Pharmacotherapeutic value and pharmaco-economic value of gemcitabine

for the treatment of pancreatic cancer

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Abbreviations

ASCO	American Society of Clinical Oncology
BOM	Beoordeling Oncologische Middelen (Dutch)
CBR	Clinical Benefit Rate
CI	Confidence Interval
CT-scan	Computed Tomography scan
DCR	Disease Control Rate
ECG	Electrocardiography
EGFR	Epidermal Growth Factor Receptor
ESMO	European Society for Medical Oncology
FDA	United States Food and Drug Administration
5-FU	5-fluorouracil
Gy	Gray
HER-1	EGFR in humans
HR	Hazard Ratio
ICER	Incremental Cost-Effectiveness Ratio
IGF-1R	Insulin-like Growth Factor-1 Receptor
IKNL	Integraal Kankercentrum Nederland
LAPC	Locally Advanced Pancreatic Carcinoma
LYG	Life-Years Gained
MMC	Mitomycin-C
MRI	Magnetic resonance imaging
NaCl	Sodiumchloride
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Clinical Excellence
OR	Odds Ratio
ORR	Objective Response Rate
OS	Overall Survival
PASKWIL	Palliative, Adjuvant, Side effects, Quality of life, Level of evidence
PEG	Percutaneous Endoscopic Gastrostomy
PFS	Progression Free Survival
QALY	Quality Adjusted Life Year
QoL	Quality of Life
Q-TWiST	Quality-adjusted Time Without Symptoms or Toxicity
RTx	Radiotherapy
TTP	Time To Progression
VEGFR	Vascular Endothelial Growth Factor Receptor

Samenvatting

Nederlandse samenvatting

Inleiding
Pancreascarcinoom is een van de dodelijkste vormen van kanker. De incidentie in Nederland is ongeveer 2000 nieuwe patiënten per jaar, van wie er na vijf jaar nog slechts 5% in leven is. De meerderheid van de patiënten heeft bij diagnose al vergevorderde ziekte. Indien radicale resectie mogelijk is kan de ziekte genezen worden. In de andere gevallen is verbetering van kwaliteit van leven en verlenging van overleving het doel van de behandeling.

Methoden
Om de farmacotherapeutische en farmaco-economische waarde van gemcitabine en andere middelen voor pancreascarcinoom vast te stellen onderzochten wij de klinische effectiviteit, kosten-effectiviteit en veiligheid van deze middelen in een literatuur onderzoek. Om het gebruik van deze middelen in de dagelijkse praktijk in Nederland na te gaan hebben wij medisch oncologen geïnterviewd en apothekers en patiënten betrokken. Ter illustratie evalueerden wij de behandelkeuzes in een academisch centrum. Tevens berekenden wij ter illustratie het werkelijke kostenbeslag van gemcitabine in Nederland voor de indicatie pancreascarcinoom.

Richtlijnen
De Nederlandse richtlijn is onlangs herzien en komt grotendeels overeen met de Europese (ESMO) en Amerikaanse (NCCN) richtlijn. Behandeling in studieprotocollen wordt aanbevolen. Neoadjuvante therapie voor resectabele tumoren wordt alleen geadviseerd in studieverband. Adjuvante chemotherapie (gemcitabine of 5-FU) is standaard therapie na resectie. Indien er borderline resectabiliteit is, kan neo-adjuvante chemoradiotherapie worden overwogen. Bij lokaal gevorderde ziekte wordt palliatieve chemoradiotherapie alleen aanbevolen in klinische studies. Bij lokaal gevorderede en gemetastaseerde ziekte is de standaard behandeling palliatieve chemotherapie met gemcitabine. Combinatie therapie (gemcitabine met erlotinib of een platinum- of fluoropyrimidine-analoog) wordt in de Nederlandse en Europese richtlijn niet geadviseerd, maar in de Amerikaanse richtlijn wel ter overweging gegeven. Er is geen standaard tweedelijns behandeling. De Commissie BOM heeft gemcitabine als adjuvante behandeling positief beoordeeld. Gemcitabine als palliatieve behandeling is door de Commissie BOM in 2001 negatief beoordeeld, maar werd vanwege het ontbreken van een alternatief en een gunstig bijwerkingenprofiel bij geselecteerde patiënten wel verdedigbaar geacht.

