic chemotherapy

Table 101: Full GRADE profile for intra-arterial chemotherapy versus systemic chemotherapy in adults with locally advanced or metastatic pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intra-arterial chemotherapy	Control (systemic chemotherapy)	Relative (95% CI)	Absolute		
Overall response rate (CR + PR)												
3[1,2,3]	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30/98 (30.6%)	6/83 (7.2%)	RR 2.76 (1.23-6.18)	180 more per 1000 (from 41 more to 487 more)	LOW	CRITICAL
Overall Survival												
1[2]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[6]	none	-	-	HR 1.02 (0.63 to 1.66)	-	LOW	CRITICAL
Grade 3/4 toxicities - Trombocytopenia												
1[2]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	17/71 (23.9%)	1/67 (1.5%)	RR 16.04 (2.2 to 117.24)	224 more per 1000 (from 18 more to	MODERATE	CRITICAL

										1000 more)		
Grade 3/4 toxicities - Nausea/vomiting												
1[2]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[7]	none	0/71 (0%)	3/67 (4.5%)	RR 0.13 (0.01 to 2.56)	39 fewer per 1000 (from 44 fewer to 70 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities - Diarrhoea												
1[2]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[7]	none	0/71 (0%)	2/67 (3%)	RR 0.19 (0.01 to 3.86)	24 fewer per 1000 (from 30 fewer to 85 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities - Leukopenia												
1[2]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[8]	none	14/71 (19.7%)	5/67 (7.5%)	RR 2.64 (1.01 to 6.94)	122 more per 1000 (from 1 more to 443 more)	LOW	CRITICAL

[1] Aigner et al., 1998
[2] Cantore et al., 2004
[3] Ji et al., 2003
[4] The quality of the evidence was downgraded because of the unclear risk of selection bias in two studies (Aigner et., 1998 and Ji 2003), the potential risk of performance bias (no blinding of patients/ care providers delivering the interventions) and detection bias all studies included in the meta-analysis.
[5] The quality of the evidence was downgraded because of the unclear risk of performance bias (no blinding of patients/ care providers delivering the interventions) and detection bias (no blinding of investigators/outcome assessors).
[6] The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant.
[7] The quality of the evidence was downgraded due to very serious imprecision as 95%CI crossed two default MIDs
[8] The quality of the evidence was downgraded due to serious imprecision as 95%CI crossed one default MID

I.17.81 Chemotherapy versus chemotherapy and prophylactic anticoagulant

Table 102: Full GRADE profile for gemcitabine versus gemcitabine and weight-adjusted dalteparin in adults with locally advanced or metastatic pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GEM alone chemotherapy +	Novel agent + gemcitabine	Relative (95% CI)	Absolute		
Overall Survival												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision[1,4]	none	-	-	-[3]	-	MODERATE	CRITICAL
Adverse effects: Grade 3/4 toxicities - Haematological												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[5]	none	21/57 (36.8%)	25/59 (42.4%)	RR 0.87 (0.55 to 1.37)	55 fewer per 1000 (from 191 fewer to 157 more)	VERY LOW	CRITICAL
Adverse effects: Grade 3/4 toxicities - Hepatic function impairment												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[5]	none	19/57 (33.3%)	18/59 (30.5%)	RR 1.09 (0.64 to 1.86)	27 more per 1000 (from 110 fewer to 262 more)	VERY LOW	CRITICAL

[1] Maraveyas et al., 2012

[2] The quality of the evidence was downgraded because of the unclear risk of performance bias (no blinding of patients/ care providers delivering the interventions). Furthermore

due to unclear risk of selective outcome reporting and potential risk of detection bias, the quality of the evidence was further downgraded to moderate.
[3] Median OS was 9.7 months for GEM and 8.7 months for GEMWAD (p = 0.682)
[4] From data provided by the authors about this outcome, is not possible estimate the precision in the effect size estimates.
[5] The quality of the evidence was further downgraded from moderate to low due to very serious imprecision as 95%CI crossed two default MIDs

Table 103: Full GRADE profile for gemcitabine and enoxaparin versus gemcitabine in adults with locally advanced or metastatic pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GEM combination chemotherapy	Novel agent + GEM combination	Relative (95% CI)	Absolute		
Progression Free Survival												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	-	-	HR 1.06 (0.84 to 1.34)	-	LOW	CRITICAL
Overall Survival												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	-	-	HR 1.1 (0.87 to 1.39)	-	LOW	CRITICAL
Adverse effects: vascular thromboembolism (VTE) - Symptomatic VTE												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	10/160 (6.3%)	22/152 (14.5%)	RR 0.43 (0.21 to 0.88)	82 fewer per 1000 (from 17 fewer to 114 fewer)	MODERATE	CRITICAL
Adverse effects: vascular thromboembolism (VTE) - Major hemorrhages												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	13/160 (8.1%)	10/152 (6.6%)	RR 1.24 (0.56 to 2.73)	16 more per 1000 (from 29	VERY LOW	CRITICAL

										fewer to 114 more)		

