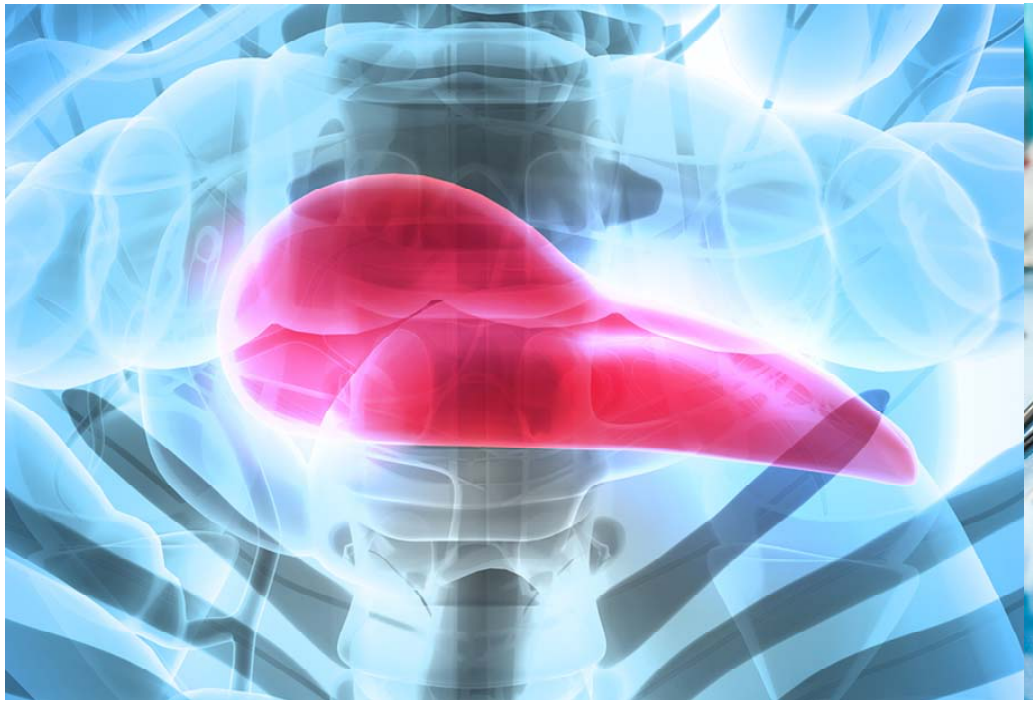
KCE REPORT 286

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

MANAGEMENT OF PANCREATIC CANCER – PART 3: NEOADJUVANT AND INDUCTION THERAPY



KCE REPORT 286
GOOD CLINICAL PRACTICE

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MANAGEMENT OF PANCREATIC CANCER – PART 3: NEOADJUVANT AND INDUCTION THERAPY

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse event
CI	Confidence interval
CRT	Chemoradiotherapy
DFS	Disease free survival
FLEC	5-FU, leucovorin, carboplatin, epirubicin
FOLFIRINOX	Folinic acid (leucovirin), fluorouracil (5-FU), irinotecan, oxaliplatin
FU	Fluorouracil
GDG	Guideline development group
HR	Hazard ratios
KCE	Belgian health care knowledge centre
LAPC	Locally advanced pancreatic cancer
OS	Overall survival
PC	Pancreatic cancer
PFS	Progression free survival
P.I.C.O.	Population-intervention-comparator-outcome
QoL	Quality of life
RCT	Randomised controlled trial
RoB	Risk of bias
RQ	Research question
RR	Risk ratio
S-1	Tegafur/gimeracil/oteracil
SR	Systematic review
yrs	Years

SCIENTIFIC REPORT

1 INTRODUCTION

This chapter addresses neoadjuvant treatment in patients with pancreatic cancer (PC). A tumour is resectable when the surgeon considers that it can be removed entirely. Resectable tumours include stages IA, IB and IIA of the TNM system,[1] i.e. lesions confined to the pancreas or having spread just outside the pancreas without invading major blood vessels, nerves or lymph nodes. There is however no absolute link between resectability and TNM classification since even a small local tumour can invade the surrounding vasculature. Borderline resectable cancer involves stage III that may be considered resectable by the surgeon. Locally advanced pancreatic cancer (LAPC) and metastatic cancer are considered unresectable. However, attempts may be made to resect LAPC, especially after chemotherapy, then called induction therapy.

This chapter covers one main research question (RQ) divided into three sub-questions:

Is neoadjuvant treatment with chemotherapy, radiotherapy or both, followed by surgery, associated with better survival, resectability, quality of life (QoL) and complication rate compared to no neoadjuvant treatment?

- RQa: In patients with resectable pancreatic cancer?
- RQb: In patients with borderline resectable pancreatic cancer?
- RQc: In patients diagnosed with LAPC, does induction treatment with chemotherapy, radiotherapy or both, lead to surgery and is it associated with better survival, resectability, QoL and complication rate compared to any other type of treatment?

The following P.I.C.O.s were considered:

Table 1 – RQ a & b

Is neoadjuvant treatment with chemotherapy, radiotherapy or both, followed by surgery, associated with better survival, resectability, QoL and complication rate compared to no neoadjuvant treatment? in patients with resectable pancreatic cancer? in patients with borderline resectable pancreatic cancer?	
P	patients with pancreas cancer: a: resectable, b: borderline resectable
I	neoadjuvant chemotherapy, radiotherapy or both
C	upfront surgery and adjuvant therapy for groups a and b systemic therapy only for group b
O	per subgroup and definition: OS, disease free survival (DFS), QoL, resection rate and R0 resections, adverse events (AE)

Table 2 – RQ c

For patients diagnosed with LAPC, is induction treatment with chemotherapy, radiotherapy or both, followed by surgery, associated with better survival, resectability, QoL and complication rate compared to any other type of treatment	
P	patients with LAPC
I	induction with chemotherapy, radiotherapy or both
C	surgery or systemic therapy (any other type of therapy)
O	OS, DFS, QoL, resection rate and R0 resections, AEs

2 SELECTING STUDIES AND QUALITY APPRAISAL

2.1 Selection of systematic reviews

On May 9, 2016 a search was performed in MEDLINE, Embase and The Cochrane Library (from 2008 onwards) to identify systematic reviews (SR) regarding the effect of neoadjuvant chemotherapy, radiotherapy or chemoradiotherapy followed by surgery in patients with resectable, borderline resectable or LAPC. In total, 758 studies were identified. After deduplication, 588 potentially relevant references remained (Figure 3). Based on title and abstract 548 references were excluded. Of the remaining 40 articles, 10 were suitable for inclusion (Table 3) and 30 were excluded with reason Table 7. Three reviews addressed patients with resectable PC,[2-4] two addressed patients with borderline resectable PC[5, 6] and five reviews were directed to the treatment of patients with locally advanced PC.[7-11]

Table 3 – Possible included SRs (n= 10)

Reference	Search date	In- and exclusion criteria	Interventions
Resectable PC			
D'Angelo 2015[2]	September 2015	Randomized controlled trials (RCT) published in English addressing adjuvant and neoadjuvant treatment of resectable PC. Studies had to report the protocols per study arm, inclusion/exclusion criteria and survival outcomes. RCTs were excluded if a protocol, overall survival results, mean age and number of patients per arm were not reported or if they included other than PC histologies, locally advanced/unresectable and metastatic disease.	Adjuvant and neoadjuvant chemotherapy, radiotherapy or both vs upfront surgery (amongst others)
Liu 2016[3]	November 2014	RCTs, two-arm prospective studies or retrospective studies. Studies had to address patients with resectable or borderline resectable pancreatic adenocarcinoma who had undergone either surgery alone or neo-adjuvant chemoradiation followed by surgery Exclusion criteria: reviews, protocols, letters, comments, editorials, case reports, proceedings, personal communications, and single-arm studies; unresectable pancreatic adenocarcinoma; studies that compared treatments other than surgery and neo-adjuvant CRT; absence of quantitative outcomes or incomplete data for analysis.	Neoadjuvant chemoradiotherapy vs upfront surgery
Xu 2014[4]	July 2013	RCTs, phase I–II clinical trials, published in English or Chinese Patients with histologically proven resectable PC or periampullary cancer, who were assigned to radiotherapy combined with chemotherapy Studies without a surgical intervention, not reporting survival outcomes or without a control group were excluded	Neoadjuvant chemoradiotherapy vs upfront surgery
Borderline resectable PC			
Festa 2013[5]	September 2012	Prospective studies regarding preoperative chemotherapy or chemoradiotherapy in patients with borderline resectable PC, carried out according to predefined protocols, approved by institutional boards Retrospective studies, reports of identical patient cohorts, and reports available only in abstract form, studies from which separate results from patients with different stages of disease were not retrievable, studies regarding intraoperative radiotherapy and studies without information regarding pancreatic resection rates were excluded.	Neoadjuvant chemotherapy or chemoradiotherapy (no RCTs or comparative observational studies were identified)
Tang 2016[6]	February 2015	Prospective studies regarding preoperative chemotherapy or chemoradiotherapy in patients with borderline resectable PC, carried out according to predefined protocols, approved by institutional boards	Neoadjuvant chemotherapy or chemoradiotherapy (no RCTs or comparative observational studies were identified)

Reference	Search date	In- and exclusion criteria	Interventions
		Retrospective studies, reports of identical patient cohorts, and reports available only in abstract form, studies from which separate results were not retrievable and studies without information regarding pancreatic resection rates were excluded.	
LAPC			
Chen 2013[7]	October 2012	RCTs addressing radiotherapy and/or chemotherapy in patients with histologically confirmed locally advanced PC judged as nonresectable due to extension to regional lymph nodes and/or vascular structures, no surgical treatment or other anti-tumour therapies before enrollment; survival as main endpoint with a follow-up of at least 6 months. Exclusion criteria: patients with metastatic PC or relapse after antitumor treatment; patients who had previously received surgical treatment; patients with non-LAPC; non-prospective and non-randomized/non-controlled studies; other interventions were applied in addition to radiotherapy and chemotherapy; only local efficacy was evaluated - no data on survival available; low-quality studies with a Jadad score <2.	Chemoradiotherapy vs chemotherapy
Chin 2017 (Protocol published as Nagrial 2013)[8, 12]	September 2015 – Updated June 30, 2016	Studies that analysed patients with pancreatic ductal adenocarcinoma, who were of locally advanced or metastatic stage with a randomised trial design, in which overall survival was an endpoint (Analyses in patients with LAPC presented separately.)	Chemotherapy, biological agents, immunotherapy, radiotherapy, alone or in combination compared with best supportive care or with each other.
Huguet 2009[9]	September 2008	Meta-analyses, systematic reviews, and phase III RCTs or, if not identified, phase II or retrospective studies. Patients with unresectable locally advanced nonmetastatic pancreatic adenocarcinoma, treated with radiotherapy or chemoradiotherapy. Exclusion criteria: studies addressing neuroendocrine pancreatic carcinomas or studies including patients with a previous incomplete resection and/or who received adjuvant treatment and/or who presented with recurrent disease.	Chemoradiotherapy versus best supportive care, radiotherapy or chemotherapy (including addition of induction chemotherapy to chemoradiotherapy and various modalities of chemoradiotherapy).
Suker 2016[10]	July 2015	Studies of treatment naïve patients who received FOLFIRINOX as first-line treatment for locally advanced PC, irrespective of subsequent other treatment. Exclusion criteria: studies that used a regimen other than FOLFIRINOX, used FOLFIRINOX in combination with other chemotherapy at the same time, if FOLFIRINOX was not being investigated as first-line treatment; studies that did not include patients with locally advanced PC, if the study was a review or if the same patient cohort was presented in another study	FOLFIRINOX vs other interventions (NB: only 1 RCT was included)
Zhu 2011[11]	December 2010	RCTs or other comparative studies in patients with LAPC who had not received prior chemotherapy or radiotherapy; overall survival as primary outcome	Gemcitabine-based chemoradiotherapy vs 5-FU-based chemoradiotherapy

2.2 Selection of primary studies

For RQa (resectable PC) the RCTs that addressed patients with resectable PC and that were included in the SRs (n=3) were cross-checked (Table 4). It was decided to process those RCTs further (instead of summarising the respective reviews) and to update the search from 2015 onwards. For RQb (borderline resectable PC), no RCT or non-randomised comparative study was identified in any of the included SRs. The searches for primary studies were also updated from 2015 onwards.

On July 13, 2016 a search was performed in MEDLINE, Embase and CENTRAL to identify RCTs and comparative observational studies regarding the effect of neoadjuvant therapy in patients with resectable or borderline resectable PC and published from January 1, 2015 onwards. In total 1135 potentially relevant references were identified (Figure 4).

After deduplication, 782 references remained. Based on title and abstract 716 references were excluded. Of the remaining 66 references, one considering patients with borderline resectable PC was included[13] (Table 5) and 65 were excluded with reason (Table 8). Thus, for the comparison 'neoadjuvant therapy followed by surgery vs upfront surgery' no new studies were identified that addressed patients with resectable PC. The one comparative observational study that was identified addressed patients with borderline resectable PC (Table 5). Six other studies did address this comparison, but these were excluded, because they either excluded patients in the neoadjuvant group who had not undergone subsequent surgery or excluded those patients from the analyses (Table 8).[14-19]

Table 4 – Included RCTs regarding RQa (resectable PC) (n= 3)

	Definition of resectability	Interventions
Casadei 2015[20]	"Tumors were considered resectable in all cases in which there were no distant metastases and there was less than 180° maximal involvement of the superior mesenteric and portal veins with clear fat planes around the celiac axis, hepatic artery, and superior mesenteric artery. In particular, the involvement of the superior mesenteric/portal vein was graded according to the Ishikawa classification and only grades ranging from 0 to 2 were considered resectable."	Preoperative chemoradiotherapy (initial gemcitabine followed by combined chemoradiotherapy with conventional radiotherapy and gemcitabine) vs upfront surgery.
Golcher 2015[21]	"Resectability was defined as no organ infiltration except the duodenum and maximal involvement of peripancreatic vessels ≤180°confirmed by high resolution CT. At exploration, distant metastases had to be ruled out. Local resectability was assessed and in case of vascular tumor infiltration the decision to resect the tumor with adjacent vessels was completely left to the surgeon and the individual situation."	Preoperative chemoradiotherapy (gemcitabine and cisplatin on days 1, 8, 22 and 29 of radiotherapy) vs upfront surgery.
Palmer 2007[22]	"Patients with tumor surrounding >180° of the circumference of the portal or superior mesenteric vein, or direct tumor extension to either the superior mesenteric artery or the coeliac axis, or with evidence of extrapancreatic disease were considered nonresectable."	Preoperative chemotherapy with gemcitabine plus cisplatin vs preoperative chemotherapy with gemcitabine alone

Table 5 – Included comparative observational study regarding RQb (borderline resectable PC) (n= 1)

Reference	Definition of borderline resectability	Interventions
Masui 2016[13]	"The diagnosis was based on our modified criteria of superior mesenteric artery (SMA) or common hepatic artery (CHA) abutment and either tumor encasement of a short segment of the hepatic artery or tumor abutment of the SMA involving less than 180° of the vessel circumference."	Preoperative chemotherapy with gemcitabine and oral Tegafur/gimeracil/oteracil (S-1) vs upfront surgery

For RQc (LAPC) the RCTs included in the SRs addressing patients with LAPC were cross-checked. Because the ongoing (and available) Cochrane review of Chin and colleagues[8] was up-to-date, no update for new RCTs was performed. The RCTs that were selected from the reviews (n= 5), are presented in Table 6.