Klinische effectiviteit
Adjuvante chemotherapie met gemcitabine gedurende 6 maanden geeft een mediane overlevingswinst van bijna 3 maanden en een verdubbeling van de 5-jaars overleving van 11 naar 22%. Neo-adjuvante therapie is niet in fase III onderzoek geëvalueerd. Chemoradiotherapie voor lokaal gevorderd pancreascarcinoom is voor de overleving niet superieur aan chemotherapie. De plaatsbepaling van chemoradiotherapie bij lokaal gevorderd pancreascarcinoom is onderwerp van onderzoek. In 1997 werd gemcitabine vergeleken met 5-FU bij lokaal gevorderd of gemetastaseerd pancreascarcinoom en bleek er een voordeel in kwaliteit van leven en een gering mediaan overlevingsvoordeel (van 4.4 naar 5.7 maanden) in de gemcitabine groep. Sindsdien zijn vele chemotherapie-schema's onderzocht, maar alleen de combinatie gemcitabine met erlotinib liet een significant, maar zeer gering overlevingsvoordeel zien. Recente, nog niet gepubliceerde resultaten van de combinatie behandeling FOLFIRINOX zijn hoopgevend, hoewel het veel bijwerkingen heeft en alleen bij fitte patiënten kan worden voorgeschreven. Er zijn maar weinig data betreffende tweedelijns behandeling.

Gezien het palliatieve karakter van de behandeling is verbetering van kwaliteit van leven een belangrijk doel. Helaas ontbreekt het in veel studies aan uniforme en valide evaluatie van kwaliteit van leven. De voor pancreascarcinoom veel gebruikte CBR (*Clinical benefit ratio*) is geen patiënt-gerapporteerde uitkomst.

Kosten-effectiviteit
Er zijn meerdere kosten-effectiviteit evaluaties uitgevoerd voor de palliatieve behandeling met gemcitabine. Drie evaluaties op basis van de gesponsorde studie door Burris et al uit 1997 toonden aan dat gemcitabine kosten-effectief is ten opzichte van 5-FU, maar dat de resultaten erg afhankelijk zijn van het overlevingsvoordeel. De data over kwaliteit van leven zijn erg zwak. De incrementele kosten per gewonnen levensjaar zijn bij extrapolatie van Zweedse en Britse evaluaties tussen de €15,000 en €20,000. Echter, de directe kosten van gemcitabine zijn na het beschikbaar komen van generieke preparaten belangrijk gedaald. Er zijn geen goede evaluaties betreffende kwaliteit-gecorrigeerde uitkomsten (QALY's). Wel wordt aangenomen dat correctie voor kwaliteit van leven de overlevingswinst reduceert en daarmee ook de kosten-effectiviteit. De combinatie van gemcitabine met erlotinib is in een Amerikaanse evaluatie niet kosten-effectief gebleken, door het geringe overlevingsvoordeel van slechts 0.4 maanden en de hoge kosten (incrementele kosten per QALY ruim boven €300,000).

Ervaring, gebruiksgemak en bijwerkingen
Gemcitabine is het middel van keuze in de adjuvante behandeling, in chemoradiotherapie schema's en in de palliatieve behandeling van pancreascarcinoom. Er is ruime ervaring met gemcitabine. In één cyclus wordt gemcitabine wekelijks toegediend gedurende 3 weken, gevolgd door een week rust. De dosis is 1000 mg/m2 per infusie en wordt poliklinisch toegediend. De belangrijkste bijwerking is beenmergdepressie, maar deze is slechts in 19% dosis-limiterend. Gemcitabine wordt meestal erg goed verdragen. Reden om de behandeling te stoppen is meestal progressie van ziekte.

Dagelijkse praktijk
In de dagelijkse praktijk wordt er meestal volgens de Nederlandse richtlijn behandeld. Dit wordt ondersteund door het illustratieve praktijkvoorbeeld in één academisch centrum. Opvallend is dat combinatiebehandeling met gemcitabine en erlotinib wordt aangeboden in enkele ziekenhuizen, ondanks dat deze behandeling niet kosten-effectief is. Omdat combinatie-behandelingen in het buitenland (bijvoorbeeld Belgie en Duitsland) wel worden gegeven, is er een groep patiënten die zich daar laat behandelen.

Werkelijk kostenbeslag en generieke producten
Sinds 2009 zijn generieke preparaten beschikbaar. De prijs van gemcitabine (200mg ampul) bedroeg €47 in 2008 en thans €20-€43. Een illustratieve berekening van het jaarlijkse werkelijke kostenbeslag van gemcitabine voor pancreascarcinoom in Nederland is door ons uitgevoerd op basis van alleen de geneesmiddelkosten zonder BTW. Uitgaande van 2000 nieuwe patiënten per jaar, bedragen de totale kosten voor gemcitabine in de adjuvante behandeling €1,302,480 (variatie in sensitiviteits analyse €868,320 tot €1,890,000), de kosten voor gemcitabine in chemoradiotherapie €223,300 en de kosten voor palliatieve behandeling €1,809,000 (variatie in sensitiviteits analyse €1,286,400 tot €5,880,000).