[1] *Pelzer et al., 2015*
[2] *The quality of the evidence was downgraded because of the high risk of performance bias (no blinding of patients/ care providers delivering the interventions) and the unclear risk of detection bias (no details about the blinding of outcome assessors)*
[3] *The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant.*
[4] *The quality of the evidence was further downgraded from moderate to low due to very serious imprecision as 95%CI crossed two default MIDs*

I.17.97 Second-line chemotherapy versus best supportive care

Table 104: Full GRADE profile for second-line chemotherapy versus best supportive care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Chemotherapy (second-line) *versus* BSC**	**Control**	**Relative (95% CI)**	**Absolute**		
Progression Free Survival												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	-	-	HR 0 (0.57 to 1.01)	-	LOW	CRITICAL
Overall Survival												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	-	-	HR 0.85 (0.66 to 1.09)	-	LOW	CRITICAL
Grade 3/4/5 adverse effects - Asthenia/fatigue												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	12/141 (8.5%)	11/145 (7.6%)	RR 1.12 (0.51 to 2.46)	9 more per 1000 (from 37 fewer to 111 more)	VERY LOW	CRITICAL
Grade 3/4/5 adverse effects - Abdominal pain												

1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	11/141 (7.8%)	13/145 (9%)	RR 0.87 (0.4 to 1.88)	12 fewer per 1000 (from 54 fewer to 79 more)	VERY LOW	CRITICAL
Grade 3/4/5 adverse effects - Anaemia												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	7/141 (5%)	3/145 (2.1%)	RR 2.4 (0.63 to 9.1)	29 more per 1000 (from 8 fewer to 168 more)	VERY LOW	CRITICAL
Grade 3/4/5 adverse effects - Vomiting												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	7/141 (5%)	2/145 (1.4%)	RR 3.6 (0.76 to 17.03)	36 more per 1000 (from 3 fewer to 221 more)	VERY LOW	CRITICAL
Grade 3/4/5 adverse effects - Nausea												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	6/141 (4.3%)	2/145 (1.4%)	RR 3.09 (0.63 to 15.03)	29 more per 1000 (from 5 fewer to 194 more)	VERY LOW	CRITICAL
Grade 3/4/5 adverse effects - Deep vein thrombosis												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	5/141 (3.5%)	1/145 (0.69%)	RR 5.14 (0.61 to 43.46)	29 more per 1000 (from 3 fewer to 293 more)	VERY LOW	CRITICAL
Grade 3/4/5 adverse effects - Renal failure												

1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	5/141 (3.5%)	0/145 (0%)	RR 11.31 (0.63 to 202.65)	-	VERY LOW	CRITICAL
Grade 3/4/5 adverse effects - Hyperbilirubinemia												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	4/141 (2.8%)	2/145 (1.4%)	RR 2.06 (0.38 to 11.05)	15 more per 1000 (from 9 fewer to 139 more)	VERY LOW	CRITICAL
Grade 3/4/5 adverse effects - Leukopenia												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	4/141 (2.8%)	0/145 (0%)	RR 9.25 (0.5 to 170.31)	-	VERY LOW	CRITICAL

[1] *Ciuleanu et al., 2009*
[2] *The quality of the evidence was downgraded because of the unclear risk of selection bias and the potential risk of performance bias (no blinding of patients/ care providers)*
[3] *The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant.*
[4] *The quality of the evidence was further downgraded from moderate to low due to very serious imprecision as 95%CI crossed two default MIDs*

I.17.10 Second-line chemotherapy versus other chemotherapy regimens

Table 105: Full GRADE profile for LV5FU2-CDDP then gemcitabine versus gemcitabine then LV5FU2-CDDP in adults with metastatic pancreatic cancer

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LV5FU2-CDDP followed by gemcitabine**	**GEM followed by LV5FU2-CDDP**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Overall response rate (CR + PR)												

1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	19/102 (18.6%)	22/100 (22%)	RR 0.85 (0.49 to 1.47)	33 fewer per 1000 (from 112 fewer to 103 more)	LOW	CRITICAL
Progression free-survival												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	-	-	HR 1.06 (0.80 to 1.40)	-	MODERATE	CRITICAL
Overall survival												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	-	-	HR 0.97 (0.73 to 1.79)	-	MODERATE	CRITICAL
Grade 3/4 toxicities: Nausea/vomiting												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	14/102 (13.7%)	15/100 (15%)	RR 0.92 (0.47 to 1.8)	12 fewer per 1000 (from 80 fewer to 120 more)	LOW	CRITICAL