Table 6 – Included RCTs regarding RQc (LAPC) (n= 5)

Reference	Definition of locally advanced PC / non-resectability	Interventions
Cantore 2004[23]	"Histologically-proven adenocarcinoma of the pancreas not suitable for curative resection" and "absence of peritoneal metastases". No further details provided.	Chemotherapy with FLEC (5-FU, leucovorin, carboplatin and epirubicin) vs chemotherapy with gemcitabine
Chauffert 2008[24]	Histologically proven ductal adenocarcinoma of the pancreas, no distant metastases. "Tumors were judged as nonresectable due to extension to regional lymph nodes and/or vascular structures such as the superior mesenteric artery or the celiac trunk or the existence of a portal or superior mesenteric–portal venous confluent thrombosis."	Chemoradiotherapy with 5-FU and cisplatin vs chemotherapy with gemcitabine, both with maintenance treatment with gemcitabine
Chung 2004[25]	Histologically proven pancreatic adenocarcinoma. "Unresectability was judged by the following criteria: involvement of the superior mesenteric arteries or celiac axis, and occlusion of the portal or superior mesenteric vein."	Chemoradiotherapy with gemcitabine and doxifluridine vs chemoradiotherapy with paclitaxel and doxifluridine, both followed by operation or chemotherapy with gemcitabine and doxifluridine
Mukherjee 2013 / Hurt 2015[26, 27]	Histologically or cytologically proven, locally advanced, nonmetastatic, inoperable (or operable but medically unfit for surgery) PC with a tumour diameter of ≤7 cm. In addition: "Patients were eligible for random allocation if they had responding or stable disease after three cycles of induction gemcitabine and capecitabine; tumour diameter of ≤6 cm; WHO PS 0–1; adequate haematological, liver, and renal function and less than 10% weight loss from baseline."	Induction chemotherapy with gemcitabine and capecitabine. If eligible for randomisation: further cycle of gemcitabine and capecitabine, followed by chemoradiotherapy in combination with with capecitabine (group 1) or gemcitabine (group 2)
Wilkowsky 2009[28]	Histologically confirmed, non-resectable pancreatic cancer (stages III and IVA). "Non-resectability criteria included at least one of the following CT findings: nodal involvement; retroperitoneal infiltration; infiltration of the arteria mesenterica superior, vena mesenterica superior, arteria hepatica, or portal vein. At least one bi-dimensionally measurable lesion had to be present."	Chemoradiotherapy with gemcitabine and cisplatin with concurrent radiotherapy (1) vs chemoradiotherapy with gemcitabine and cisplatin with concurrent radiotherapy followed by sequential full-dose gemcitabine and cisplatin (2) vs chemoradiotherapy with 5-FU with concurrent radiotherapy (reference)

2.3 Assessment of risk of bias

The risk of bias assessments of the three included RCTs with regard to resectable PC (RQa) are summarised in Figure 5. All studies scored high risk of performance bias and detection bias for subjective outcomes. Concealment of allocation was unclear in one study,[22] unclear selective reporting was observed in another study[20] and in two studies the risk of other bias was unclear.[20, 21]

The risk of bias assessment of the one included comparative observational study with regard to borderline resectable PC (RQb) is summarised in Figure 6.[13] The study scored high risk of selection bias, performance bias and detection bias for subjective outcomes. Comparability of the treatment groups could not be assessed, because it was not reported.

The risk of bias assessments of the five included RCTs with regard to LAPS (RQc) are summarised in Figure 7.[23-28] All studies scored high or unclear risk of performance bias and detection bias for subjective outcomes. Concealment of allocation was unclear in three studies,[24, 25, 28] unclear risk of attrition bias was observed in another study[25] and in one study the risk of other bias was unclear.[24]

3 EVIDENCE DESCRIPTION

For more detail, evidence tables can be found in the appendix (Table 9,Table 10,Table 11). Grade profiles of the individual outcomes are also provided insection 5.4.

3.1 RQa: What is the clinical effectiveness of neoadjuvant treatment with chemotherapy, radiotherapy or both, followed by surgery in patients with resectable PC?

3.1.1 Neoadjuvant chemoradiotherapy followed by surgery vs upfront surgery

Two RCTs were included that addressed the effectiveness of neoadjuvant chemoradiotherapy (CRT) followed by surgery versus upfront surgery in patients with resectable PC.[20, 21] No studies regarding the effect of only neoadjuvant radiotherapy or chemotherapy were identified.

The first study included 38 patients with histologically proven resectable pancreatic adenocarcinoma aged 18 to 80 years without previous pancreatic resection or PC.[20] In the intervention group 18 patients were treated with CRT followed by surgery. The other 20 patients underwent upfront surgery. CRT consisted of initial gemcitabine for 6 weeks followed by gemcitabine combined with radiotherapy for 6 weeks. Surgical treatment consisted of pancreaticoduodenectomy or total pancreatectomy according to Whipple. In both groups adjuvant chemotherapy was recommended. The study was stopped early due to low accrual rate (intended sample size 32 patients per treatment arm). The study was considered high risk of bias for subjective outcomes due to lack of blinding and risk of detection bias.

The second study assessed the effectiveness of neoadjuvant CRT with gemcitabine/cisplatin and surgery versus immediate surgery.[21] Patients with resectable, histologically or cytologically proven adenocarcinoma of the pancreatic head were included. In the intervention group 33 patients received gemcitabine and cisplatin on days 1, 8, 22 and 29 of radiotherapy. In the control group 33 patients were treated with surgery. The study was stopped early due to low accrual rate.

The intended sample size was 127 patients per treatment arm. The study was considered high risk of bias for subjective outcomes due to lack of blinding and risk of detection bias.

Disease-free survival

Both studies addressed disease-free survival (DFS), but only the second study reported the results. Median disease-free survival was 13.7 vs 12.1 months (p= 0.83).[21]

Overall survival

Median overall survival (OS) was 22.4 (10.2–34.6) vs 19.5 (7.5–31.5) months in one study (P= 0.97) and 17.4 vs 14.4 months in the other (P= 0.96). In the last study, 31/33 vs 29/33 patients died (risk ration (RR) = 1.07; 95% confidence interval (CI) 0.92 to 1.95), whereas the total number of deaths was not reported in the other study.

Progression-free survival

In one study median time to progression was 8.4 vs 8.7 months (p= 0.95).[21]

Quality of life

No study did address this outcome.

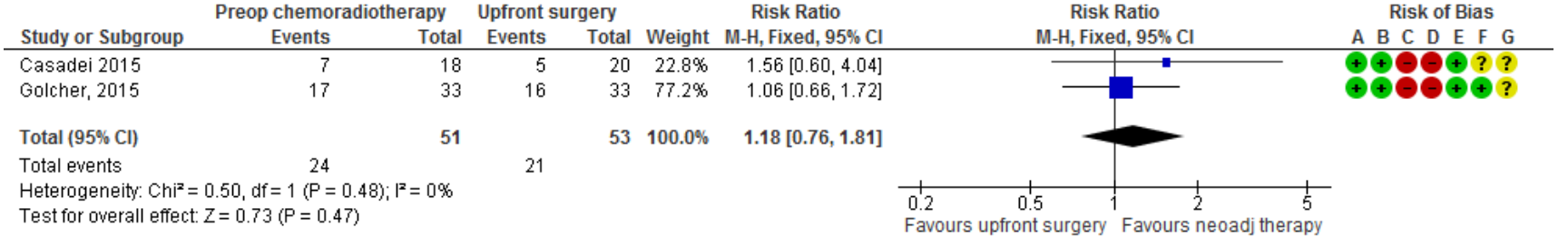
Resectability

In the first study pancreatic resections were performed in 11/18 (61%) vs 15/20 (75%) patients and in the second study in 19/33 (58%) vs 23/33 (70%). The pooled RR was 0.82 (95% CI 0.62 to 1.09) (Figure 1). R0 resections occurred in 7/18 (39%) vs 5/20 (25%) and in 17/33 (52%) vs 16/33 (48%), respectively. The pooled RR was 1.18 (95% CI 0.76 to 1.81) (Figure 2).

Figure 1 – Forest plot and risk of bias plot for resection rates after neoadjuvant CRT vs upfront surgery in patients with resectable PC

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

Figure 2 – Forest plot and risk of bias plot for R0 resections after neoadjuvant CRT vs upfront surgery in patients with resectable PC



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

Adverse events

In the first study 'post-treatment morbidity' occurred in 10/18 (56%) vs 9/20 (45%) patients (RR= 1.23; 95% CI 0.65 to 2.33) and post-treatment mortality in 1/18 (6%) vs 2/20 (10%) (RR= 0.56; 95% CI 0.05 to 5.62). In the first study severe grade ≥3 acute toxicity occurred in 7/18 (39%) in the CRT group and in 15/33 (46%) in the second study.

3.1.2 Neoadjuvant chemotherapy vs another type of neoadjuvant chemotherapy (both followed by surgery)

One RCT compared two types of neoadjuvant chemotherapy in patients with clinical and radiological evidence of cancer of the head of pancreas that was considered to be resectable on CT scan and suitable for surgical exploration.[22] The first group (26 patients) received preoperative chemotherapy with gemcitabine plus cisplatin while the other group (24 patients) received preoperative chemotherapy with gemcitabine alone. The study was closed after a second planned review of the data by an independent data monitoring committee (the intended sample size was 35 patients per treatment arm). The study was considered high risk of bias for subjective outcomes due to lack of blinding and risk of detection bias.

Disease-free survival

This outcome was not addressed.

Overall survival

Median OS was 15.6 vs 9.9 months. At 12 months 10/26 patients in the combined group (38%) had died compared to 14/24 (58%) in the gemcitabine alone group (RR= 0.66; 95% CI 0.36 to 1.19). During the whole study period these numbers were 15/26 (58%) and 19/24 (79%), respectively (RR= 0.73; 95% CI 0.49 to 1.07).

Progression-free survival

This outcome was not addressed.

Quality of life

This outcome was not addressed.

Resectability

Pancreatic resection was performed in 18/26 patients (69%) in the combined group compared to 9/24 (38%) in the gemcitabine alone group (RR= 1.85; 95% CI 1.04 to 3.29). R0 resections occurred in 12/26 (46%) vs 6/24 (25%) patients, respectively (RR= 1.85; 95% CI 0.82 to 4.14).

Adverse events

Haematological toxicity grade 3 or more occurred in 10/26 (38%) vs 9/24 (38%) patients (RR= 1.03; 95% CI 0.50 to 2.08). Four episodes of non-haematological toxicity grade 3 or more occurred in the combined chemotherapy group versus none in the gemcitabine only group. There were no differences with respect to postoperative complications.

3.2 RQb: What is the effect of neoadjuvant treatment with chemotherapy, radiotherapy or both, followed by surgery in patients with borderline resectable PC?

3.2.1 Neoadjuvant chemo(radio)therapy followed by surgery vs upfront surgery

One non-randomised comparative observational study was included.[13] No RCTs were identified for this research question. This phase 2 study included patients with borderline resectable PC and compared 18 patients who were treated with neoadjuvant chemotherapy and 19 patients who denied enrolling in the study and who were treated with upfront resection during the same period. Preoperative CRT consisted of gemcitabine and oral tegafur/gimeracil/oteracil (S-1). The study was considered high risk of bias due to selection bias, performance bias and detection bias (subjective outcomes).

Disease-free survival

This outcome was only reported for the patients in the neoadjuvant group who underwent surgery.

Overall survival

Median OS was 21.7 vs 21.1 months (P= 0.098).

Progression-free survival

This outcome was not addressed. The recurrence rate was 13/18 (72%) vs 16/19 (84%): RR= 0.86 (95% CI 0.61 to 1.21).

Quality of life

This outcome was not addressed.

Resectability

Surgery was performed in 15/18 (83%) vs 19/19 (100%) (RR= 0.84; 95% CI 0.67 to 1.05). The R0 resection rates were 12/18 (67%) vs 10/19 (53%) (RR= 1.27; 95% CI 0.74 to 2.17).

Adverse events

This outcome was not addressed.

3.3 RQc: For patients diagnosed with LAPC, does induction treatment with chemotherapy, radiotherapy or both, lead to surgery and is it associated with better survival, resectability, QoL and complication rate compared to any other type of treatment?

3.3.1 Induction chemotherapy versus another type of induction chemotherapy

One RCT was included that addressed patients with PC not suitable for curative resection and without peritoneal metastases.[23] An intra-arterial regimen of a combination of leucovorin, 5- fluorouracil (FU), carboplatin and epirubicin (FLEC; 71 patients) was compared with gemcitabine administered intravenously (67 patients). The study was considered high risk of performance bias and detection bias (subjective outcomes).

Disease-free survival

This outcome was not addressed.

Overall survival

Median OS was 7.9 vs 5.9 months (P= 0.0361). A multivariate survival analysis (with sex, stage, performance status as covariates) revealed superiority for FLEC (P= 0.010), but the hazard ratio (HR) was not reported.

Progression-free survival

This outcome was not addressed.

Quality of life

This outcome was not addressed.

Resectability

This outcome was not addressed.

Adverse events

At least one grade 3/4 toxicity occurred in 34/71 (48%) vs 15/67 (22%) patients (RR= 2.14; 95% CI 1.29 to 3.55). Compared to gemcitabine the incidence of anaemia (14% vs 2.9%), leukopenia (19.7% vs 7.9%) and thrombocytopenia (25.3% vs 1.4%) was higher for FLEC.

3.3.2 Induction chemoradiotherapy versus induction chemotherapy

One RCT was included that addressed patients with PC with extension to regional lymph nodes and/or vascular structures without distant metastases.[24] Radiotherapy plus concomitant 5-FU and cisplatin (59 patients) was compared with gemcitabine (60 patients). Both groups received maintenance treatment: with gemcitabine until disease progression or excessive toxicity. The study was considered high risk of performance bias and detection bias (subjective outcomes).

Disease-free survival

This outcome was not addressed.

Overall survival

Median OS was 8.6 vs 13.0 months (P= 0.03). The crude HR was 1.45 (99% CI 0.88 to 2.44) and the HR adjusted for stratification criteria and main clinical factors at inclusion was 1.85 (99% CI 1.04 to 3.23) in favour of chemotherapy with gemcitabine.

Progression-free survival

Median Progression-free survival (PFS) was in favour of gemcitabine (P= 0.025), but details were not reported. The HR was 1.39 (99% CI 0.85 to 2.27) and one-year PFS was observed in 8/59 (14%) vs 19/60 (32%) of the patients (RR= 0.43; 95% CI 0.20 to 0.90) in favour of chemotherapy with gemcitabine.

Quality of life

This outcome was not addressed.

Resectability

Secondary surgery was performed in 2/59 (3%) vs 3/60 (5%) patients (RR= 0.68; 95% CI 0.12 to 3.91). R0 resection rates were not reported.

Adverse events

More grade 3/4 overall toxicity was observed in the CRT group: 36/59 (61%) vs 22/60 (37%); RR= 1.66 (95% CI 1.13 to 2.46). This also applied for grade 3/4 haematological toxicity (17/59 (29%) vs 15/60 (25%); RR= 1.15 (95% CI 0.64 to 2.09)) and grade 3/4 non-haematological toxicity (24/59 (41%) vs 10/60 (17%); RR= 2.44 (95% CI 1.28 to 4.65)).

3.3.3 Induction chemoradiotherapy versus another type of induction chemoradiotherapy

Three RCTs with different interventions and treatment schedules addressed this comparison.[25-28]

The first RCT addressed patients with PC with involvement of the superior mesenteric arteries or celiac axis, and/or occlusion of the portal or superior mesenteric vein.[25] Paclitaxel in combination with doxifluridine (24 patients) was compared with gemcitabine in combination with doxifluridine (22 patients). In both groups concomitant radiotherapy was prescribed and after 4-week rest, surgery or continuation with gemcitabine and doxifluridine was provided. The study was considered unclear risk of selection bias (concealment of allocation), performance bias, detection bias (subjective outcomes) and attrition bias.

The second RCT addressed patients with locally advanced, non-metastatic, inoperable PC with a tumour diameter ≤7 cm.[26, 27] All patients received induction chemotherapy with gemcitabine and capecitabine. Patients eligible for randomisation were then treated with a further cycle of gemcitabine and capecitabine, followed by either capecitabine in combination with radiotherapy (36 patients) or gemcitabine in combination with radiotherapy (38 patients). The study was considered high risk of performance bias and detection bias (subjective outcomes).

The third RCT addressed patients with non-resectable PC due to nodal involvement, retroperitoneal infiltration, infiltration of the arteria mesenterica superior, vena mesenterica superior, arteria hepatica or portal vein.[28] Two gemcitabine regimens were compared with 31 patients who received 5-FU with concurrent radiotherapy: gemcitabine and cisplatin with concurrent radiotherapy (32 patients), the same regimen, but followed by sequential full-dose gemcitabine and cisplatin (31 patients). The study was considered unclear risk of selection bias (allocation concealment), performance bias and detection bias (subjective outcomes).