Lacunes

- ontwikkelen van nieuwe effectieve behandelschema's voor pancreascarcinoom in zowel neo-adjuvante, adjuvante en palliatieve setting.
- ontwikkelen van orale behandelschema's (met bijvoorbeeld capecitabine) in adjuvante setting
- adequate selectie van patiëntenpopulaties voor klinische studies (bijvoorbeeld scheiding lokaal gevorderde en gemetastaseerde tumoren in inclusiecriteria)
- adequate evaluatie van kwaliteit van leven in klinische studies (patiënt-gerapporteerd)
- gebruik van moleculaire predictieve factoren voor resultaat behandelschema's patiënt tevredenheidsonderzoek en evaluatie redenen voor second opinion

Summary

Research question

1. To evaluate the pharmacotherapeutic value of gemcitabine and other anticancer agents for the treatment of pancreatic cancer, in terms of effectiveness, cost-effectiveness, adverse effects, safety and clinical implications.
2. To evaluate the use of gemcitabine and other anticancer agents for pancreatic cancer in Dutch clinical practice.

Methods

Systematic review of literature concerning effectiveness
Systematic review of treatment protocols and guidelines
Systematic review of literature concerning cost-effectiveness
Structured interviews with clinical experts
Illustration on daily practice in one academic centre
Illustrative economic evaluation concerning direct costs of gemcitabine in pancreatic cancer

Results and conclusion

Pancreatic cancer is diagnosed in approximately 2000 patients annually in the Netherlands. Curative resection is the therapy of choice. However, the majority of patients (80%) has advanced disease at diagnosis. 5-Year survival is only 5% of all pancreatic cancer patients.

Guidelines
The Dutch (oncoline), European (ESMO) and American (NCCN) guidelines have been updated recently and essentially do not differ. Neoadjuvant therapy in resectable disease is only considered in clinical trials. Adjuvant chemotherapy is standard of care. In locally advanced pancreatic carcinoma (LAPC) and metastasized disease palliative chemotherapy is considered. However, gemcitabine-based combination therapy (including gemcitabine + erlotinib) in LAPC and metastasized disease is only considered in the NCCN guideline and not advised in the Dutch and ESMO guideline.
The BOM committee judged positively for gemcitabine as adjuvant therapy, but not for gemcitabine as palliative therapy. However, because of low toxicity and no alternative treatment, gemcitabine can be considered in this situation.

Clinical effectiveness
Neo-adjuvant therapy has not been evaluated in phase III trials. Adjuvant therapy is standard therapy, either gemcitabine-based or 5-FU-based. Adjuvant therapy with 6 months of gemcitabine resulted in survival benefit (median survival benefit of 3 months and 5-year survival of 22% versus 11% without adjuvant therapy). Chemoradiotherapy for LAPC is not superior to chemotherapy in terms of survival benefit. Since the Burris trial in 1997, gemcitabine is standard therapy in LAPC and metastasized pancreatic cancer. In that trial, a small survival benefit was reported (5.7 versus 4.4 months) and an improvement of clinical benefit ratio (CBR). Several chemotherapy regimens have been evaluated since. Only gemcitabine + erlotinib have been reported to significantly increase median survival compared with gemcitabine, although only 0.4 months. Recently, unpublished results of the FOLFIRINOX regimen have shown a promising survival benefit but also more toxicity. Data on second-line therapy are scarce.

Palliation is an important goal of therapy and therefore evaluation of quality of life is pivotal. Unfortunately, uniform and valid evaluation of quality of life is lacking. In pancreatic cancer, CBR is widely used as an outcome parameter. However, CBR is not patient reported.

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Cost-effectiveness
Cost-effectiveness evaluations of gemcitabine are based on the Burris trial, which was sponsored by the drug company. Gemcitabine is cost-effective compared to 5-FU, but the results are very sensitive to estimates of survival benefit. The evidence for the quality of life benefit of gemcitabine was considered to be poor. When extrapolating results of the UK (NICE) and Sweden evaluations to the Dutch situation, the incremental cost-effectiveness ratio (ICER) per life-year gained is likely to range from €15,000 to €20,000. However, the costs of gemcitabine are decreasing since generic preparations are available and therefore the cost-effectiveness is expected to be increased. According to illustrative analyses by NICE, the survival benefit will be reduced when adjusted for quality of life. When extrapolating results of an American evaluation, the combination of gemcitabine + erlotinib is not cost-effective, according to the ICER per quality-adjusted life year of more than €300,000.

Experience, ease of use and toxicity
Experience with gemcitabine is extensive. Gemcitabine is used in cycles of 3 weekly infusions of gemcitabine followed by 1 week of rest. De dose is 1,000 mg/m2 per infusion and the drug can be administered in the outpatient clinic. Neutropenia is dose-limiting in approximately 19%. Gemcitabine is well tolerated. Generally, the reason to stop treatment is progressive disease.

Daily practice
In daily practice the majority of medical oncologists treats patients according to the Dutch guideline. This is supported by the results of the illustration of one academic centre. However, the combination of gemcitabine + erlotinib is prescribed by some medical oncologists in the Netherlands despite this treatment is not cost-effective. A subgroup of patients seeks combination-therapy abroad.