[1] *Dahan et al., 2010*
[2] *Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs*
[3] *The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant.*

Table 106: Full GRADE profile for irinotecan and raltitrexed versus raltitrexed in adults with metastatic pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Irinotecan + raltitrexed	Raltitrexed alone	Relative (95% CI)	Absolute		

Objective response												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/19 (0%)	3/19 (15.8%)	RR 0.14 (0.01 to 2.59)	136 fewer per 1000 (from 156 fewer to 251 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities - Leukocytopenia												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/19 (26.3%)	4/19 (21.1%)	RR 1.25 (0.4 to 3.95)	53 more per 1000 (from 126 fewer to 621 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities - Neutropenia												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/19 (21.1%)	3/19 (15.8%)	RR 1.33 (0.34 to 5.17)	52 more per 1000 (from 104 fewer to 658 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities - Thrombocytopenia												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/19 (0%)	0/19 (0%)	-	-	VERY LOW	CRITICAL
Grade 3/4 toxicities - Nausea/vomiting												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/19 (5.3%)	1/19 (5.3%)	RR 1 (0.07 to 14.85)	0 fewer per 1000 (from 49 fewer to 729 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities - Stomatitis												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/19 (0%)	0/19 (0%)	-	-	VERY LOW	CRITICAL

Grade 3/4 toxicities - Fatigue												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/19 (0%)	0/19 (0%)	-	-	VERY LOW	CRITICAL
Grade 3/4 toxicities - Diarrhoea												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/19 (10.5%)	2/19 (10.5%)	RR 1 (0.16 to 6.38)	0 fewer per 1000 (from 88 fewer to 566 more)	VERY LOW	CRITICAL

[1] *Ulrich-Pur et al., 2003*
[2] *The quality of the evidence was downgraded because of the unclear risk of performance bias (no details given about the blinding of patients/ care providers delivering the interventions), besides the unclear risk of detection bias (no details given in the text)*
[3] *Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs*
[5] *The quality of the evidence was downgraded because of the unclear risk of performance bias and the unclear risk of detection bias (no details given in the text), besides the potential risk of selective findings reporting for this outcome..*
[6] *From data provided by the authors about this outcome, it was not possible estimate the precision in the effect size estimates.*

Table 107: GRADE Profile 10.2: Second-line chemotherapy versus other (LV5FU2-CDDP then gemcitabine versus gemcitabine followed by LV5FU2-CDDP)

Quality assessment							**No of patients**		**Effect**			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LV5FU2-CDDP followed by gemcitabine**	**GEM followed by LV5FU2-CDDP**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Overall response rate (CR + PR)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	19/102 (18.6%)	22/100 (22%)	RR 0.85 (0.49 to 1.47)	33 fewer per 1000 (from 112 fewer to 103 more)	LOW	CRITICAL

Progression free-survival												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	-	-	HR 1.06 (0.80 to 1.40)	-	MODERATE	CRITICAL
Overall survival												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	-	-	HR 0.97 (0.73 to 1.79)	-	MODERATE	CRITICAL
Grade 3/4 toxicities: Nausea/vomiting												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	14/102 (13.7%)	15/100 (15%)	RR 0.92 (0.47 to 1.8)	12 fewer per 1000 (from 80 fewer to 120 more)	LOW	CRITICAL

[1] *Dahan et al., 2010*
[2] *Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs*
[3] *The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant.*

Table 108: Full GRADE profile for Oxaliplatin and 5-FU versus bolus 5-FU and bolus folinic acid in adults with locally advanced or metastatic pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oxaliplatin + 5-FU**	**Bolus leucovorin + bolus 5-FU**	**Relative (95% CI)**	**Absolute**		
Overall response rate (CR + PR)												

1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/24 (12.5%)	2/24 (8.3%)	RR 1.5 (0.27 to 8.19)[4]	42 more per 1000 (from 61 fewer to 599 more)	VERY LOW	CRITICAL
Progression Free Survival[5]												
1[1]	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision[6]	none	-	-	not estimated[5]	not estimated[5]	LOW	CRITICAL
Overall Survival[5]												
1[1]	randomised trials	very serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision[6]	none	-	-	not estimated[5]	not estimated[5]	LOW	CRITICAL
Grade 3/4 toxicities - Diarrhoea												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/24 (20.8%)	5/24 (20.8%)	RR 1 (0.33 to 3.01)	0 fewer per 1000 (from 140 fewer to 419 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities - Nausea/vomiting												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/24 (16.7%)	3/24 (12.5%)	RR 1.33 (0.33 to 5.33)	41 more per 1000 (from 84 fewer to 541 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities - Stomatitis												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/24 (4.2%)	1/24 (4.2%)	RR 1 (0.07 to 15.08)	0 fewer per 1000 (from 39 fewer to 587 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities - Hematological												