Disease-free survival

This outcome was not addressed in any of the studies.

Overall survival

In the first two RCTs median OS was 14 vs 12 months (P= 0.951) and 15.2 vs 13.4 months (P= 0.025), respectively, in favour of the non-gemcitabine regimens. At one year the RR of death was 0.75 (95% CI 0.39 to 1.46) and 0.53 (95% CI 0.24 to 1.16), respectively. In the second study the HR was 0.50 (95% CI 0.27 to 0.93) in favour of the non-gemcitabine regimen.

In the third RCT no significant differences were observed between the three groups for median OS (9.3 vs 7.3 vs 9.6 months; P= 0.61), risk of death at 9 months (48% vs 55% vs 42%; P= 0.61) or at 18 months (89% vs 78% vs 89%; P-value not reported).

Progression-free survival

In the first two RCTs median PFS did not differ significantly between the groups (12.5 vs 12.0 months (P= 0.541) and 12.0 vs 10.4 months (P= 0.102), respectively). In the second study the HR was 0.64 (95% CI 0.37 to 1.09).

In the third RCT no significant differences were observed between the three groups for median PFS (5.6 vs 6.0 vs 4.0 months; P= 0.21).

Quality of life

This outcome was only addressed in the second study. [26, 27] No significant differences between the groups were observed for QLQ-C30 scores at week 23 (immediately after completion of CRT) (P= 0.14; n=48) or changes in scores from week 17 (time of randomisation / before chemoradiation treatment) to week 23 (P= 0.13; n=45). According to the authors “Differences in changes in HRQL scores between trial arms rarely reached statistical significance; however, where they did, they favored capecitabine therapy.” and “The median change between week 17 [the point of randomisation] and later time points was never worse in the Cap-CRT arm than in the Gem-CRT arm.”

Resectability

In the first study surgery was performed in 2/24 (8%) vs 1/22 (5%) of the patients (RR= 1.83; 95% CI 0.18 to 18.84) with a R0 resection rate of 2/24 (8%) vs 0/22 (0%) (RR= 4.60; 95% CI 0.23 to 90.84).

In the second study surgery was performed in 2/36 (6%) vs 3/38 (8%) (RR= 0.70; 95% CI 0.12 to 3.97), and all were R0 resections.

In the third study the secondary resection rates were 25% vs 19% vs 13%. R0 resection rates were not reported per study arm, but overall 8 of 18 patients who underwent surgery, had a R0 resection.

Adverse events

In the first RCT few grade 3/4 haematological or non-haematological toxicities were observed (“Toxicities were acceptable in both groups”).

In the second study, any grade 3/4 toxicity occurred less often in the capecitabine group (RR= 0.32; 95% CI 0.12 to 0.88) compared to the gemcitabine group. This also applied to the situation when toxicities were subdivided into any haematological grade 3/4 toxicity (RR= 0.07; 95% CI 0.00 to 1.25) and any non-haematological grade 3/4 toxicity (RR= 0.45; 95% CI 0.15 to 1.29), but due to the low number of events these differences were not significant.

In the third study more acute haematological grade 3/4 toxicities (anaemia, leukocytopaenia and thrombocytopaenia; upper and lower GI tract toxicities) occurred after both gemcitabine / cisplatin regimens compared to the 5-FU regimen. Of the non-haematological grade 3/4 toxicities the gemcitabine / cisplatin regimen followed by sequential full-dose gemcitabine and cisplatin had the least fatigue and infection without neutropaenia. Nausea was most observed in the gemcitabine / cisplatin only group. The occurrence of weight loss, diarrhoea and febrile neutropaenia was similar in all groups.

4 CONCLUSIONS, OTHER CONSIDERATIONS AND RECOMMENDATIONS

4.1 Conclusions

Conclusions regarding resectable PC

- In patients with resectable PC a difference in DFS, OS, PFS, resection rate, R0 resections or adverse effects between preoperative CRT versus upfront surgery could neither be demonstrated nor refuted ((very) low level of evidence).
- No RCTs or comparative observational studies could be identified that compared QoL of preoperative CRT with upfront surgery in patients with resectable PC.
- Severe grade ≥3 toxicity occurs in 39% to 46% of the patients with resectable PC who were treated with neoadjuvant CRT.
- In patients with resectable PC a difference in OS, R0 resections or grade 3 or more haematological AEs between preoperative neoadjuvant therapy with gemcitabine plus cisplatin versus gemcitabine alone could neither be demonstrated nor refuted ((very) low level of evidence).
- There is evidence of low quality that preoperative neoadjuvant therapy with gemcitabine plus cisplatin results in larger resection rates compared to gemcitabine alone in patients with resectable PC (low level of evidence).
- No RCTs or comparative observational studies could be identified that compared DFS, PFS or QoL of preoperative neoadjuvant therapy with gemcitabine plus cisplatin versus gemcitabine alone in patients with resectable PC.

Conclusions regarding borderline resectable PC

- In patients with borderline resectable PC a difference in OS, PFS (recurrence rate), resection rate or R0 resections between preoperative chemotherapy and upfront surgery could neither be demonstrated nor refuted (very low level of evidence).
- No RCTs or comparative observational studies could be identified that compared DFS, QoL or AEs of preoperative chemotherapy versus upfront surgery in patients with borderline resectable PC.

Conclusions regarding LAPC

[Chemotherapy vs Chemotherapy]

- There is evidence of moderate quality that induction therapy with intra-arterial FLEC results in longer OS compared to gemcitabine given intravenously in patients with LAPC (moderate level of evidence).
- There is evidence of low quality that induction therapy with intra-arterial FLEC results in more grade 3/4 toxicities compared to gemcitabine given intravenously in patients with LAPC (low level of evidence).
- DFS, PFS, QoL and resectability were not studied in the included RCT.

[CRT vs Chemotherapy]

- There is evidence of moderate quality that induction chemotherapy with gemcitabine results in longer OS compared to CRT with 5-FU and cisplatin in patients with LAPC (moderate level of evidence).
- There is evidence of low quality that induction chemotherapy with gemcitabine results in longer PFS and less grade 3/4 toxicities compared to CRT with 5-FU and cisplatin in patients with LAPC (low level of evidence).
- In patients with LAPC a difference in resection rates between induction chemotherapy with gemcitabine and induction CRT with 5-FU and cisplatin could neither be demonstrated nor refuted (very low level of evidence).
- DFS and QoL were not studied in the included RCT.

[CRT vs CRT]

- There is evidence of moderate quality that induction CRT with paclitaxel plus doxifluridine or gemcitabine plus capecitabine results in longer OS
- compared to induction CRT with gemcitabine with or without doxifluridine in patients with locally advanced PC (moderate level of evidence).
- In patients with LAPC a difference in PFS, QoL, resection rates or R0 resections between induction CRT with paclitaxel plus doxifluridine or gemcitabine plus capecitabine and induction CRT with gemcitabine with or without doxifluridine could neither be demonstrated nor refuted ((very) low level of evidence).
- There is evidence of very low quality that induction CRT with gemcitabine plus capecitabine results in less grade 3/4 toxicities.
- compared to induction CRT with gemcitabine in patients with LAPC (very low level of evidence).
- In patients with LAPC a difference in OS, PFS, resection rates or R0 resections between induction CRT with gemcitabine and cisplatin with or without sequential full-dose gemcitabine and cisplatin compared to induction CRT with 5-FU alone could neither be demonstrated nor refuted (moderate to very low level of evidence).
- There is evidence of low quality that induction CRT with gemcitabine and cisplatin with or without sequential full-dose gemcitabine and cisplatin leads to more haematological grade 3/4 toxicities compared to induction CRT with 5-FU alone in patients with LAPC (low level of evidence).

4.2 Other considerations

Factor	Comment
Balance between clinical benefits and harms	*In general:* The Guideline Development Group (GDG) underlined that study populations are difficult to define and that 'resectable' and 'borderline resectable' often overlap. Therefore study populations are heterogeneous, limiting their applicability in guideline recommendations. The diagnosis 'borderline' needs to be made by experts in the field. Portal vein involvement often allows resection whereas arterial involvement precludes resection and necessitates chemotherapy. Members of the GDG warned against delaying curative resection by neoadjuvant therapy. Only one comparative observational study on preoperative chemotherapy with gemcitabine and oral S-1 vs upfront surgery in borderline resectable PC could be identified. [13] We searched for evidence, based on the SR by Chin 2017 [8], however did not retrieve studies on radiotherapy. In clinical practice the effect of chemotherapy given to patients with borderline resectable tumours is evaluated after 6 to 8 weeks of treatment. The intention of chemotherapy in LAPC patients is not to bring the patient to surgery since LAPC is by definition considered not resectable. The standard of care is chemotherapy. The body of analysed literature described chemotherapy regimens that are considered outdated by the experts. A recent trial (LAP07) [29] was excluded because it reports on a biological (erlotinib) and because our RQ was intended to search for evidence on the use of induction therapy to render a pancreatic cancer resectable. The LAP07 trial has a complex design in which patients were first randomised to gemcitabine or gemcitabine + erlotinib (a biological). Good responders were subsequently randomised to a continuation of the same medical treatment or chemoradiotherapy. The intention was to demonstrate the added value of radiotherapy but the primary endpoint was not reached. Data that were of interest for our RQ were the number of patients that became resectable after the first part of the trial. Although this was not an endpoint of this trial, it was reported that 6 out of a total of 442 underwent a curative-intent surgery after the first part of the trial. These patients were excluded from participation of the second part of the trial, and no further data were reported on them (e.g. about their survival).. The GDG stressed that neoadjuvant chemotherapy is not indicated for LAPC within the strict definition that LAPC is not resectable. The conclusion on intra-arterial therapy (FLEC) was considered obsolete in Belgium and did therefore not qualify for a recommendation. The conclusions on chemotherapy regimens (paclitaxel plus doxifluridine or gemcitabine plus capecitabine) for LAPC were considered outdated by the GDG and not considered for recommendation. The validators pointed out that despite the lack of evidence from comparative studies, there is a strong signal in favour of FOLFIRINOX for the treatment of LAPC [10, 30]
Quality of evidence	Very low to low for recommendation 1, no evidence for recommendation 2, very low for recommendations 3 and 4
Costs (resource allocation)	Cost was in general not considered in this guideline. Although according the GDG, neoadjuvant treatment in patients with borderline resectable PC can be either chemotherapy or CRT, it can be expected that the cost of CRT is higher than chemotherapy alone.
Patients preferences	Patient organisations were consulted in a Stakeholder meeting (see section 5.5) They underlined the importance of open communication and information on benefits and harms in adapted language. The GDG also stressed that in decision making regarding neoadjuvant therapy each patient needs to be discussed individually and potential benefits and risks need to be balanced carefully. Kom op tegen Kanker pointed out that better outcomes can be expected in more experienced centers. Patient organisations further underline the need to be allowed to seek a second opinion. Given the poor prognosis of PC the need for research need to be brought to public attention.

4.3 Recommendations

Recommendation	Level of Evidence	Strength of recommendation
1. Neoadjuvant chemotherapy is not recommended for resectable PC.	very low to low	strong
2. Neoadjuvant chemotherapy for resectable PC is recommended only in the context of a clinical trial.	NA	strong
3. Neoadjuvant chemotherapy for borderline resectable PC should be considered.	very low	strong
4. Chemotherapy or radiotherapy with the intention to bring the patient to surgery is not recommended for LAPC (clearly not resectable).	very low	strong

5 APPENDIX

5.1 STUDY SELECTION

Figure 3 – Study flow of selection of SRs

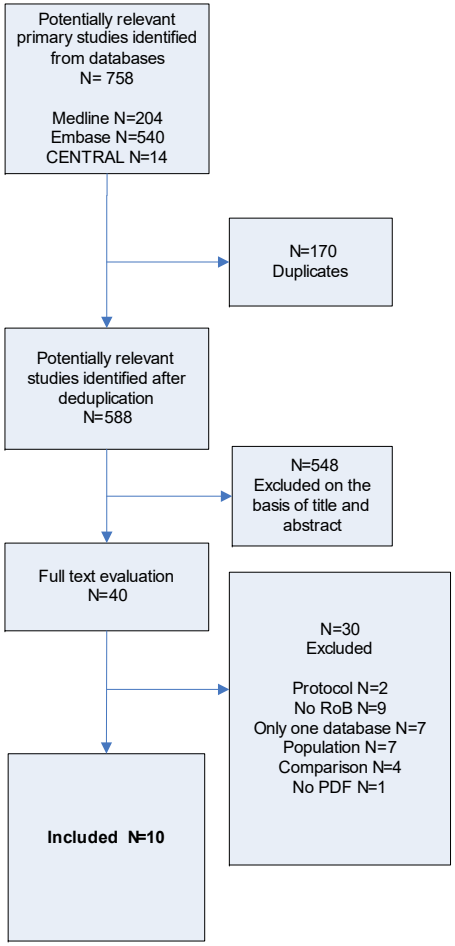


Figure 4 – Study flow of selection of RCTs or comparative observational studies regarding resectable and borderline resectable PC

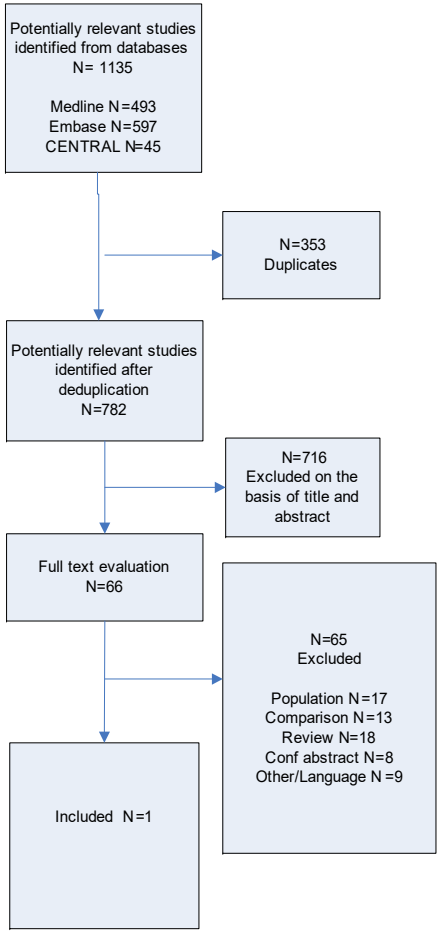


Table 7 – Excluded SRs (n= 30)

Reference	Reasons
Ambe 2015[31]	No quality assessment
Andriulli 2012[32]	Searched only MEDLINE
Assifi 2011[33]	No quality assessment
Azria 2008[34]	No PDF
Cao 2010[35]	Comparison not of interest. No quality assessment
Cao 2015[36]	Searched only PubMed
Chan 2014[37]	Mixture of patients with LAPC and metastatic PC
Chua 2011[38]	Searched only MEDLINE. No quality assessment.
Ciliberto 2013[39]	Mixture of patients with LAPC and metastatic PC. No quality assessment on study level
Gillen 2010[40]	No quality assessment on study level
Gresham 2014[41]	Trials had to include >50% patients with metastatic PC
Gurusamy 2014[42]	Intervention not of interest
Heinemann 2008[43]	Searched only PubMed
Hu 2011[44]	Mixture of patients with LAPC and metastatic PC. Searched only PubMed. No quality assessment
Keane 2014[45]	No quality assessment
Kristensen 2016[46]	Mixture of patients with LAPC and metastatic PC. No quality assessment
Laurence 2011[47]	No quality assessment
Lee 2016[48]	Protocol for a systematic review
Li 2016[49]	Mixture of patients with LAPC and metastatic PC
Morganti 2010[50]	Comparisons not of interest
Petrelli 2015[51]	No quality assessment
Ren 2012[52]	Adjuvant therapy after resection
Sultana 2014[53]	Protocol for a Cochrane review
Sun 2012[54]	Mixture of patients with LAPC and metastatic PC
Tsvetkova 2014[55]	Searched only PubMed. No quality assessment.
Tu 2015[56]	No quality assessment.