Cost-assessment
Generic preparations of gemcitabine have become available since 2009. Direct costs of gemcitabine (200 mg vial) decreased from €47 in 2008 to €20-€43 in the Netherlands in 2011. An illustrative calculation of direct costs of gemcitabine for pancreatic cancer in the Netherlands per year was conducted (based on direct drugs costs only and no VAT included). Based on an annual incidence rate of 2000 patients, the total costs of gemcitabine for the adjuvant treatment are €1,302,480 (range in sensitivity analyses €868,320 to €1,890,000). The costs for gemcitabine in chemoradiotherapy are €223,300 and the costs for palliative treatment are €1,809,000 (range in sensitivity analyses €1,286,400 to €5,880,000).

Unexplored areas

- development of new effective treatment regimens for pancreatic carcinoma in neoadjuvant, adjuvant and palliative setting
- development of oral treatment schedules (e.g. capecitabine) in the adjuvant setting
- adequate selection of patients for clinical trials (e.g. no inclusion of non-metastasized patients in trials on palliative regimens)
- adequate evaluation of quality of life in clinical trials (e.g. patient-reported)
- use of predictive molecular factors for the result of treatment regimens
- patient's satisfaction evaluation and reasons for second opinion

1. Introduction

1.1 Type of disease/disorder

Diagnosis
Pancreatic cancer can be anatomically divided in tumors of the pancreatic head, body or tail. Clinical presentation of pancreatic cancer of the head is generally characterized by weight loss and painless jaundice. Pancreatic cancer of body and tail can be accompanied by pain. New onset of diabetes and pancreatitis may also be the first clinical feature. Smoking, diet (lack of fruit and vegetables or excess alcohol), diabetes and pancreatitis are identified as risk factors. A positive family history of pancreatic cancer is also a risk factor. The occurrence of pancreatic cancer can be associated with several genetic syndromes (1-4).

Staging
The majority of patients present with advanced disease. At presentation, only 20% of patients have resectable disease. CT-scan, MRI and/or endoscopic ultrasound (EUS) are appropriate for staging. In selected cases a diagnostic laparoscopy can be considered. In case of metastasis or irresectability, cytological or histological confirmation of malignancy is warranted before the start of palliative chemotherapy or radiotherapy. Adenocarcinomas account for 90% of pancreatic neoplasms. Mutations in the K-ras oncogene are present in the majority (90%) of pancreatic cancers (5). Staging groups are shown in Table 1. In 2002 the sixth edition of the Cancer Staging Manual by the American Joint Committee on Cancer was published, with a change in stage grouping to define stage III as unresectable, locally advanced pancreatic cancer (6). Publications of studies using a previous stage grouping should be interpreted with care.

Staging groups	TNM staging	Incidence in the Netherlands 2003-2007 (%) (7)	5-year survival in the Netherlands 2003-2007 (%)
IA	T1N0M0	2	30
IB	T2N0M0	5	11
IIA	T3N0M0	7	10
IIB	T1-3N1M0	14	7
III	T4 any N M0	13	2
IV	Any T any N M1	56	1

Table 1 Stage grouping in pancreatic cancer (6).

General principles of management
Due to improving imaging techniques (high-quality cross-sectional imaging), localized pancreatic cancer can be divided into resectable, borderline resectable and locally advanced.
Therapy of choice in resectable disease (confined to the pancreas and draining lymph nodes with a patent superior mesenteric vein and portal vein and non-involvement of the visceral arteries, stage I or II) is radical pancreatic resection followed by adjuvant chemotherapy. This surgical procedure is named after Whipple, a surgeon who perfected the pancreatic head resection in 1934. It includes end-to-side choledochojejunostomy, end-to-side pancreaticojejunostomy and end-to-side gastrojejunostomy (8). Resection margins are classified by R classification: R0 for negative resection margin, R1 for microscopically positive resection margin and R2 for macroscopically residual tumor (6).
In locally advanced pancreatic carcinoma (LAPC; stage III) resection is not always possible. There is no consensus as to what constitutes a borderline resectable tumor

with respect to large vessel involvement. A definition is abutting 180 degrees or less of the superior mesenteric artery, encasing a short segment of the common hepatic artery or causing segmental venous occlusion (9). In case of borderline resectability, neo-adjuvant therapy (chemoradiotherapy or chemotherapy) can be considered to downsize the tumor. In unresectable LAPC, palliative chemoradiotherapy can be considered.
In case of distant metastases (stage IV) or recurrent disease palliative chemotherapy or best supportive care is considered. Jaundice and gastric outlet obstruction can be treated by endoscopic placement of biliary drainage stents and palliative surgery. Radiotherapy may be a treatment modality with transient effect on pain which is often present in patients with pancreatic cancer. A review of clinical effectiveness of therapy is reported in Section 3.2.