1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/24 (12.5%)	2/24 (8.3%)	RR 1.5 (0.27 to 8.19)	42 more per 1000 (from 61 fewer to 599 more)	VERY LOW	CRITICAL

[1] *Azmy et al., 2013*
[2] *The quality of the evidence was downgraded because of the unclear risk of detection bias (no details given in the text to ascertain these criteria) and the high risk of performance bias (no blinding of patients/ care providers delivering the interventions).*
[3] *Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs*
[4] *No complete response in both groups*
[5] *There was no statistical significance in progression-free survival between the 2 regimens (p value by log rank test = .4619),and so was the situation in overall survival (p-value by log rank test = .5248).*
[6] *From data provided by the authors about this outcome., is not possible estimate the precision in the effect size estimates*
[7] *The quality of the evidence was downgraded because of the unclear risk of detection bias (no details given in the text to ascertain these criteria), the high risk of performance bias (no blinding of patients/ care providers delivering the interventions), and the potential risk of selective reporting of findings for this outcome.*

Table 109: Full GRADE profile for mFOLFOX6 versus 5-FU and folinic acid in adults with locally advanced or metastatic pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**MFOLFOX6**	**Leucovorin/5-FU**	**Relative (95% CI)**	**Absolute**		
Overall response rate (CR + PR)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	7/54 (13%)	5/54 (9.3%)	RR 1.4 (0.47 to 4.14)	37 more per 1000 (from 49 fewer to 291 more)	VERY LOW	CRITICAL
Progression Free Survival												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[5]	none	-	-	HR 1 (0.66 to 1.52)	-	LOW	CRITICAL

Overall Survival												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 1.78 (1.08 to 2.93)	-	MODERATE	CRITICAL
Grade 3/4 toxicities - Neutropenia												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	16/49 (32.7%)	2/53 (3.8%)	RR 8.65 (2.1 to 35.72)	289 more per 1000 (from 42 more to 1000 more)	MODERATE	CRITICAL
Grade 3/4 toxicities - Febrile neutropenia												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/49 (4.1%)	0/53 (0%)	RR 5.4 (0.27 to 109.76)	-	VERY LOW	CRITICAL
Grade 3/4 toxicities - Fatigue												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[5]	none	7/49 (14.3%)	1/53 (1.9%)	RR 7.57 (0.97 to 59.34)	124 more per 1000 (from 1 fewer to 1000 more)	LOW	CRITICAL
Grade 3/4 toxicities - Thrombocytopenia												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/49 (8.2%)	1/53 (1.9%)	RR 4.33 (0.5 to 37.39)	63 more per 1000 (from 9 fewer to 687 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities - Dehydration												

1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/49 (8.2%)	0/53 (0%)	RR 9.72 (0.54 to 176)	-	VERY LOW	CRITICAL
Grade 3/4 toxicities - Pulmonary embolism												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/49 (4.1%)	0/53 (0%)	RR 5.4 (0.27 to 109.76)	-	VERY LOW	CRITICAL
Grade 3/4 toxicities - Vomiting												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/49 (4.1%)	0/53 (0%)	RR 5.4 (0.27 to 109.76)	-	VERY LOW	CRITICAL
Grade 3/4 toxicities - Hypokalemia												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/49 (4.1%)	0/53 (0%)	RR 5.4 (0.27 to 109.76)	-	VERY LOW	CRITICAL
Grade 3/4 toxicities - Peripheral neuropathy												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/49 (4.1%)	0/53 (0%)	RR 5.4 (0.27 to 109.76)	-	VERY LOW	CRITICAL
Health Related Quality of Life												
1[1]	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	no estimable[6]	none	-	-	No significant differences were observed in time to deterioration on the EORTC QLQ-C30 global	-	LOW	CRITICAL

									health scale.			