Verma 2016[57]	Searched only MEDLINE. No quality assessment. Invalid analysis.
Yang 2013[58]	Mixture of patients with LAPC and metastatic PC. No quality assessment
Yang 2015[59]	No quality assessment on study level (NB: patients with LAPC only; no RCTs identified)
Zygogianni 2011[60]	Searched only PubMed. No quality assessment.

Table 8 – Excluded primary studies regarding research question a (resectable PC) and b (borderline resectable PC) (n= 65)

Reference	Reasons
Andre 2015[61]	Conference abstract
Badiyan 2016[62]	Mixed population: patients with borderline resectable PC and LAPC, but not presented or analysed separately
Blazer 2015[63]	Not a comparative study
Cloyd 2016[64]	Mixed population: patients with resectable PC, borderline resectable PC and LAPC, but not presented or analysed separately
Collins 2015[65]	Systematic review
Cooper 2015[66]	Mixed population: patients with resectable PC, borderline resectable PC and LAPC, but not presented or analysed separately
D'Angelo 2016[2]	Systematic review
Ducreux 2015[67]	Guideline
Ettrich 2015[68]	Conference abstract
Evans 2015[69]	Opinion paper
Fathi 2015[70]	Opinion paper
Ferrone 2015[14]	Selection of patients based on having undergone surgery (i.e. patients who had received neoadjuvant therapy which was not followed by surgery were excluded)
Fujii 2016 [15]	Selection of patients based on having undergone surgery (i.e. patients who had received neoadjuvant therapy which was not followed by surgery were excluded)
Godhi 2015[71]	Letter to the editor
Gong 2016[72]	Systematic review
Hackert 2016a[73]	Patients with LAPC; selection of patients based on having undergone surgery (i.e. patients who had received neoadjuvant therapy which was not followed by surgery were excluded from the analysis)
Hackert 2016b[74]	Non-systematic review
Hammel 2016[29]	Patients with LAPC
Heestand 2015[75]	Non-systematic review

Herman 2015[76]	Patients with LAPC – not a comparative study
Hirono 2016[16]	Patients who had progressive disease after neoadjuvant therapy, were excluded
Hozaeel 2015[77]	Conference abstract
Huguet 2015[78]	Non-systematic review
Kennoki 2016[79]	Not a comparative study
Khushman 2015[80]	Patients with LAPC – not a comparative study
Lee 2015a[17]	Patients in the neoadjuvant group undergoing and not undergoing surgery were analysed separately
Lee 2015b[81]	Not a comparative study
Lee 2016[48]	Protocol for a systematic review
Li 2015[82]	Non-systematic review
Liu 2016[3]	Systematic review
Marthey 2015[83]	Patients with LAPC – not a comparative study
Matsukawa 2015[84]	Article in Japanese
Mellon 2015[85]	No comparison of interventions (outcomes of patients with borderline resectable PC were compared with those of patients with LAPC)
Miura 2015[86]	No comparison of interventions (outcomes of patients with resectable PC were compared with those of patients with borderline resectable PC)
Motoi 2015[87]	Conference abstract in Japanese (PDF not available)
Murakami 2016[88]	Adjuvant therapy
Nanda 2015[89]	Not a comparative study
Nitsche 2015[90]	Not a comparative study
Nywening 2016[91]	Intervention not of interest
Paik 2015[92]	Not a comparative study
Petrelli 2015[51]	Systematic review
Pietrasz 2015[93]	Not a comparative study
Pross 2015[94]	Non-systematic review
Rashid 2016[95]	Not a comparative study
Ravikumar 2015[96]	Editorial comment
Rocha 2015[97]	Conference abstract

Roeder 2016[98]	Review (PDF not available)
Roland 2015[18]	Non-randomised study in patients with resectable PC. Selection of patients in principle valid, but results in the neoadjuvant treatment group were only presented for those who had received surgery. In addition, for RQ2a RCTs regarding the same comparison were already included.
Russo 2016[99]	Review (PDF not available)
Sajjad 2016[100]	Patients with LAPC
Sano 2015[101]	Not a comparative study
Sho 2015[19]	Selection of patients based on having undergone surgery (i.e. patients who had received neoadjuvant therapy which was not followed by surgery were excluded)
Shafi 2015[102]	Conference abstract
Silvestris 2016[103]	Non-systematic review
Suker 2016[10]	Systematic review
Takahashi 2015[104]	Reply to comment
Tang 2016[6]	Systematic review
Ueno 2016[105]	Patients with advanced PC refractory to first-line treatment with gemcitabine
Unno 2015[106]	Conference abstract
Van Vliet 2015[107]	Patients with neuroendocrine tumours
Verma 2016[57]	Systematic review
Versteijne 2016[108]	Protocol for a RCT in patients with (borderline) resectable patients (trial ID NTR3709)
Winner 2015[109]	Opinion paper
Wong 2016[110]	Review (PDF not available)
Yanagimoto 2015[111]	Conference abstract

5.2 CRITICAL APPRAISAL

Figure 5 – Risk of bias summary of RCTs regarding RQa (resectable PC)

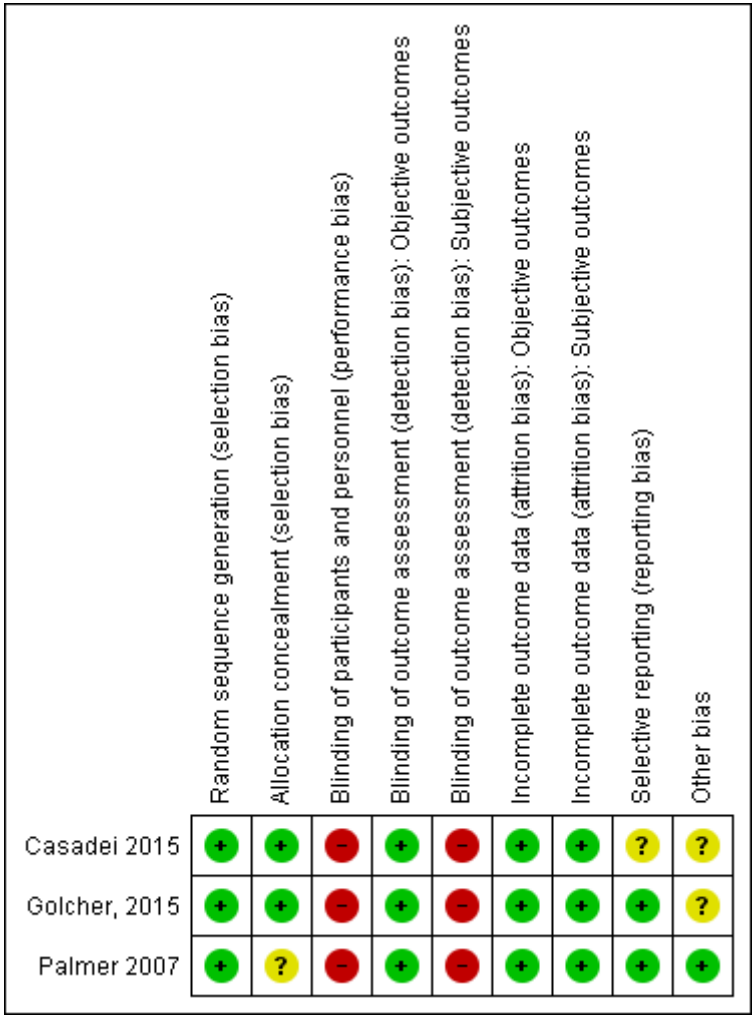


Figure 6 – Risk of bias summary of the comparative observational study regarding RQb (borderline resectable PC)

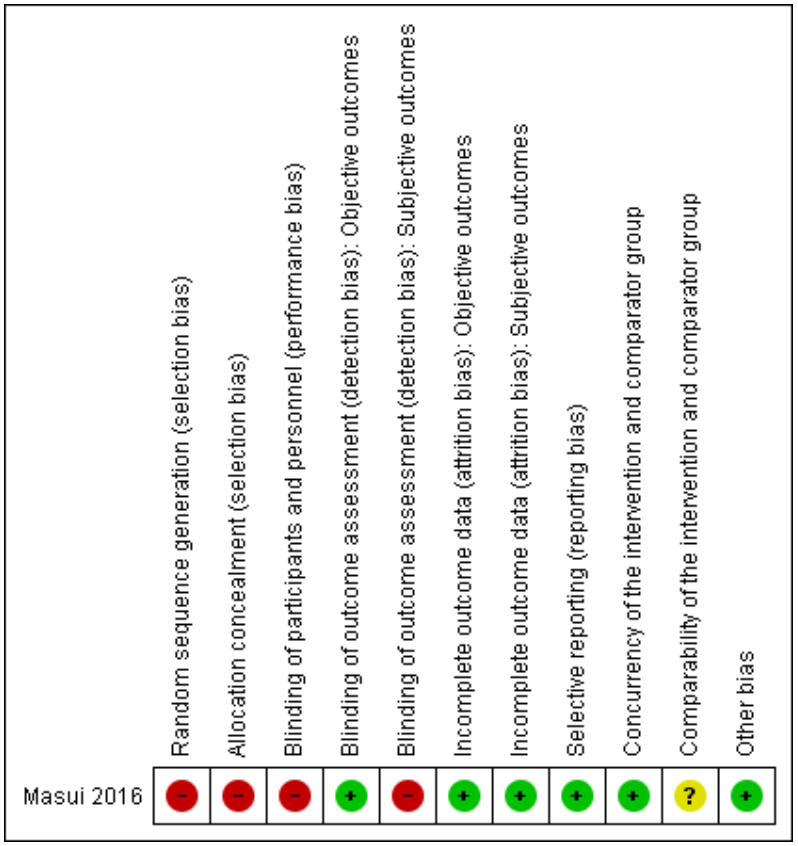
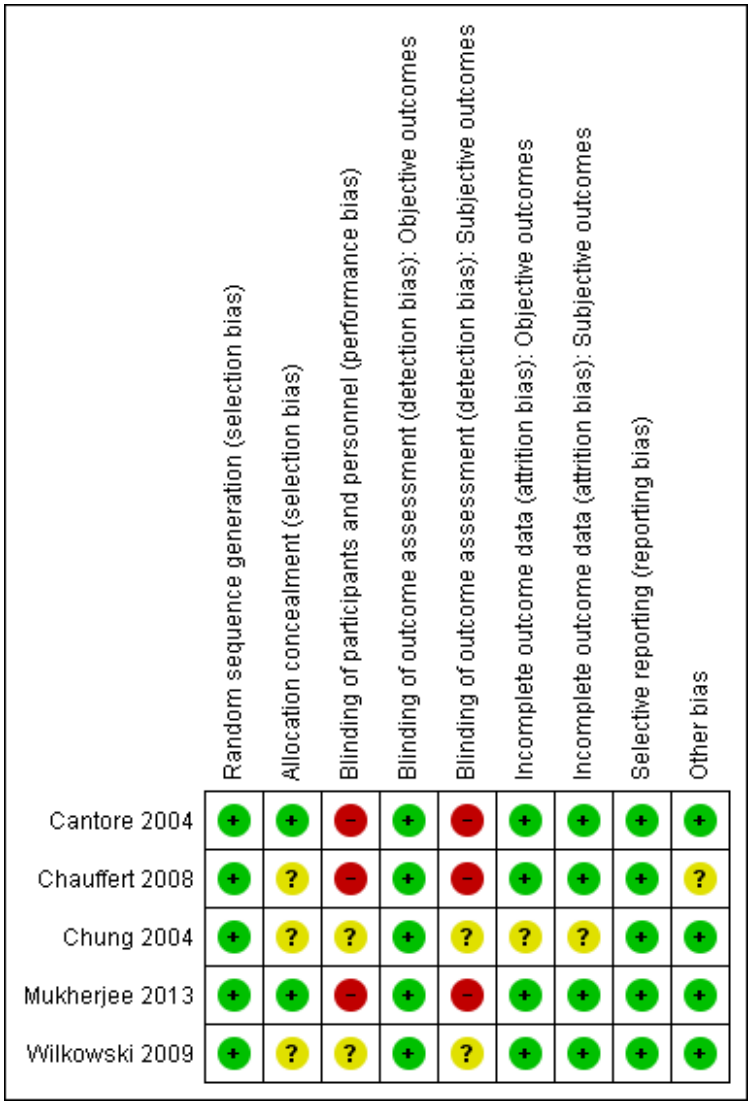


Figure 7 – Risk of bias summary of the RCTs regarding RQc (LAPC)



Risk of bias assessments primary studies (RCTs) of RQa (resectable PC)

Casadei 2015[20]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Eligible patients were randomly assigned to either of two study groups on a 1:1 basis using a central randomization procedure which was carried out at the coordinating center of the trial using a computer-generated procedure."
Allocation concealment (selection bias)	Low risk	Randomization centrally carried out at the coordinating center
Blinding of participants and personnel (performance bias)	High risk	Blinding not possible
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Lack of blinding unlikely to influence assessment of objective outcomes
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	Blinding not possible
Incomplete outcome data (attrition bias) Objective outcomes	Low risk	100% were included in the analysis
Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	100% were included in the analysis
Selective reporting (reporting bias)	Unclear risk	Disease-free survival not reported
Other bias	Unclear risk	Trial had to stop early because of low accrual. Baseline imbalances regarding gender, presence of jaundice and clinical T category (but very small trial).

Golcher, 2015[21]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was carried out centrally by fax by an independent contract research organization with stratification according to the clinical center and according to whether or not a laparoscopy has been performed (amendment 2004). Randomization was performed in blocks with randomly selected sizes of blocks of 4
Allocation concealment (selection bias)	Unclear risk	Randomization was carried out centrally by fax by an independent contract research organization with stratification according to the clinical center and according to whether or not a laparoscopy has been performed (amendment 2004).
Blinding of participants and personnel (performance bias)	Unclear risk	Blinding not possible
Blinding of outcome assessment (detection bias) Objective outcomes	Unclear risk	Lack of blinding unlikely to influence assessment of objective outcomes
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	Blinding not possible
Incomplete outcome data (attrition bias) Objective outcomes	Low risk	3/36 vs 4/37 excluded from analysis. Apparently no selective withdrawals.
Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	3/36 vs 4/37 excluded from analysis. Apparently no selective withdrawals.
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	Trial had to stop early because of low accrual. No important baseline imbalances, except for cN1 (33% vs 9%)

Palmer 2007[22]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomized to preoperative chemotherapy with either gemcitabine or gemcitabine plus cisplatin. Randomization was stratified by surgeon.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias)	High risk	Not reported, but apparently not blinded.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Lack of blinding unlikely to influence assessment of objective outcomes.
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	Not reported, but apparently not blinded.
Incomplete outcome data (attrition bias) Objective outcomes	Low risk	All patients analysed.
Incomplete outcome data (attrition bias) Subjective outcomes	Low risk	All patients analysed.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	No evidence of other biases

Risk of bias assessments of primary comparative observational studies for RQ2b (borderline resectable PC)

Masui 2016[13]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-randomised study
Allocation concealment (selection bias)	High risk	Non-randomised study
Blinding of participants and personnel (performance bias)	High risk	Blinding not possible
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Lack of blinding unlikely to influence assessment of objective outcomes
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	Observational study. Blinded outcome assessment not reported, but unlikely
Incomplete outcome data (attrition bias) Objective outcomes	Low risk	No drop-outs reported
Incomplete outcome data (attrition bias) Subjective outcomes	Low risk	No drop-outs reported
Selective reporting (reporting bias)	Low risk	No indications of selective reporting
Concurrency of the intervention and comparator group	Low risk	"18 patients were treated with neoadjuvant therapy and 19 patients denied enrolling in this clinical study and were treated with upfront resection during the same period"
Comparability of the intervention and comparator group	Unclear risk	More males and portal vein invasion in neoadjuvant group
Other bias	Low risk	No indications of other bias

Risk of bias assessments of primary studies for RQ2c (LAPC)

Cantore 2004[23]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A pre-randomised list of treatment allocation was computer-generated and was kept at the Mantova Department of Oncology by an independent data manager. The inclusion forms and the other clinical registration forms were sent by fax from each center to the coordination center to verify the randomisation checklist before registration and the endpoints of the study."
Allocation concealment (selection bias)	Low risk	"A pre-randomised list of treatment allocation was computer-generated and was kept at the Mantova Department of Oncology by an independent data manager. The inclusion forms and the other clinical registration forms were sent by fax from each center to the coordination center to verify the randomisation checklist before registration and the endpoints of the study."
Blinding of participants and personnel (performance bias)	High risk	Open trial
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Lack of blinding unlikely to influence assessment of objective outcomes
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	Open trial
Incomplete outcome data (attrition bias) Objective outcomes	Low risk	No drop-outs reported
Incomplete outcome data (attrition bias) Subjective outcomes	Low risk	No drop-outs reported
Selective reporting (reporting bias)	Low risk	No indications of selective reporting
Other bias	Low risk	No indications of other bias

Chauffert 2008[24]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomly allocated 1 : 1 to either the CHRT or gemcitabine alone (GEM) group using a minimization technique with stratification according to the center, the WHO PS (0–1 versus 2), prior exploratory surgery and/or biliary drainage."
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias)	High risk	Blinding not possible
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Lack of blinding unlikely to influence assessment of objective outcomes
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	Blinding not possible (and not reported)
Incomplete outcome data (attrition bias) Objective outcomes	Low risk	All patients analysed
Incomplete outcome data (attrition bias) Subjective outcomes	Low risk	All patients analysed
Selective reporting (reporting bias)	Low risk	No indications of selective reporting
Other bias	Unclear risk	Protocol amendment approved by the ethics committee in October 2002: "Only the absence of metastatic disease on the CT scan was required thereafter". "Due to the low recruitment, an unplanned interim analysis was carried out at the request of both the ethics committee and an Independent Data Monitoring Committee (IDMC). According to IDMC recommendations, the study was stopped before the completion of recruitment due to a lower survival rate among patients in the CHRT arm."