1.2 Dutch epidemiological data

Epidemiology (general)
Pancreatic cancer is the 10th most frequent cancer in Europe, accounting for approximately 2.6% of malignancies in both sexes. More than 75% of patients are over 65 years of age. Pancreatic cancer is one of the most fatal cancer types, with more than 95% of patients dying of this disease. Without therapy, the median survival after diagnosis is 4 to 6 months. 5-Year survival in patients after pancreatic resection is 20% and in all stages 5-year survival is only 4% (10-12).

Epidemiology (the Netherlands)
The absolute annual incidence of pancreatic cancer in the Netherlands in 2008 was 1935 new patients and the crude annual incidence rate was 12.0/100,000 persons (7). No exact figures of the Dutch national prevalence are currently available. The absolute mortality caused by pancreatic cancer in the Netherlands accounted for 2378 deaths in 2008. Dutch pancreatic cancer mortality rates were 10.8/100,000 persons in 2008. The almost similar mortality rate and incidence rate reflect the poor prognosis of this disease (7).

Dutch epidemiological data of subgroups are provided in Appendix A.

1.2.1 Burden of disease

The course of pancreatic cancer is usually very aggressive. Disease-specific symptoms are significant weight loss (95%), pain (75%), anorexia (64%), nausea (50%), lethargy, depression, and weakness, and consequently patients often have an impaired performance status. Approximately 65-75% of patients develop symptomatic biliary obstruction. Palliation can be provided by an endoscopic biliary stent. A common complication is stent occlusion and cholangitis. An alternative can be percutaneous biliary drainage. Patients with potentially resectable disease, but with unresectable tumors at laparotomy can be palliated by an open biliary-enteric bypass. Symptomatic gastric outlet or duodenal obstruction occurs in 10-25% of patients. Endoscopic stenting is a palliative option. Cancer-related pain can be treated with analgesics or local therapy, including celiac plexus neurolysis and/or radiotherapy. Other disease-specific problems include pancreatic insufficiency, requiring oral pancreatic enzyme replacement therapy. Pancreatic cancer patients have a substantially increased risk of developing thromboembolic complications (4).

Quality of life
In Germany, health-related quality of life was assessed in a representative group of stage I to stage IV pancreatic carcinoma. Generic health status as expressed by the EQ-5D instrument was more likely to be impaired in all five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) (13).

1.3 Registered indication of the drug

In the Netherlands, gemcitabine, 5-fluorouracil, mitomycin C and erlotinib are licensed for the treatment of pancreatic adenocarcinoma.

Gemcitabine is indicated for treatment of patients with locally advanced or metastatic adenocarcinoma of the pancreas. The registration date of gemcitabine (Gemzar, Eli Lilly) in the Netherlands was in 1995. Since then, experience with gemcitabine is extensive. Gemcitabine is also indicated for other malignancies at specified stages, including non-small cell lung cancer, breast cancer and bladder cancer. Since 2009, generic preparations are available.

Mechanism of action
Gemcitabine (2′-2′-difluorodeoxycytidine) is a deoxycytidine analogue and inhibits DNA synthesis via inhibition of the enzyme ribonucleotidereductase and competition for incorporation in DNA with deoxycytidinetriphosphate, subsequently leading to apoptosis and cell death. It is inactive in its parent form and requires intracellular activation for its cytotoxic effects.

Dosing
The recommended dose of gemcitabine is 1,000 mg/m2, given by 30 minute intravenous infusion. This allows treatment in the outpatient clinic. The dose should be repeated once weekly for up to 7 weeks followed by one week of rest. Subsequent cycles should consist of infusions once weekly for 3 consecutive weeks out of every 4 weeks. Dose reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient. Alternative dosing regimens are fixed dose rate (FDR; 1,500 mg/m2 over 150 minutes q3/4w), low-dose (250 mg/m2 q1w) and dose-dense (2,200 mg/m2 q2w) regimes, but these regimens are not routinely administered (14;15). When combined with radiotherapy, different dosing regimens have been evaluated, often in a lower dose than the standard dose because of increased hematological toxicity. A common chemoradiotherapy regimen is gemcitabine 300 mg/m2 weekly for 6 weeks, combined with radiotherapy 1.8 Gy daily for 38 days (total 50.4 Gy).

Adverse effects
In general, gemcitabine has a relatively low toxicity profile and is well tolerated. The most common mild (grade 1 or 2) adverse drug reactions associated with gemcitabine treatment include: nausea with or without vomiting, raised liver transaminases (AST/ALT) and alkaline phosphatase, reported in approximately 60% of patients; mild proteinuria and hematuria reported in approximately 50% of patients; transient flu-like symptoms occur in 45% of patients; dyspnoea reported in 10-40% of patients (highest incidence in lung cancer patients); allergic skin rashes occur in approximately 25% of patients and are associated with itching in 10% of patients. Dose-limiting toxicity is caused by neutropenia (approximately 19% of patients), and to a lesser extent by trombopenia and anemia (16).