[1] *Gill et al., 2016*
[2] *The quality of the evidence was downgraded because of the unclear risk of selection bias (no details given in the text about methods of allocation) and potential risk of performance bias (open-label trial)*
[3] *Evidence was downgraded by 2 due to very serious imprecision as 95%CI crossed two default MIDs*
[4] *The quality of the evidence was downgraded because of the unclear risk of selection bias (no details given in the text about methods of allocation), potential risk of performance bias (open-label trial) and the high risk of selective reporting of study findings for this outcome.*
[5] *The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs. Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant.*
[6] *From data provided by the authors about this outcome., is not possible estimate the precision in the effect size estimates.*

Table 110: Full GRADE profile for for capecitabine and erlotinib then gemcitabine versus gemcitabine and erlotinib then capecitabine in adults with locally advanced or metastatic pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Capecitabine + erlotinib followed by gemcitabine	GEM + erlotinib followed by capecitabine	Relative (95% CI)	Absolute		
Overall response rate (CR + PR)												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/63 (3.2%)	5/77 (6.5%)	RR 0.49 (0.1 to 2.29)	33 fewer per 1000 (from 58 fewer to 84 more)	VERY LOW	CRITICAL
Overall survival												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	-	-	HR 1.02 (0.79 to 1.32)	-	LOW	CRITICAL
Grade 3/4 toxicities - Nausea/vomiting												

1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	7/62 (11.3%)	10/77 (13%)	RR 0.87 (0.35 to 2.15)	17 fewer per 1000 (from 84 fewer to 149 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities - Diarrhoea												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/62 (0%)	3/77 (3.9%)	RR 0.18 (0.01 to 3.36)	32 fewer per 1000 (from 39 fewer to 92 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities - Leucocytopenia												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/62 (3.2%)	4/77 (5.2%)	RR 0.62 (0.12 to 3.28)	20 fewer per 1000 (from 46 fewer to 118 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities - Thrombocytopenia												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/62 (3.2%)	5/77 (6.5%)	RR 0.5 (0.1 to 2.47)	32 fewer per 1000 (from 58 fewer to 95 more)	VERY LOW	CRITICAL

1 *[1] Heinemann et al., 2012*
2 *[2] The quality of the evidence was downgraded because of the high risk of detection bias (no masking of investigators/outcome assessors) and the high risk of performance bias*
3 *(no blinding of patients/ care providers delivering the interventions).*
4 *[3] The quality of the evidence was downgraded due to very serious imprecision as 95%CI crossed two default MIDs*
5 *[4] The committee decided to consider all survival outcomes that were statistically significant, regardless of whether the 95% confidence interval crossed the default MIDs.*
6 *Survival outcomes were therefore downgraded for imprecision by one level only if they were not statistically significant.*

Table 111: Full GRADE profile for 5-FU and folinic acid versus oxaliplatin and 5-FU in adults with locally advanced or metastatic pancreatic cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FA + 5-FU	Oxaliplatin + 5-FU	Relative (95% CI)	Absolute		
Progression Free Survival												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.68 (0.49 to 0.94)	-	MODERATE	CRITICAL
Overall Survival												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.66 (0.48 to 0.91)	-	MODERATE	CRITICAL
Grade 3/4 toxicities - Anaemia												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/76 (3.9%)	2/84 (2.4%)	RR 1.66 (0.28 to 9.66)	16 more per 1000 (from 17 fewer to 206 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities - Nausea/emesis												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/76 (1.3%)	3/84 (3.6%)	RR 0.37 (0.04 to 3.47)	23 fewer per 1000 (from 34 fewer to 88 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities - Paresthesia												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/76 (3.9%)	0/84 (0%)	RR 7.73 (0.41 to 147.21)	-	VERY LOW	CRITICAL

Grade 3/4 toxicities - Pain												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	24/76 (31.6%)	34/84 (40.5%)	RR 0.78 (0.51 to 1.19)	89 fewer per 1000 (from 198 fewer to 77 more)	VERY LOW	CRITICAL
Grade 3/4 toxicities - Leukopenia												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/76 (0%)	0/84 (0%)	-	-	VERY LOW	CRITICAL
Grade 3/4 toxicities - Thrombocytopenia												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/76 (1.3%)	0/84 (0%)	RR 3.31 (0.14 to 80.09)	-	VERY LOW	CRITICAL
Grade 3/4 toxicities - Diarrhoea												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/76 (1.3%)	0/84 (0%)	RR 3.31 (0.14 to 80.09)	-	VERY LOW	CRITICAL

1 *[1] Oettle et al., 2014*
2 *[2] The quality of the evidence was downgraded because of the unclear risk of detection bias (no details given in the text to ascertain these criteria) and the high risk of*
3 *performance bias (no blinding of patients/ care providers delivering the interventions).*
4 *[3] The quality of the evidence was downgraded due to very serious imprecision as 95%CI crossed two default MIDs*

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