Chung 2004[25]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"All patients were randomly assigned to either of groups (GEM group or PAC group) by a computer-driven randomization procedure before the treatment."
Allocation concealment (selection bias)	Unclear risk	Unclear / not reported: "All patients were randomly assigned to either of groups (GEM group or PAC group) by a computer-driven randomization procedure before the treatment."
Blinding of participants and personnel (performance bias)	Unclear risk	Not reported (apparently not blinded)
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Not reported. In the case of lack of blinding unlikely to influence assessment of objective outcomes
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Objective outcomes	Unclear risk	Two of 24 patients initially allocated to the gemcitabine group were excluded from the analysis because of self-withdrawal of informed consent and deterioration of the general condition
Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	Two of 24 patients initially allocated to the gemcitabine group were excluded from the analysis because of self-withdrawal of informed consent and deterioration of the general condition
Selective reporting (reporting bias)	Low risk	No indications of selective reporting
Other bias	Low risk	No indications of other bias

Mukherjee 2013 / Hurt 2015[26, 27]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"After three cycles of induction chemotherapy, eligible patients were randomly assigned in a 1:1 ratio to receive either gemcitabine-based or capecitabine-based CRT, by use of the method of minimisation with a random element (80:20). Randomisation was stratified by recruiting hospital, WHO performance status (0 vs 1), and disease location (head vs body or tail)."
Allocation concealment (selection bias)	Low risk	"The research nurses who recruited the patients telephoned the WCTU, where randomisation was done on a computerized system by a trial or data manager."
Blinding of participants and personnel (performance bias)	High risk	"The study had an open label design, so treatment allocation was not masked from patients or investigators."
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Not reported. In the case of lack of blinding unlikely to influence assessment of objective outcomes
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	"The study had an open label design, so treatment allocation was not masked from patients or investigators."
Incomplete outcome data (attrition bias) Objective outcomes	Low risk	All patients analysed
Incomplete outcome data (attrition bias) Subjective outcomes	Low risk	All patients analysed
Selective reporting (reporting bias)	Low risk	Report according to trial protocol (ISRCTN96169987)
Other bias	Low risk	No indications of other bias

Wilkowsky 2009[28]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"In this explorative phase II trial the patients were randomised in a 1 : 1 : 1 ratio to the three treatment arms, after stratification for performance status and centre."
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias)	Unclear risk	Not reported (apparently not blinded)
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Not reported. In the case of lack of blinding unlikely to influence assessment of objective outcomes
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) Objective outcomes	Low risk	Few drop-outs
Incomplete outcome data (attrition bias) Subjective outcomes	Low risk	Few drop-outs
Selective reporting (reporting bias)	Low risk	No indications of selective reporting
Other bias	Low risk	No indications of other bias

5.3 EVIDENCE TABLES

5.3.1 Evidence tables of RCTs regarding the effect of neoadjuvant treatment with chemotherapy, radiotherapy or both, followed by surgery in patients with resectable PC (RQa)

Table 9 – Evidence tables RQa

Neoadjuvant CRT and surgery versus surgery alone in resectable pancreatic cancer: a single-center prospective, randomized, controlled trial which failed to achieve accrual targets; Casadei 2015[20]	
Methods	
• **Design**	• Single-center, open RCT
• **Source of funding and competing interest**	• Source of funding: "No commercial interest, financial source, or material support to disclose." • Declaration of interest: none declared
• **Setting**	• Tertiary referral University Center of S.Orsola-Malpighi Hospital, Bologna, Italy
• **Sample size**	• N=38 of whom 18 received neoadjuvant chemoradiation therapy followed by surgery and 20 surgery alone. The study was stopped early due to low accrual rate. The intended sample size was 32 patients per treatment arm.
• **Duration**	• Patient enrolment between May 2007 and July 2013
• **Follow-up**	• Not reported. Follow-up terminated December 31, 2014
• **Statistical analysis**	• Intention-to-treat analysis. Fisher's exact test and chi-squared test for categorical data and Mann–Whitney U test for continuous data. Kaplan-Meier and log-rank test for survival data.
Patient characteristics	
• **Eligibility criteria**	• Patients with histologically proven resectable pancreatic adenocarcinoma, aged 18 to 80 years without previous pancreatic resection or PC. Eastern Cooperative Oncology Group (ECOG) score 0–125, American Society of Anesthesiologists (ASA) score <4 and good renal, hepatic, cardiac, and haematological functions. • Definition of resectability: "Tumors were considered resectable in all cases in which there were no distant metastases and there was less than 180° maximal involvement of the superior mesenteric and portal veins with clear fat planes around the celiac axis, hepatic artery, and superior mesenteric artery. In particular, the involvement of the superior mesenteric/portal vein was graded according to the Ishikawa classification and only grades ranging from 0 to 2 were considered resectable."
• **Exclusion criteria**	• Chemoradiation therapy in the preceding 6 months, other neoplastic diseases diagnosed in the past 5 years, major surgery, biopsy or a traumatic event in the past 28 days and HIV positivity.
• **Patient & disease characteristics**	• Median age 71.5 (range 51-78) vs 67.5 years (range 48-79) • Males 44% vs 70%

	• BMI 22.8 (19.9–32.0) vs 24.4 (18.0–36.5) • Jaundice 44% vs 95% • Site Head/Body tail: 15/3 vs 20/0 • Clinical T category (cT1/cT2/cT3): 2/6/10 vs 1/0/19 • Clinical N category (cN0/cN1): 4/14 vs 4/16 • Clinical UICC stage (IA/IB/IIA/IIB): 2/2/0/14 VS 0/0/4/16 • Superior mesenteric/portal vein involvement (G0/G1-2): 11/7 vs 12/8 • Grading (Unknown/G1/G2/G3): 3/2/10/3 vs 2/6/11/1 • Biliary stent before randomization: 8/18 (44%) vs 8/20 (40%)
• **Intervention group**	• Preoperative CRT followed by surgery. • CRT consisted of initial gemcitabine alone 1000 mg/m2 on days 1 and 8 every 21 days for two cycles (total of 6 weeks) followed by combined CRT for a total of 6 weeks (conventional radiotherapy with 45 Gy and a boost of 9 Gy on the pancreatic lesion; chemotherapy with gemcitabine 50 mg/m2 twice weekly). Adjuvant chemotherapy according to the CONKO-001 study protocol was recommended. • Surgical consisted of pancreaticoduodenectomy or total pancreatectomy according to Whipple.
• **Control group**	• Surgery alone. Adjuvant chemotherapy according to the CONKO-001 study protocol was recommended.
Results	
• **Disease-free survival**	• Not reported
• **Overall survival**	• Median 22.4 (10.2–34.6) vs 19.5 (7.5–31.5) months (P= 0.973) • Total number of deaths not reported
• **Progression-free survival**	• Not assessed
• **Quality of life**	• Not assessed
• **Resectability**	• Resection rate: 11/18 (61%) vs 15/20 (75%): RR= 0.81 (95% CI 0.52 to 1.27) • R0 resections: 7/18 (39%) vs 5/20 (25%); RR= 1.56 (95% CI 0.60 to 4.04)
• **Adverse events**	• Post-treatment morbidity: 10/18 (56%) vs 9/20 (45%): RR= 1.23 (95% CI 0.65 to 2.33) • Post-treatment mortality: 1/18 (6%) vs 2/20 (10%): RR= 0.56 (95% CI 0.05 to 5.62) • Severe acute toxicity (grade ≥3) in the CRT group: 7/18 (39%) • Haematological: 6/18 (33%) • Non-haematological 3/18 (17%)

Limitations and other comments	
• **Limitations**	• Low risk of selection bias, detection bias (objective outcomes) and attrition bias. High risk of performance bias and detection bias (subjective outcomes). Unclear risk of bias for selective reporting and other bias. • NB: the study was stopped early due to low accrual rate. The intended sample size was 32 patients per treatment arm.
• **Neoadjuvant chemoradiation therapy with gemcitabine/cisplatin and surgery versus immediate surgery in resectable pancreatic cancer; Golcher 2014[21]**	
Methods	
• **Design**	• Multicenter RCT
• **Source of funding and competing interest**	• Source of funding: Deutsche Krebshilfe and Verein zur Förderung des Tumorzentrums der Universität Erlangen-Nürnberg e. V • Declaration of interest: one author received honoraria from Eli Lilly, Fresenius SE & Co. KGaA, and Hoffmann-La Roche. Other authors: none declared.
• **Setting**	• Eight university hospitals and tertiary referral centres in Germany and Switzerland
• **Sample size**	• N= 66 (initially N= 73: seven patients (3 vs 4) were excluded because of withdrawal of consent, lack of data, or other type of tumour)
• **Duration**	• June 2003 until December 2009. In December 2009, enrolment was terminated because of poor recruitment rate
• **Follow-up**	• At least 36 months at 3-month intervals until 2 years and 6-month intervals thereafter.
• **Statistical analysis**	• Intention-to-treat analysis. Kaplan-Meier and log-rank test for survival data. Chi-square test or Fisher's exact test for categorical outcomes.
Patient characteristics	
• **Eligibility criteria**	• Patients with resectable, histologically or cytologically proven adenocarcinoma of the pancreatic head • Definition of resectability: "Resectability was defined as no organ infiltration except the duodenum and maximal involvement of peripancreatic vessels ≤180°confirmed by high resolution CT. At exploration, distant metastases had to be ruled out. Local resectability was assessed and in case of vascular tumor infiltration the decision to resect the tumor with adjacent vessels was completely left to the surgeon and the individual situation."
• **Exclusion criteria**	• Ampullary carcinoma; carcinoma of the pancreatic corpus or tail (tumours between the left edge of the superior mesenteric vein and the left edge of the aorta or between the left edge of the aorta and the splenic hilum); tumour-specific prior treatment; recurrent tumour; liver cirrhosis with thrombocytes < 100,000 / mm3 or PTT < 70%; serum creatinine > 1.5 mg/dl, creatinine clearance < 70 ml/min (24 hour collection phase); severe cardio-pulmonary concomitant disease, respiratory global insufficiency or any other serious disease, that could interfere with complete therapy as rated by the surgeons or radiation oncologists who participate in the treatment; HIV infection; Karnofsky performance status < 70
• **Patient & disease characteristics**	• Median age (range) 62.5 (33-76) versus 65.1 (46-73)

	• Males 55% versus 52% • Karnofsky Performance Status • 100: 18% versus 21% • 90: 64% versus 46% • 80: 15% versus 21% • 70: 3% versus 12% • Clinical tumour status • cT1: 3% versus 3% • cT2: 45% versus 45% • cT3: 49% versus 52% • cT4: 3% versus 0% • cN0: 67% versus 91% • cN1: 33% versus 9% • cM0: 94% versus 100% • cM1: 6% versus 0% • UICC stage I: 39% versus 48% • UICC stage II: 55% versus 52% • UICC stage III: 0% versus 0% • UICC stage IV: 6% versus 0% • Exploratory surgery: 58% versus 52% • Laparoscopy: 39% versus 46% • Laparotomy: 18% versus 6% • Not done: 42%versus 48% • Biliary stent before randomization: 88% versus 85%
• **Intervention group**	• Preoperative CRT, followed by surgery: 300 mg/m2 gemcitabine and 30 mg/m2 cisplatin on days 1, 8, 22 and 29 of radiotherapy. Three-dimensional treatment planning for radiotherapy at 1.8 Gy to 55.8 Gy (tumour) or 50.4 Gy [regional lymph nodes, planning target volume (PTV ≤ 800 ml)]. Dose modifications in case of toxicity of chemotherapy were specified separately for gemcitabine and cisplatin.
• **Control group**	• Surgery alone: three step surgical procedure with exploration, tumour resection and lymph node dissection. At exploration, distant metastases had to be ruled out. Local resectability was assessed and in case of vascular tumour infiltration the decision to resecting the tumour with adjacent vessels was completely left to the surgeon and the individual situation.

Results	
• **Disease-free survival**	• Median 13.7 vs 12.1 months (P= 0.83)
• **Overall survival**	• Median 17.4 vs 14.4 months (P= 0.96) • Died: 31/33 (94%) vs 29/33 (88%): RR= 1.07 (95% CI 0.92 to 1.95)
• **Progression-free survival**	• Median time to progression 8.4 vs 8.7 months (p= 0.95)
• **Quality of life**	• Not assessed
• **Resectability**	• Resection rate: 19/33 (58%) vs 23/33 (70%): RR= 0.83 (95% CI 0.57 to 1.20) • R0 resections: 17/33 (52%) vs 16/33 (48%): RR= 1.06 (95% CI 0.66 to 1.72)
• **Adverse events**	• Severe adverse events (grade ≥3): 15/33 (46%) during CRT until surgery
Limitations and other comments	
• **Limitations**	• Low risk of selection bias, detection bias (objective outcomes), attrition bias and selective reporting. High risk of performance bias and detection bias (subjective outcomes). Unclear risk of other bias. • NB: the study was stopped early due to low accrual rate. The intended sample size was 127 patients per treatment arm.