5-fluorouracil (5-FU) is indicated for several malignancies, including treatment of pancreatic adenocarcinoma.

Mechanism of action
5-FU is an analogue of uracil, a component of ribonucleic acid. It is metabolized by enzymes to active metabolites and functions as an antimetabolite. It inhibits cell division by interfering in the synthesis of DNA (inhibition of the enzyme thymidylatesynthetase and incorporation of 5-FU metabolites in DNA and RNA). The reduced folate leucovorin (LV) is used as the main biochemical modulator of 5-FU to enhance antitumor activity.

Dosing
Selection of an appropriate dose and treatment regimen depends upon the condition of the patient, the type of carcinoma being treated and whether 5-FU is to be administered alone or in combination with other anticancer agents. Intravenous use can be dosed 15 mg/kg bodyweight but not more than 1 g per infusion, diluted in 300 – 500 ml of 5% glucose or 0.9% NaCl and given over 4 hours. Alternatively the daily dose may be infused over 30 - 60 minutes or may be given as a continuous infusion over 24 hours. The infusion may be repeated daily until there is evidence of toxicity or a total dose of 12 – 15 g has been reached. Established 5-FU schedules in pancreatic cancer include:
Mayo Clinic schedule: folinic acid, 20 mg/m2, intravenous bolus injection, followed by 5-FU, 425 mg/m2 intravenous bolus injection given day 1-5 every 28 days.
Weekly bolus schedule (Roswell Park): folinic acid 500 mg/m2, intravenous bolus injection, followed by 5-FU, 500-600 mg/m2 intravenous bolus injection once per week for 6 consecutive weeks (weeks 1-6) every 8 weeks.
Infusional schedule: 5-FU 300 mg/m2 per day every day by continuous intravenous infusion.
FOLFIRINOX schedule: 5-FU based combination therapy every 2 weeks, consisting of oxaliplatin 85 mg/m2 and irinotecan 180 mg/m2 plus LV 400 mg/m2 followed by bolus 5-FU 400 mg/m2 on day 1, then 5-FU 2,400 mg/m2 as a 46-hour continuous infusion.

Adverse effects
The spectrum of toxicity is dose- and schedule-dependent. Adequate treatment with fluorouracil is usually followed by leucopenia. Diarrhoea, nausea and vomiting are observed quite commonly during therapy and may be treated symptomatically. An anti-emetic may be given for nausea and vomiting. Mild hair loss may be seen in a substantial number of cases particularly in females. Other side-effects include dermatitis, pigmentation, changes in the nails, ataxia, hand-foot syndrome and fever. There have been reports of chest pain, tachycardia, breathlessness and ECG changes after administration of fluorouracil. Special attention should be paid in treating patients with a history of coronary heart disease or those who develop chest pain during treatment (16).

Mitomycin-C (MMC) is an antitumor antibiotic that is activated in the tissues to an alkylating agent which disrupts deoxyribonucleic acid (DNA) in cancer cells by forming a complex with DNA. It also acts by inhibiting division of cancer cells by interfering with the biosynthesis of DNA. It is licensed for the treatment of pancreatic adenocarcinoma, but is not routinely administered to patients in the Netherlands (16).

Erlotinib (Tarceva, Roche) in combination with gemcitabine is licensed for the treatment of patients with metastatic pancreatic cancer. Erlotinib is an epidermal growth factor receptor/human epidermal growth factor receptor type 1 (EGFR, also known as HER1) tyrosine kinase inhibitor. Erlotinib potently inhibits the intracellular phosphorylation of EGFR. EGFR is expressed on the cell surface of normal cells, but may be overexpressed on cancer cells. Erlotinib is orally administered as a film-coated tablet. The regimen used in pancreatic cancer is erlotinib 100 mg once daily on a continuous schedule, added to the standard gemcitabine regimen. The most important grade 3 side effects of erlotinib when added to gemcitabine are skin rash (5%) and diarrhoea (5%). (16).

Capecitabine (Xeloda, Roche) is not licensed for the treatment of pancreatic adenocarcinoma. However, it could well be expected that this agent will be evaluated as an oral substitute for 5-FU in treating pancreatic cancer, similarly to other malignancies. It is rapidly and extensively absorbed by the gut mucosa and is activated by enzymatic conversion by the enzyme thymidine phosphorylase being expressed at much higher concentrations in tumor cells. Capecitabine doses are variable, depending on the combination regimen. Usually it is prescribed twice daily for two weeks, followed by one week of rest. The main toxicities include diarrhoea and hand-foot syndrome.

1.4 Research question / objective

1. To evaluate the pharmacotherapeutic value of gemcitabine and other anticancer agents for the treatment of pancreatic cancer, in terms of effectiveness, cost-effectiveness, adverse effects, safety and clinical applicability.
2. To evaluate the use of gemcitabine and other anticancer agents for pancreatic cancer in Dutch clinical practice.

2. Methods

2.1 Methods literature search

A systematic literature search was performed in collaboration with a clinical librarian. The Dutch concept national guideline on pancreatic cancer, published in 2010 and accessible via www.oncoline.nl, was considered the basis of the literature (12;17;18). The search was therefore limited to articles published after 1st of January, 2010. A search of relevant databases (Medline, Embase, Cochrane) was performed and articles were included if published before the 4th of November, 2010. The search terms included pancreatic neoplasms and gemcitabine, and the search was limited to clinical trials, guidelines, meta-analyses or systematic reviews, published from 2010 (see appendix C for full literature search protocol). A total of 144 unique articles were screened for relevance, by evaluation of titles and abstracts. Full paper manuscripts of potentially relevant articles were obtained and assessed for inclusion. Inclusion criteria were studies on patients with pancreatic cancer and treatment with anticancer agents, phase III clinical trials, meta-analyses, systematic reviews, guidelines and English or Dutch language. Studies concerning non-adenocarcinoma pancreatic cancer (including pancreatic neuro-endocrine tumors) were excluded. The list was expanded by related articles, such as relevant phase II articles, and relevant articles from the reference list of the Dutch national guideline.

The search for economic studies was not limited to date and the search terms cost and cost analysis were added, leading to a total of 76 unique articles screened for relevance. Inclusion criteria were cost-effectiveness analysis, cost-utility analysis and cost-minimisation analysis.

Clinical guidelines from Oncoline (Dutch), ESMO (Europe) and NCCN (USA) were reviewed. Reports of the BOM-committee were obtained from the website www.nvmo.org.

Ongoing clinical trials on pancreatic cancer were searched on the Clinical Trials Registry of the U.S. National Library of Medicine (www.clinicaltrials.org, accessed December 2010).

2.2 Methods evaluation on daily practice

Medical oncologists were invited for a structured interview. When accepted, they received a list of the items addressed in the interview. These items were general characteristics of the hospital (region, hospital type and size, number of medical oncologists, number of oncology beds, number of new outpatient oncology contacts per annum, number of pancreatic cancer patients), regimens used in treating pancreatic cancer (neo-adjuvant, adjuvant, locally advanced and metastasized), experiences in efficacy and toxicity, participation in study protocols, means of informing patients, means of counselling patients, and experiences with referral for second opinion in the Netherlands and abroad. Each medical oncologist was visited for an interview of approximately one hour. The interviews were recorded for processing only.

A representative of the Dutch patient association, SPKS (Stichting van Patiënten met Kanker aan het Spijsverteringskanaal), was interviewed to obtain input from the patients.

Input from pharmacists was obtained by cooperation of a hospital pharmacist in the project team. The input included, but was not limited to, data on generic products, the actual costs of anticancer agents in the Netherlands and illustrative data on anticancer agent use in daily practice.

3. Results

3.1 Review of guidelines

The Dutch national guideline on pancreatic adenocarcinoma has been published in 2001 and is currently updated with a concept version in 2010 (12;17). The concept guideline is reviewed here.
If possible, curative radical resection is the treatment of choice. Pre-operative (neo-adjuvant) chemotherapy or chemoradiotherapy warrants histologically proven malignant diagnosis. Level 3 evidence (only phase II studies and observational studies) for pre-treatment suggests benefit in terms of percentage radical (R0) surgery and local recurrence. Neoadjuvant chemotherapy or chemoradiotherapy in resectable pancreatic carcinoma should preferably be given in clinical trials, because higher level evidence is lacking.
In borderline resectability pre-operative chemoradiotherapy can be considered.
Post-operative (adjuvant) chemoradiotherapy is only advised as part of a clinical trial.
Adjuvant chemotherapy after surgery is indicated and considered standard therapy, either gemcitabine- or 5-FU-based.
In LAPC or metastasized pancreatic carcinoma or recurrent disease, palliative chemotherapy (gemcitabine-based) is considered. Combination therapy with erlotinib or capecitabine is not recommended because of minimal benefit and more toxicity.
Chemoradiotherapy is only recommended as part of a clinical trial. In case of pain palliation in locally advanced pancreatic carcinoma, chemoradiotherapy can be considered (12).

The European (ESMO) guideline has been published in 2010 (11).
In resectable disease, radical pancreatic resection followed by adjuvant 6 cycles of 5-FU- or gemcitabine-based chemotherapy may be given. The role of adjuvant chemoradiotherapy is controversial. Especially in individual patients with pancreatic head cancer, large tumors (>3 cm) and in patients with irradical resection, chemoradiotherapy as described in the RTOG 97-04 protocol may be an option. Neo-adjuvant treatment in clinical trials (e.g. gemcitabine-based chemoradiotherapy) can identify a subgroup of patients unlikely to benefit from surgical resection.
In borderline resectable disease neo-adjuvant therapy (chemoradiotherapy) can increase the rate of radical resections. Intra-operative radiotherapy is not recommended on a routine basis.
Irresectable locally advanced pancreatic cancer can be treated with gemcitabine and if not progressing after three months and in case of a good clinical performance status, chemoradiotherapy can be added to the treatment. In Stage IV palliative treatment with gemcitabine may be a reasonable choice, and the combination with other agents is not recommended. There is no standard treatment after progression in first-line treatment. Enrolment in clinical trials is recommended. Otherwise 5-FU/oxaliplatin should be considered as standard second line treatment (11).