A randomized phase 2 trial of neoadjuvant chemotherapy in resectable pancreatic cancer: gemcitabine alone versus gemcitabine combined with cisplatin; Palmer 2007[22]	
Methods	
• **Design**	Phase 2 RCT
• **Source of funding and competing interest**	Sources of funding: Eveson Charitable Trust and an educational grant from Eli Lilly. Declaration of interest: not provided
• **Setting**	Single centre academic hospital.
• **Sample size**	N= 50
• **Duration**	November 1999 to May 2003
• **Follow-up**	Not reported. Median follow-up of 16 patients still alive: 28 months (range 15–58)
• **Statistical analysis**	Intention-to-treat analysis. Kaplan-Meier and logrank test for survival data.
Patient characteristics	
• **Eligibility criteria**	Patients with clinical and radiological evidence of cancer of the head of pancreas that was considered to be resectable on CT scan and suitable for surgical exploration; Karnofsky Performance Status score >60%; adequate haematological function; adequate renal function (glomerular filtration rate >60 mL/min); adequate liver function (bilirubin <50 /m/L after biliary stenting if necessary). Definition of resectability: “Patients with tumor surrounding >180° of the circumference of the portal or superior mesenteric vein, or direct tumor extension to either the superior mesenteric artery or the coeliac axis, or with evidence of extrapancreatic disease were considered nonresectable.”
• **Exclusion criteria**	Tumour surrounding >180 of the circumference of the portal or superior mesenteric vein, or direct tumour extension to either the superior mesenteric artery or the coeliac axis, or with evidence of extrapancreatic disease; previous treatment for PC; patients whose malignant pancreatic disease was clinically or radiologically in doubt.
• **Patient & disease characteristics**	Median age (range) 66 y (47-78) versus 66 y (40-79) Male 50% versus 54% Median no. of days of diagnosis to entry (range):13 (3-49) versus 22 (0-71) Karnofsky performance status: 70: 4% versus 4% 80: 4% versus 17% 90: 19% versus 21% 100: 62% versus 50%

	Missing: 11% versus 8% Smoking status Never: 35% versus 50% Past: 38% versus 33% Present: 23% versus 17% Unknown: 4% versus 0%
• **Intervention group**	Preoperative chemotherapy with gemcitabine plus cisplatin
• **Control group**	Preoperative chemotherapy with gemcitabine
Results	
• **Disease-free survival**	Not assessed
• **Overall survival**	Median 15.6 vs 9.9 months Died at 12 months: 10/26 (38%) vs 14/24 (58%); RR= 0.66 (95% CI 0.36 to 1.19) Died in whole study period: 15/26 (58%) vs 19/24 (79%); RR= 0.73 (95% CI 0.49 to 1.07)
• **Progression-free survival**	Not assessed
• **Quality of life**	Not assessed
• **Resectability**	Pancreatic resection: 18/26 (69%) vs 9/24 (38%): RR= 1.85 (95% CI 1.04 to 3.29) R0 resection rate: 12/26 (46%) vs 6/24 (25%): RR= 1.85 (95% CI 0.82 to 4.14)
• **Adverse events**	Grade ≥3 haematological toxicity: 10/26 (38%) vs 9/24 (38%); RR= 1.03 (95% CI 0.50 to 2.08) Grade ≥3 non-haematological toxicity: “one episode of nausea, two episodes of fatigue, and one episode of constipation vs none” No differences in the frequency of postoperative complications
Limitations and other comments	
• **Limitations**	Low risk of detection bias (objective outcomes), attrition bias, selective reporting and other bias. High risk of performance bias and detection bias (subjective outcomes). Unclear risk of selection bias.. NB: the study was closed after a second planned review of the data by an independent data monitoring committee (the intended sample size was 35 patients per treatment arm).

5.3.2 *Evidence tables of comparative observational studies regarding the effect of neoadjuvant treatment with chemotherapy, radiotherapy or both, followed by surgery in patients with borderline resectable PC (RQb)*

Table 10 – Evidence table RQb

Concurrent gemcitabine+S-1 neoadjuvant chemotherapy contributes to the improved survival of patients with small borderline-resectable pancreatic cancer tumors; Masui 2016[13]	
Methods	
• **Design**	Prospective, non-randomised phase 2 study
• **Source of funding and competing interest**	Source of funding: not reported Declaration of interest: none declared
• **Setting**	Department of surgery of an academic hospital, Kyoto, Japan
• **Sample size**	N= 37
• **Duration**	January 2005 to December 2010
• **Follow-up**	At least 36 months
• **Statistical analysis**	Kaplan-Meier and logrank test and Cox regression for survival data.
Patient characteristics	
• **Eligibility criteria**	Diagnosis of borderline histopathologically proven ductal adenocarcinoma of the pancreas; 18 patients were treated with neoadjuvant therapy and 19 patients denied enrolling in this clinical study and were treated with upfront resection during the same period. Definition of borderline resectability: “The diagnosis was based on our modified criteria of SMA or CHA abutment and either tumor encasement of a short segment of the hepatic artery or tumor abutment of the SMA involving less than 180° of the vessel circumference.”
• **Exclusion criteria**	None reported
• **Patient & disease characteristics**	Median age (range) 63 (43–73) vs 66 (56–80) years Male 44% vs 32% Tumour location (head/body-tail): 13/5 vs 13/6 Tumour size (mm): 33 (18–50) vs 32 (17–75) Invasion of the portal vein: 50% vs 37% Comorbid disease: 33% vs 32%

• **Intervention group**	Preoperative chemotherapy with three cycles of gemcitabine (1000 mg/m2) intravenously, on days 1 and 8 of a 21-day cycle, and oral S-1 (80 mg/m2), twice daily at a dose according to body surface area (BSA) on days 1–14
• **Control group**	Upfront surgery
Results	
• **Disease-free survival**	Only presented for those who underwent surgery
• **Overall survival**	Median 21.7 vs 21.1 months (P= 0.098)
• **Progression-free survival**	Not assessed. Recurrence: 13/18 (72%) vs 16/19 (84%): RR= 0.86 (95% CI 0.61 to 1.21)
• **Quality of life**	Not assessed
• **Resectability**	Surgery performed: 15/18 (83%) vs 19/19 (100%): RR= 0.84 (95% CI 0.67 to 1.05) R0 resection rate: 12/18 (67%) vs 10/19 (53%): RR= 1.27 (95% CI 0.74 to 2.17)[a]
• **Adverse events**	Not reported
Limitations and other comments	
• **Limitations**	Non-randomised study. Low risk of detection bias (objective outcomes), attrition bias, reporting bias, concurrency of both treatment groups and other bias. High risk of selection bias, performance bias and detection bias (subjective outcomes). Unclear risk of bias for comparability of the intervention and comparator group.

[a] In the text the authors state: “However, the frequency of pathologically curative resection (R0) was significantly higher in the NAC+ group (87 %) than in the NAC− group (53 %, p = 0.002).” Apparently, this was based on 13/15 vs 10/19, but in Table 2, R0 resections are reported for 12 and 10 patients, respectively. The figures were recalculated based on those of Table 2 with all patients in both groups as denominator (18 vs 19).

5.3.3 *Evidence tables of RCTs regarding the effect of neoadjuvant (induction) treatment with chemotherapy, radiotherapy or both, followed by surgery in patients with LAPC (RQc)*

Table 11 – Evidence tables RQc

Gemcitabine Versus FLEC Regimen Given Intra-Arterially to Patients with Unresectable Pancreatic Cancer: A Prospective, Randomized Phase III Trial of the Italian Society for Integrated Locoregional Therapy in Oncology; Cantore 2004[23]	
Methods	
• **Design**	Multicenter, open phase 3 RCT
• **Source of funding and competing interest**	Source of funding: not reported Declaration of interest: not reported
• **Setting**	Nine Italian Oncological Departments
• **Sample size**	N= 138 (37 other patients originally allocated to a third treatment arm that was discontinued were not further included)
• **Duration**	June 1997 to June 2001
• **Follow-up**	Median 23 months
• **Statistical analysis**	Kaplan-Meier and logrank test and Cox regression for survival data
Patient characteristics	
• **Eligibility criteria**	Histologically-proven adenocarcinoma of the pancreas not suitable for curative resection. Karnofsky performance status 50 or more, adequate bone marrow reserve (WBC count >3,500/μL, platelet count >100,000 μL, and hemoglobin level >9.5 gm/dL), adequate hepatic function (total bilirubin level <2.0 mg/dL, AST and ALT < three times the upper limits of normal), adequate renal function (serum creatinine concentration <1.5 mg/dL) Definition of locally advanced PC: no details provided; PC 'not suitable for curative resection' and absence of peritoneal metastases.
• **Exclusion criteria**	Peritoneal metastases, previous chemotherapy or radiotherapy or both, previous myocardial infarction, severe coagulopathy, second malignancy, pregnancy.
• **Patient & disease characteristics**	Median age (range) 61 (38-76) vs 64 (37-79) years Male 63.3% vs 70.1% Karnofsky performance status 50-70: 25.4% vs 32.8% 80-90: 74.6% vs 67.2% Pain intensity score

	0 -19: 50.7% vs 56.7% 20-29: 12.6% vs 13.4% 30-39: 8.4% vs 8.9% 40-49: 16.9% vs 7.5% 50-100: 11.2% vs 13.4% Stage III: 49.2% vs 47.7% IV: 50.7% vs 52.2% Tumour Location Head: 59.1% vs 59.7% Body: 26.8% vs 28.3% Tail: 14.1% vs 11.9%
• **Intervention group**	FLEC (intra-arterial) at 3-wk intervals: leucovorin 100 mg/m2; 5-FU 1000 mg/m2; carboplatin 300 mg/m2; epirubicin 60 mg/m2. In addition, granisetron (an antiemetic) and famotidine (an H2-receptor antagonist) intravenously, plus filgrastim (hematological growth factor) 5 µg/d from day 10 to day 16 after therapy.
• **Control group**	Gemcitabine (administered intravenously): 1,000 mg/m2 once weekly for up to 7 weeks; then once weekly for 3 consecutive out of every 4 weeks.
Results	
• **Disease-free survival**	Not assessed
• **Overall survival**	Median 7.9 vs 5.9 months (P= 0.0361) Cox-analysis (with sex, stage, performance status as covariates): “FLEC superior to gemcitabine” (P= 0.010; HR not reported) Deceased[b] at 6 months: 27/71 (38%) vs 36/67 (53%): RR= 0.71 (95% CI 0.49 to 1.03) at 12 months: 46/71 (65%) vs 53/67 (79%): RR= 0.82 (95% CI 0.66 to 1.01) at 18 months: 60/71 (85%) vs 60/67 (90%): RR= 0.94 (95% CI 0.83 to 1.07)
• **Progression-free survival**	Not assessed
• **Quality of life**	Not assessed

[b] In the article the results were reported for patients who survived

• **Resectability**	Not assessed
• **Adverse events**	At least one grade 3/4 toxicity: 34/71 (48%) vs 15/67 (22%): RR= 2.14 (95% CI 1.29 to 3.55) FLEC: anaemia (14%), leukopenia (19.7%), thrombocytopenia (25.3%), gastrointestinal bleeding (1.4%), alopecia (8.4%), asthenia (2.8%) Gemcitabine: anaemia (2.9%), leukopenia (7.5%), thrombocytopenia (1.4%), gastrointestinal bleeding (1.4%), vomiting (4.4%), diarrhea (2.9%), fever (1.4%), mucositis (1.4%)
Limitations and other comments	
• **Limitations**	Low risk of selection bias, detection bias (objective outcomes), attrition bias, reporting bias and other bias. High risk of performance and detection bias (subjective outcomes) The study started with three treatment arms; one treatment arm was discontinued by the scientific committee due to increasing reluctance of both patients and referring medical practitioners to have patients randomised to this arm.

Phase III trial comparing intensive induction CRT (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer. Definitive results of the 2000–01 FFCD/SFRO study; Chauffert 2008[24]	
Methods	
• **Design**	Multicentre Phase 3 RCT
• **Source of funding and competing interest**	Source of funding: Ligue Nationale Contre le Cancer; Lilly Laboratories. Declaration of interest: not reported
• **Setting**	22 French oncology centres
• **Sample size**	N= 119
• **Duration**	From March 2000 to July 2005
• **Follow-up**	Median 31 vs 33 months
• **Statistical analysis**	Kaplan-Meier and logrank test and Cox regression for survival data (with 99% CIs)
Patient characteristics	
• **Eligibility criteria**	Histologically proven ductal adenocarcinoma of the pancreas, no distant metastases; World Health Organization (WHO) performance status (PS) 0-2; granulocyte count ≥1500/mm3; platelet count ≥100 000 /mm3, serum bilirubin ≥50 mM/l; serum creatinine <130 mM/l; prothrombin rate >80%. Definition of locally advanced PC/non-resectability: extension to regional lymph nodes and/or vascular structures (superior mesenteric artery or celiac trunk; existence of a portal or superior mesenteric–portal venous confluent thrombosis).

• **Exclusion criteria**	Not specifically reported
• **Patient & disease characteristics**	Age median (range): 60 (41-79) vs 62 (38-80) years Male 52.5% vs 58.3% WHO Performance Status: 0/1: 91.5% vs 76.7% 2: 8.5% vs 23.3% Weight median (range): 62 (40-105) vs 62 (35-88) kg No initial laparotomy: 57.6% vs 58.3% Tumour location (head/other): 46/13 vs 40/20 Lymph node > 1 cm: 32.2% vs 37.3% Vascular invasion: None: 22.0% vs 20.0% Arterial: 18.6% vs 28.3% Venous: 25.4% vs 28.3% Mixed: 30.5% vs 20.0% Not assessable: 3.4% vs 3.3% Peritoneal cytology negative: 26.4% vs 23.1%
• **Intervention group**	Radiotherapy (total planned dose 60 Gy delivered in 30 fractions of 2 Gy per day, five fractions per week) plus concomitant 5-FU (continuous infusion of 300 mg/m2/day from days 1 to 5 of each week throughout the irradiation) and cisplatin (20 mg/m2/day from days 1 to 5 only during weeks 1 and 5). An oral proton pump inhibitor was recommended. Maintenance treatment: gemcitabine (1000 mg/m2 weekly in 30 min for 3 weeks every 4 weeks) until disease progression or excessive toxicity.
• **Control group**	Gemcitabine 1000 mg/m2 weekly in 30 min for 7 weeks. Maintenance treatment: gemcitabine (1000 mg/m2 weekly in 30 min for 3 weeks every 4 weeks) until disease progression or excessive toxicity.
Results	
• **Disease-free survival**	Not assessed
• **Overall survival**	Median 8.6 vs 13.0 months (P= 0.03)

	HR= 1.45 (99% CI 0.88 to 2.44)[c] Adjusted for stratification criteria and main clinical factors at inclusion: HR= 1.85 (99% CI 1.04 to 3.23) Deceased[d] at 1 year: 40/59 (68%) vs 28/60 (47%); RR= 1.45 (95% CI 1.05 to 2.01)
• **Progression-free survival**	Median PFS in favour of gemcitabine (P= 0.025) HR= 1.39 (99% CI 0.85 to 2.27) 1-year PFS 8/59 (14%) vs 19/60 (32%): RR= 0.43 (95% CI 0.20 to 0.90)
• **Quality of life**	Not assessed
• **Resectability**	Secondary surgery 2/59 (3%) vs 3/60 (5%): RR= 0.68 (95% CI 0.12 to 3.91)
• **Adverse events**	Grade 3/4 overall toxicity 36/59 (61%) vs 22/60 (37%): RR= 1.66 (95% CI 1.13 to 2.46) Grade 3/4 haematological toxicity 17/59 (29%) vs 15/60 (25%): RR= 1.15 (95% CI 0.64 to 2.09) Grade 3/4 non-haematological toxicity 24/59 (41%) vs 10/60 (17%): RR= 2.44 (95% CI 1.28 to 4.65)
Limitations and other comments	
• **Limitations**	Low risk of selection bias (random sequence generation), detection bias (objective outcomes), attrition bias and reporting bias. High risk of performance and detection bias (subjective outcomes). Unclear risk of selection bias (concealment of allocation) and other bias. "Due to the low recruitment, an unplanned interim analysis was carried out at the request of both the ethics committee and an Independent Data Monitoring Committee (IDMC). According to IDMC recommendations, the study was stopped before the completion of recruitment due to a lower survival rate among patients in the CHRT arm."

[c] In the article the HR is presented for gemcitabine vs CRT with 99% CI: HR= 0.69 (99% CI 0.41 to 1.14). We have reversed this HR so that the comparison is CRT vs gemcitabine

[d] In the article the results were reported for patients who survived

A prospective randomized study of gemcitabine with doxifluridine versus paclitaxel with doxifluridine in concurrent CRT for locally advanced pancreatic cancer; Chung 2004[25]	
Methods	
• **Design**	Single-centre RCT
• **Source of funding and competing interest**	Source of funding: Brain Korea 21 Project for Medical Sciences Declaration of interest: not reported
• **Setting**	Yonsei University Medical Center, Seoul, South Korea
• **Sample size**	N= 48 (two patients from the gemcitabine group excluded from the analysis because of self-withdrawal of informed consent (1) and deterioration of general condition (1))
• **Duration**	January 1997 to July 2002
• **Follow-up**	Not reported
• **Statistical analysis**	Kaplan-Meier and logrank test for survival data
Patient characteristics	
• **Eligibility criteria**	Histologically proven pancreatic adenocarcinoma; 18-75 years of age; Karnofsky performance score ≥60; granulocyte count ≥1500/mm3; platelet count ≥100,000/mm3; serum creatinine <2 mg/dL; aspartate or alanine aminotransferase <5 times the upper limit of normal. Definition of locally advanced PC / unresectability: involvement of the superior mesenteric arteries or celiac axis, and occlusion of the portal or superior mesenteric vein.
• **Exclusion criteria**	Prior chemotherapy or radiotherapy; other malignancy; active ulcer in the gastrointestinal tract; other serious medical conditions.
• **Patient & disease characteristics**	Age median (range): 62 (39-74) vs 62 (51-74) years Male 42% vs 59% Karnofsky Performance Status: 90-100: 8% vs 5% 80-90: 29% vs 41% 70-80: 50% vs 45% 60-70: 13% vs 9% Pain intensity (VAS; median (range)): 50 (30-75) vs 46.4 (0-90) Tumour size (mean (range)): 4.0 (2-7) vs 4.3 (3-9) cm Tumour location (head/body-tail): 18/6 vs 16/6

	Lymph node metastases: 42% vs 36%
• **Intervention group**	Paclitaxel 50 mg/m2/week intravenously and doxifluridine 600 mg/m2/day per os Concomitant radiotherapy (4500 cGy in 25 fractions over 5 weeks) After 4-week rest, operation or chemotherapy with gemcitabine 1000 mg/m2/week and doxifluridine 600 mg/m2/day was prescribed
• **Control group**	Gemcitabine 1000 mg/m2/week intravenously and doxifluridine 600 mg/m2/day per os Concomitant radiotherapy (4500 cGy in 25 fractions over 5 weeks) After 4-week rest, operation or chemotherapy with gemcitabine 1000 mg/m2/week and doxifluridine 600 mg/m2/day was prescribed
Results	
• **Disease-free survival**	Not assessed
• **Overall survival**	Median 14 vs 12 months (P= 0.951) Deceased[e] at 1 year: 9/24 (37.5%) vs 11/22 (50%): RR= 0.75 (95% CI 0.39 to 1.46)
• **Progression-free survival**	Median 12.5 vs 12.0 months (P= 0.541)
• **Quality of life**	Not assessed
• **Resectability**	Surgery performed 2/24 (8%) vs 1/22 (5%): RR= 1.83 (95% CI 0.18 to 18.84) R0 resection rate 2/24 (8%) vs 0/22 (0%): RR= 4.60 (95% CI 0.23 to 90.84)
• **Adverse events**	Grade 3/4 haematological toxicity: Neutropenia (including sepsis) 3 vs 4 Anemia 1 vs 1 Thrombocytopenia 1 vs 1 Grade 3/4 non-haematological toxicity Anorexia/nausea/vomiting 4 vs 7 Diarrhea 1 vs 3 Mucositis 1 vs 2 Hypersensitivity 1 vs 0 Hand-foot syndrome 0 vs 3

[e] In the article the results were reported for patients who survived

	Radiation gastroenteropathy 2 vs 3 "Toxicities were acceptable in both groups"
Limitations and other comments	
• **Limitations**	Low risk of selection bias (random sequence generation), detection bias (objective outcomes), reporting bias and other bias. Unclear risk of selection bias (concealment of allocation), performance bias, detection bias (subjective outcomes) and attrition bias. Two of 24 patients from the gemcitabine group were excluded from the analysis because of self-withdrawal of informed consent and deterioration of general condition.

Gemcitabine-based or capecitabine-based CRT for locally advanced pancreatic cancer (SCALOP): a multicentre, randomised, phase 2 trial; Mukerherjee 2013[26] Health-Related Quality of Life in SCALOP, a Randomized Phase 2 Trial Comparing Chemoradiation Therapy Regimens in Locally Advanced Pancreatic Cancer; Hurt 2015[27]	
Methods	
• **Design**	Multi-centre open-label phase 2 RCT
• **Source of funding and competing interest**	Source of funding: Cancer Research UK Declaration of interest: none declared
• **Setting**	28 cancer centres, United Kingdom
• **Sample size**	N= 114 patients were treated with induction chemotherapy, of whom 74 were eligible for randomisation for the second phase
• **Duration**	December 24, 2009 to October 25, 2011
• **Follow-up**	12 months
• **Statistical analysis**	Kaplan-Meier and logrank test and Cox regression for survival data
Patient characteristics	
• **Eligibility criteria**	Age ≥18 years; histologically or cytologically proven, locally advanced, nonmetastatic, inoperable (or operable but medically unfit for surgery) PC with a tumour diameter of ≤7 cm; WHO PS 0-2, adequate haematological, liver, and renal function. In addition: patients were eligible for random allocation if they had responding or stable disease after three cycles of induction gemcitabine and capecitabine; tumour diameter of ≤6 cm; WHO PS 0–1; adequate haematological, liver, and renal function and less than 10% weight loss from baseline. Definition of locally advanced PC / unresectability: Nonmetastatic, inoperable (or operable but medically unfit for surgery) PC with a tumour diameter of ≤7 cm.

	"All potential patients were discussed at regional pancreatic multidisciplinary team meetings in the presence of specialist pancreatic surgeons and radiologists for decisions about inoperability, but the exact criteria for inoperability were left to the treating multidisciplinary team. Decisions with respect to patients deemed medically unfit for surgery were taken by the treating clinicians, on the basis of the patient's comorbidities and the team's opinion about whether or not they could withstand major pancreatic surgery."
• **Exclusion criteria**	Women who are pregnant or breast feeding; any evidence of severe uncontrolled systemic diseases including uncontrolled coronary artery disease; myocardial infarction or stroke within the last six months; previous malignancies in the preceding five years; renal abnormalities such as polycystic kidneys or hydronephrosis or ipsilateral single kidney; previous radiotherapy to upper abdomen; recurrent cancer following definitive pancreatic surgery
• **Patient & disease characteristics**	Median age (IQR) 63.1 (56.5-70.2) vs 66.0 (57.7-70.3) Male 47% vs 63% WHO Performance Status: 0: 42% vs 42% 1: 58% vs 58% Tumour location (head/body-tail): 31/5 vs 32/6 Mean estimated longest diameter of primary lesion (SD): 4.0 (1.2) vs 4.0 (1.5) cm
• **Intervention group**	Induction chemotherapy: three cycles of gemcitabine (1000 mg/m² intravenously for 1 h on days 1, 8, and 15 of a 28 day cycle) and capecitabine (830 mg/m² orally, twice daily on days 1–21 of a 28 day cycle). If eligible for randomisation: Further cycle of gemcitabine and capecitabine, followed by Capecitabine (830 mg/m² twice daily) in combination with radiotherapy (50.4 Gy in 28 fractions)
• **Control group**	Induction chemotherapy: three cycles of gemcitabine (1000 mg/m² intravenously for 1 h on days 1, 8, and 15 of a 28 day cycle) and capecitabine (830 mg/m² orally, twice daily on days 1–21 of a 28 day cycle). If eligible for randomisation: Further cycle of gemcitabine and capecitabine, followed by Gemcitabine (300 mg/m² once per week, total six doses) in combination with radiotherapy (50.4 Gy in 28 fractions)
Results	
• **Disease-free survival**	Not assessed
• **Overall survival**	Median 15.2 (95% CI 13.9 to 19.2) vs 13.4 months (95% CI 11.0 to 15.7) (P= 0.025) HR= 0.50 (95% CI 0.27 to 0.93) For randomisation stratification factors adjusted HR= 0.39 (95% CI 0.18 to 0.81)

	Deceased[f] at 12 months: 20.8% (95% CI 10.5 to 38.9) vs 35.8% (95% CI 22.5 to 53.6): RR= 0.53 (95% CI 0.24 to 1.16)
• **Progression-free survival**	Median 12.0 (95% CI 10.2–14.6) vs 10.4 months (95% CI 8.9–12.5) (P= 0.102) HR= 0.64 (95% CI 0.37 to 1.09) For randomisation stratification factors adjusted HR= 0.60 (95% CI 0.32 to 1.12)
• **Quality of life**	QLQ-C30 scores at week 23 (immediately after completion of CRT): no significant differences (P= 0.14; n=48) changes in scores from week 17 (time of randomisation / before chemoradiation treatment) to week 23: no significant differences (P= 0.13; n=45) From Hurt 2015 [27]: “Differences in changes in HRQL scores between trial arms rarely reached statistical significance; however, where they did, they favored capecitabine therapy.” “The median change between week 17 [the point of randomisation] and later time points was never worse in the Cap-CRT arm than in the Gem-CRT arm.” Statistically significant differences between arms (in favour of capecitabine): Between week 17 and 23: cognitive functioning (P=.036), fatigue (P=.046), bloating (P=.035) and dry mouth (P=.029) Between weeks 17 and 26: future health (P=.033) Between weeks 17 and 39: cognitive functioning (P=.011), dry mouth (P=.001) and body image (P=.022)
• **Resectability**	Resection rate 2/36 (6%) vs 3/38 (8%): RR= 0.70 (95% CI 0.12 to 3.97) R0 resection 2/36 (6%) vs 3/38 (8%): RR= 0.70 (95% CI 0.12 to 3.97)
• **Adverse events**	Any grade 3/4 toxicity: 4/34 (12%) vs 14/38 (37%): RR= 0.32 (95% CI 0.12 to 0.88) Any haematological grade 3/4 toxicity: 0/34 (0%) vs 7/38 (18%): RR= 0.07 (95% CI 0.00 to 1.25) Any non-haematological grade 3/4 toxicity: 4/34 (12%) vs 10/38 (26%): RR= 0.45 (95% CI 0.15 to 1.29)
Limitations and other comments	
• **Limitations**	Low risk of selection bias, detection bias (objective outcomes), attrition bias, reporting bias and other bias. High risk of performance and detection bias (subjective outcomes). Study protocol published at http://www.isrctn.com/ISRCTN96169987.

[f] In the article the results were reported for patients who survived

CRT with concurrent gemcitabine and cisplatin with or without sequential chemotherapy with gemcitabine/cisplatin vs CRT with concurrent 5-fluorouracil in patients with locally advanced pancreatic cancer – a multi-centre randomised phase II study; Wilkowsky 2009[28]	
Methods	
• **Design**	Multi-centre phase 2 RCT
• **Source of funding and competing interest**	Source of funding: Eli Lilly, Germany Declaration of interest: not reported
• **Setting**	12 German oncologic centres
• **Sample size**	N= 95
• **Duration**	February 2002 to July 2005
• **Follow-up**	Median 8.6 months (range 1.4-9.5)
• **Statistical analysis**	Kaplan-Meier and logrank test for survival data
Patient characteristics	
• **Eligibility criteria**	Age 18-75 years; histologically confirmed, non-resectable PC (stages III and IVA); WBC ≥3.5 per 10^9 l, platelet count ≥100 per 10^9 l, haemoglobin, ≥100 g/l. Definition of locally advanced PC / unresectability: nodal involvement, retroperitoneal infiltration, infiltration of the arteria mesenterica superior, vena mesenterica superior, arteria hepatica or portal vein.
• **Exclusion criteria**	Distant metastasis, previous radiotherapy; pregnant or lactating patients; poor performance status (KPS <70%); insufficient renal function (creatinine clearance <80 ml/min); active infections.
• **Patient & disease characteristics**	Age median (range): 63 (40-75) vs 65 (41-75) vs 63 (42-74) years Male 50% vs 65% vs 48% Karnofsky Performance Status: 90-100: 47% vs 39% vs 58% 70-80: 47% vs 55% vs 39% Adenocarcinoma: 84% vs 87% vs 87% Tumour location (head/body/tail/overlapping): 22/6/1/3 vs 20/6/2/3 vs 25/6/0/0 T stage T2: 0% vs 0% vs 3% T3: 25% vs 26% vs 23% T4: 75% vs 74% vs 74%

	N stage N0: 38% vs 39% vs 16% N1: 62% vs 55% vs 77% Nx: 0% vs 6% vs 6%
• **Intervention group 1**	Gemcitabine (300 mg/m2), cisplatin (30 mg/m2) on days 1, 8, 22 and 29 with concurrent radiotherapy (external beam irradiation) 5 days per week (total dose 50 Gy)
• **Intervention group 2**	Gemcitabine (300 mg/m2), cisplatin (30 mg/m2) on days 1, 8, 22 and 29 with concurrent radiotherapy (external beam irradiation) 5 days per week (total dose 50 Gy) followed by sequential full-dose gemcitabine (1000 mg/m2) and cisplatin (50 mg/m2) every 2 weeks
• **Control group**	5-FU (350 mg/m2 per day on each day of radiotherapy) with concurrent radiotherapy (external beam irradiation) 5 days per week (total dose 50 Gy)
Results	
• **Disease-free survival**	Not assessed
• **Overall survival**	Median 9.3 vs 7.3 vs 9.6 months (P= 0.61) Deceased[g] at 9 months: 48% vs 55% vs 42% (P= 0.61) at 18 months: 89% vs 78% vs 89% (P-value not reported)
• **Progression-free survival**	Median 5.6 vs 6.0 vs vs 4.0 months (P= 0.21)
• **Quality of life**	Not assessed
• **Resectability**	Secondary resection: 8/32 (25%) vs 6/31 (19%) vs 4/31 (13%) R0 resection rate: not reported per study arm (8 of 18 patients had a R0 resection)
• **Adverse events**	Grade 3/4 acute toxicity (RTOG): Leukocytopaenia: 52% vs 62% vs 4% Thrombocytopaenia: 52% vs 38% vs 4% Anaemia: 7% vs 4% vs 0% Upper GI tract: 20% vs 8% vs 0% Lower GI tract: 10% vs 0% vs 4% Skin: 0% vs 0% vs 0%

g In the article the results were reported for patients who survived

	Grade 3/4 non-haematological toxicity (NCI-CTC) Fatigue: 13% vs 4% vs 10% Weight loss: 3% vs 0% vs 0% Diarrhoea: 3% vs 0% vs 10% Nausea: 13% vs 4% vs 0% Febrile neutropaenia: 0% vs 0% vs 0% Infection without neutropaenia: 3% vs 0% vs 7%
Limitations and other comments	
• **Limitations**	Low risk of selection bias (random sequence generation), detection bias (objective outcomes), attrition bias, reporting bias and other bias. Unclear risk of selection bias (allocation concealment), performance and detection bias (subjective outcomes).

5.4 GRADE EVIDENCE PROFILES

Question: Preoperative CRT compared to upfront surgery in patients with resectable PC

Bibliography: Casadei 2015; Golcher 2015

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**preoperative CRT**	**upfront surgery**	**Relative (95% CI)**	**Absolute (95% CI)**		
Disease-free survival												
1	randomised trials	serious [1,2]	not serious	not serious	very serious [3]	none	Median DFS 13.7 vs 12.1 months (P= 0.83)				⊕◯◯◯ VERY LOW	CRITICAL
Overall survival												
2	randomised trials	not serious [4]	not serious	not serious	very serious [3]	none	Median OS 22.4 (10.2–34.6) vs 19.5 (7.5–31.5) months (P= 0.97) and 17.4 vs 14.4 months (P= 0.96). In one study, 31/33 vs 29/33 patients died (RR= 1.07; 95% CI 0.92 to 1.95), whereas the total number of deaths was not reported in the other study.				⊕⊕◯◯ LOW	CRITICAL
Progression-free survival												
1	randomised trials	serious [1,2]	not serious	not serious	very serious [3]	none	Time to progression 8.4 vs 8.7 months (p= 0.95)				⊕◯◯◯ VERY LOW	CRITICAL
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Resectability: resection rate												
2	randomised trials	not serious [4]	not serious	not serious	very serious [5]	none	30/51 (58.8%)	38/53 (71.7%)	**RR 0.82** (0.62 to 1.09)	**129 fewer per 1.000** (from 65 more to 272 fewer)	⊕⊕◯◯ LOW	IMPORTANT

Resectability: R0 resections												
2	randomised trials	serious [1,2]	not serious	not serious	very serious [5]	none	24/51 (47.1%)	21/53 (39.6%)	**RR 1.18** (0.76 to 1.81)	**71 more per 1.000** (from 95 fewer to 321 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Adverse events												
2	randomised trials	serious [1,2]	not serious	not serious	very serious [3]	none	Post-treatment morbidity in 10/18 (56%) vs 9/20 (45%) (RR= 1.23; 95% CI 0.65 to 2.33); post-treatment mortality in 1/18 (6%) vs 2/20 (10%) (RR= 0.56; 95% CI 0.05 to 5.62). In the CRT group: severe grade ≥3 acute toxicity occurred in 7/18 (39%) in the first study and in 15/33 (46%) in the second study.				⊕◯◯◯ VERY LOW	CRITICAL

CI: *Confidence interval;* ***RR:*** *Risk ratio*

1. High risk of performance bias (blinding not possible)
2. High risk of detection bias
3. OIS not reached / both a beneficial and harmful effect can't be excluded
4. High risk of performance bias (blinding not possible); not downgraded
5. OIS not reached / confidence interval includes both benefit and harm

Question: Preoperative CRT compared to other preoperative CRT in patients with resectable PC

Bibliography: Palmer 2007

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**preoperative CRT**	**other preoperative CRT**	**Relative (95% CI)**	**Absolute (95% CI)**		
Disease-free survival - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Overall survival												
1	randomised trials	not serious [4]	not serious	not serious	very serious [3]	none	Median OS 15.6 vs 9.9 months. At 12 months 10 patients in the combined group (38%) had died compared to 14 (58%) in the gemcitabine alone group (RR= 0.66; 95% CI 0.36 to 1.19). During the whole study period these numbers were 15 (58%) and 19 (79%), respectively (RR= 0.73; 95% CI 0.49 to 1.07).				⊕⊕◯◯ LOW	CRITICAL
Progression-free survival - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Resectability: resection rate												
1	randomised trials	not serious [4]	not serious	not serious	very serious [5]	none	18/26 (69.2%)	9/24 (37.5%)	**RR 1.85** (1.04 to 3.29)	**319 more per 1.000** (from 15 more to 859 more)	⊕⊕◯◯ LOW	IMPORTANT

Resectability: R0 resections												
1	randomised trials	serious [1,2]	not serious	not serious	very serious [3]	none	12/26 (46.2%)	6/24 (25.0%)	**RR 1.85** (0.82 to 4.14)	**213 more per 1.000** (from 45 fewer to 785 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Adverse events												
1	randomised trials	serious [1,2]	not serious	not serious	very serious [3]	none	Haematological toxicity grade 3 or more in 10/26 (38%) vs 9/24 (38%) (RR= 1.03; 95% CI 0.50 to 2.08). Four episodes of non-haematological toxicity grade 3 or more in the combined chemotherapy group versus none in the gemcitabine only group. No differences with respect to postoperative complications.				⊕◯◯◯ VERY LOW	CRITICAL

CI: *Confidence interval;* ***RR:*** *Risk ratio*

1. High risk of performance bias (blinding not possible)
2. High risk of detection bias
3. Very small study / OIS not reached / both a beneficial and harmful effect can't be excluded
4. High risk of performance bias; not downgraded
5. Very small study / OIS not reached / very wide confidence interval (includes trivial benefit)

Question: Preoperative chemotherapy compared to upfront surgery in patients with borderline resectable PC

Bibliography: Masui 2016

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	preoperative chemotherapy	upfront surgery	Relative (95% CI)	Absolute (95% CI)		
Disease-free survival - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Overall survival												
1	observational studies	serious [4]	not serious	not serious	serious [3]	none	Median OS 21.7 vs 21.1 months (P= 0.098)				⊕◯◯◯ VERY LOW	CRITICAL
Progression-free survival: recurrence rate												
1	observational studies	serious [2,4]	not serious	not serious	very serious [5]	none	13/18 (72.2%)	16/19 (84.2%)	**RR 0.86** (0.61 to 1.21)	**118 fewer per 1.000** (from 177 more to 328 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Resectability: resection rate												
1	observational studies	serious [2,4]	not serious	not serious	very serious [5]	none	15/18 (83.3%)	19/19 (100.0%)	**RR 0.84** (0.67 to 1.05)	**160 fewer per 1.000** (from 50 more to 330 fewer)	⊕◯◯◯ VERY LOW	IMPORTANT

Resectability: R0 resections												
1	observational studies	serious [2,4]	not serious	not serious	very serious [5]	none	12/18 (66.7%)	10/19 (52.6%)	**RR 1.27** (0.74 to 2.17)	**142 more per 1.000** (from 137 fewer to 616 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Adverse events - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: *Confidence interval;* ***RR:*** *Risk ratio*

1. High risk of performance bias (blinding not possible)
2. High risk of detection bias
3. OIS not reached / both a beneficial and harmful effect can't be excluded
4. High risk of performance bias (blinding not possible); not downgraded
5. OIS not reached / confidence interval includes both benefit and harm
6. No concurrency of intervention and comparator group in one study

Question: Induction chemotherapy with an intra-arterial regimen of FLEC compared to induction chemotherapy with gemcitabine administered intravenously in patients with LAPC

Bibliography: Cantore 2004

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	induction CRT with an intra-arterial regimen of FLEC	induction chemotherapy with gemcitabine administered intravenously	Relative (95% CI)	Absolute (95% CI)		
Disease-free survival - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Overall survival												
1	randomised trials	not serious [1]	not serious	not serious	serious [2]	none	Median overall survival 7.9 vs 5.9 months (P= 0.0361). Multivariate survival analysis (with sex, stage, performance status as covariates) "revealed superiority for FLEC" (P= 0.010) (no HR reported)				⊕⊕⊕◯ MODERATE	CRITICAL
Progression-free survival - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Resectability: resection rate - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Resectability: R0 resections - not measured												

-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Adverse events												
1	randomised trials	serious [3,4]	not serious	not serious	very serious [2]	none	34/71 (47.9%)	15/67 (22.4%)	**RR 2.14** (1.29 to 3.55)	**255 more per 1.000** (from 65 more to 571 more)	⊕⊕◯◯ LOW	CRITICAL

CI: *Confidence interval;* ***RR:*** *Risk ratio*

1. High risk of performance bias (blinding not possible); not downgraded
2. OIS not reached
3. High risk of performance bias (blinding not possible)
4. High risk of detection bias

Question: Induction CRT with 5-FU and cisplatin compared to induction chemotherapy with gemcitabine in patients with LAPC

Bibliography: Chauffert 2008

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	induction radiotherapy with concomitant 5-FU and cisplatin	induction chemotherapy with gemcitabine	Relative (95% CI)	Absolute (95% CI)		
Disease-free survival - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Overall survival												
1	randomised trials	not serious [1]	not serious	not serious	serious [2]	none	Median overall survival 8.6 vs 13.0 months (P= 0.03). HR 1.45 (99% CI 0.88 to 2.44). HR adjusted for stratification criteria and main clinical factors at inclusion 1.85 (99% CI 1.04 to 3.23)				⊕⊕⊕◯ MODERATE	CRITICAL
Progression-free survival												
1	randomised trials	serious [3,4]	not serious	not serious	serious [2]	none	Median PFS in favour of gemcitabine (P= 0.025). HR 1.39 (99% CI 0.85 to 2.27). One-year PFS in 8/59 (14%) vs 19/60 (32%) of the patients (RR= 0.43; 95% CI 0.20 to 0.90)				⊕⊕◯◯ LOW	CRITICAL
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Resectability: resection rate												

1	randomised trials	serious [3,4]	not serious	not serious	very serious [5]	none	2/59 (3.4%)	3/60 (5.0%)	**RR 0.68** (0.12 to 3.91)	**16 fewer per 1.000** (from 44 fewer to 146 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Resectability: R0 resections - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Adverse events												
1	randomised trials	serious [3,4]	not serious	not serious	serious [2]	none	36/59 (61.0%)	22/60 (36.7%)	**RR 1.66** (1.13 to 2.46)	**242 more per 1.000** (from 48 more to 535 more)	⊕⊕◯◯ LOW	CRITICAL

CI: *Confidence interval;* ***RR:*** *Risk ratio*

1. High risk of performance bias (blinding not possible); not downgraded
2. OIS not reached
3. High risk of performance bias (blinding not possible)
4. High risk of detection bias
5. OIS not reached / both a beneficial and harmful effect can't be excluded

Question: Induction CRT with paclitaxel + doxifluridine or gemcitabine + capecitabine compared to induction CRT with gemcitabine with/without doxifluridine in patients with LAPC

Bibliography: Chung 2004; Mukherjee 2013/Hurt 2015

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	induction CRT with paclitaxel + doxifluridine or gemcitabine + capecitabine	induction CRT with gemcitabine (with/without doxifluridine	Relative (95% CI)	Absolute (95% CI)		
Disease-free survival - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Overall survival												
2	randomised trials	not serious [1]	not serious	not serious	serious [2]	none	Median OS 14 vs 12 months (P= 0.951) and 15.2 vs 13.4 months (P= 0.025) in favour of the non-gemcitabine regimen. RR of death at 1 year: 0.75 (95% CI 0.39 to 1.46) and 0.53 (95% CI 0.24 to 1.16). In one study: HR = 0.50 (95% CI 0.27 to 0.93) in favour of the non-gemcitabine regimen.				⊕⊕⊕◯ MODERATE	CRITICAL
Progression-free survival												
2	randomised trials	serious [3,4]	not serious	not serious	serious [5]	none	Median PFS 12.5 vs 12.0 months (P= 0.541) and 12.0 vs 10.4 months (P= 0.102). In one study HR = 0.64 (95% CI 0.37 to 1.09) in favour of the non-gemcitabine regimen.				⊕⊕◯◯ LOW	CRITICAL
Quality of life												

1	randomised trials	serious [3,4]	not serious	not serious	serious [5]	none	No significant differences between the groups for QLQ-C30 scores at week 23 (immediately after completion of CRT) (P= 0.14; n=48) or changes in scores from week 17 (time of randomisation / before chemoradiation treatment) to week 23 (P= 0.13; n=45).	⊕⊕◯◯ LOW	CRITICAL
Resectability: resection rate									
2	randomised trials	serious [3,4]	not serious	not serious	very serious [6]	none	RR= 1.83 (95% CI 0.18 to 18.84) and RR= 0.70 (95% CI 0.12 to 3.97).	⊕◯◯◯ VERY LOW	IMPORTANT
Resectability: R0 resections									
2	randomised trials	serious [3,4]	not serious	not serious	very serious [6]	none	RR= 4.60 (95% CI 0.23 to 90.84) and RR= 0.70 (95% CI 0.12 to 3.97).	⊕◯◯◯ VERY LOW	IMPORTANT
Adverse events									
2	randomised trials	serious [3,4]	serious [7]	not serious	serious [2]	none	In one study few grade 3/4 haematological or non-haematological toxicities were observed ("Toxicities were acceptable in both groups"). In second study: RR for any grade 3/4 toxicity 0.32 (95% CI 0.12 to 0.88) in favour of capecitabine.	⊕◯◯◯ VERY LOW	CRITICAL

CI: *Confidence interval;* ***RR:*** *Risk ratio*

1. High risk of performance bias (blinding not possible); not downgraded
2. OIS not reached
3. High risk of performance bias (blinding not possible)
4. High risk of detection bias
5. OIS not reached / both a beneficial and harmful effect can't be excluded
6. OIS not reached / confidence interval includes both benefit and harm
7. Large difference in the occurrence of toxicities in both studies

Question: Induction CRT with gemcitabine and cisplatin without/with sequential full-dose gemcitabine and cisplatin compared to induction CRT with 5-FU in patients with LAPC

Bibliography: Wilkowski 2009

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**induction CRT with gemcitabine and cisplatin without/with sequential full-dose gemcitabine and cisplatin**	**induction CRT with 5-FU**	**Relative (95% CI)**	**Absolute (95% CI)**		
Disease-free survival - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Overall survival												
1	randomised trials	not serious [1]	not serious	not serious	serious [2]	none	Median OS 9.3 vs 7.3 vs 9.6 months (P= 0.61); risk of death at 9 months 48% vs 55% vs 42% (P= 0.61); at 18 months 89% vs 78% vs 89% (P-value not reported).				⊕⊕⊕◯ MODERATE	CRITICAL
Progression-free survival												
1	randomised trials	serious [3]	not serious	not serious	serious [2]	none	Median PFS 5.6 vs 6.0 vs vs 4.0 months (P= 0.21)				⊕⊕◯◯ LOW	CRITICAL
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Resectability: resection rate												

1	randomised trials	serious [3]	not serious	not serious	very serious [4]	none	25% vs 19% vs 13%	⊕◯◯◯ VERY LOW	IMPORTANT
Resectability: R0 resections									
1	randomised trials	serious [3]	not serious	not serious	very serious [5]	none	Not reported per study arm; overall 8 of 18 patients who underwent surgery, had a R0 resection.	⊕◯◯◯ VERY LOW	IMPORTANT
Adverse events									
1	randomised trials	serious [3]	not serious	not serious	serious [6]	none	More acute haematological grade 3/4 toxicities (anaemia, leukocytopaenia and thrombocytopaenia; upper and lower GI tract toxicities) after both gemcitabine / cisplatin regimens compared to the 5-FU regimen.	⊕⊕◯◯ LOW	CRITICAL

CI: *Confidence interval;* ***RR:*** *Risk ratio*

1. Unclear risk of performance bias (although blinding not possible); not downgraded
2. OIS not reached / both a beneficial and harmful effect can't be excluded
3. Unclear risk of performance bias (although blinding not possible) and detection bias
4. OIS not reached / confidence interval includes both benefit and harm
5. OIS not reached; results unclear (see also outcome 'resection rates')
6. OIS not reached; results unclear

5.5 STAKEHOLDER MEETING

The Stakeholder meeting was held on February 20, 2017. Recommendations were scored (1-5) and discussed (Table 12). Patient organisations were consulted (Table 13).

Table 12 – Scoring of recommendations by Stakeholders

Neoadjuvant therapy								
Recommendations	**Level of Evidence**	**Strength of recommendation**						
1. Neoadjuvant chemotherapy is not recommended for resectable PC.	very low to low	strong	5	3	4	5	5	**NAD in resectable PC, there are some situations where we have to discuss NAD (for example if Large primary tumor,high CA 19.9 (100-400 ml/L), Peripancreatic nodal involvement).Perhaps could we make a comment in the text??**
2. Neoadjuvant chemotherapy for resectable PC is recommended only in the context of a clinical trial.	NA	strong	5	5	5	5	5	
3. Neoadjuvant chemotherapy for borderline resectable PC should be considered.	very low	strong	5	5	4	5	2	**Neoadjuvant chemotherapy for borderline resectable PC may be considered in clinical trial setting. Otherwise patients with borderline resectable PC should undergo staging laparoscopy and surgical exploration +/- resection in refrerral centres**
4. Chemotherapy with the intention to bring the patient to surgery is not recommended for LAPC (clearly not resectable).	very low	strong	5	5	5	5	2	**Significant survival improvement can be achieved with local ablation therapy of locally advanced unresectable PC. Thus, pts with unresectable locally advanced PC can still go to surgery. The definition of surgery is not always resection. Ablation too can be done via surgery (laparoscopy or laparotomy)**

Table 13 – Opinion of patient organisation

Voor Kom op tegen Kanker is het belangrijk dat de patiënt op elk ogenblik voldoende geïnformeerd wordt over zijn medische toestand, dit in een voor de patiënt begrijpelijke taal. Hierbij ook informatie over de behandelingsmogelijkheden met de voor- en nadelen. Ook dat de clinici rekening houden met de waarden en de voorkeuren van de patiënt. (p 21 van part 1, ook op p 30). Alsook dat hij of zij voldoende pychosociale ondersteuning krijgen alsook hun naasten. Er moet ook rekening gehouden worden met de kwaliteit van leven van de patiënt (komt niet terug in de uitgevoerde studies die geselecteerd werden, werd toen niet onderzocht). Voor zeldzame tumoren zoals pancreaskanker er één is, is gebleken uit vroegere KCE studie dat de resultaten van de behandeling beter zijn in een ziekenhuis die meer dan 20 pancreasoperaties per jaar uitvoeren. Als Kom op tegen Kanker pleiten we voor expertise ziekenhuizen die preferentieel deze pathologie behandelen. (zie p 20 van part 1.) Dit was niet weerhouden vermits dit eerder een zaak is van de organisatie van zorg dan van good clinical practice guidelines.

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