The American (NCCN) guideline on pancreatic adenocarcinoma has been published in 2010 (4). Participation in clinical trials is especially encouraged.
If the tumor is resectable adjuvant treatment is recommended: gemcitabine followed by 5-FU-based chemoradiotherapy or chemotherapy alone (gemcitabine preferred, alternatives are 5-FU/LV or capecitabine). If the tumor is borderline resectable, neo-adjuvant treatment is planned with regimens similar to those used to treat locally advanced disease (but there is no uniform NCCN consensus; category 2B recommendation). Locally advanced, irresectable disease must be confirmed by biopsy.
In patients with good performance status systemic chemotherapy (gemcitabine based) with or without chemoradiotherapy, or gemcitabine-based combination therapy can be considered. In metastatic disease, gemcitabine (good or poor performance status) or gemcitabine-based combination therapy (good performance status) is advised. Salvage

therapy consists of treatment in clinical trials or 5-FU-based therapy with or without oxaliplatin. In patients with poor performance status gemcitabine or best supportive care is advised. Gemcitabine-based combinations are gemcitabine/erlotinib, gemcitabine/cisplatin, gemcitabine/oxaliplatin or gemcitabine/fluoropyrimidine (4).

In the Netherlands, the BOM-committee (commissie BOM) evaluates new anticancer agents. In 2001, the conclusion based on the phase III trial by Burris et al (19), was that despite a low toxicity profile and treatment in the out-patient clinic gemcitabine could not be considered standard treatment when judged by the Dutch PASKWIL criteria (considering outcomes in terms of response rate, survival, side-effects, quality of life, impact of treatment and level of evidence). However, in selected patients with advanced pancreatic cancer palliative treatment with gemcitabine could be appropriate (20). In 2008, adjuvant treatment with gemcitabine after curative resection based on the outcome of the CONKO-001 trial (21;22) was considered appropriate as standard treatment (23;24).

3.2 Review of literature – clinical effectiveness

Neo-adjuvant therapy

There is a rationale for a neo-adjuvant approach, since a relevant percentage of pancreatic cancer patients present with non-metastatic but locally advanced disease and microscopic incomplete resections are common. However, only phase II trials and observational studies are available. Chemoradiotherapy is the general approach in this setting.

In 2006, a small randomized phase II trial in 46 patients with resectable pancreatic cancer failed to show a survival benefit after neo-adjuvant chemoradiotherapy with gemcitabine (25). In a randomized phase II study, gemcitabine has been compared with gemcitabine plus cisplatin as neo-adjuvant chemotherapy in 50 patients with initially resectable disease (26). The combination of gemcitabine+cisplatin resulted in higher resection rates (38% versus 70%, no p-value provided) and improved survival (9.9 versus 15.6 months, no p-value provided). In a larger phase II non-randomized trial neo-adjuvant chemoradiotherapy with gemcitabine in patients with initially resectable disease resulted in a resection rate of 74% (27). Median survival in patients with resected tumors was 34 months, versus 7 months in those with unresected tumors. Adding cisplatin to this regimen did not result in improved survival or resection rates (28). Treatment with 5-FU+cisplatin-based chemoradiotherapy resulted in a 63% resection rate and acceptable side-effects (29). Downsizing of unresectable or borderline resectable LAPC seemed feasible in a retrospective study (30). Chemoradiotherapy with 5-FU+MMC resulted in 48% volume reduction and 24% progression, resulting in pancreatic resection in 38 out of 120 patients. A study designed for evaluating two regimens of chemoradiotherapy in borderline resectable disease was terminated early due to poor accrual (31). In 21 patients, both regimens (gemcitabine- versus gemcitabine+5-FU+cisplatin-based chemoradiotherapy) were tolerable. Resectability and survival were comparable to previous studies.

All retrospective and prospective studies up to December 2009 concerning neo-adjuvant chemotherapy (gemcitabine, fluoropyrimidines, mitomycin C and/or platinum analogues) combined with radiotherapy or not were included in a meta-analysis (32). In patients with initially resectable tumors, resection frequencies and survival after neo-adjuvant therapy are similar to those of patients with primarily resected tumors and adjuvant therapy. Approximately one-third of patients with initially staged non-resectable tumors would be expected to have resectable tumors following neo-adjuvant therapy, leading to a comparable survival as that in initially resectable tumor patients. Due to the heterogeneity of study protocols, the optimal chemotherapeutic and radiotherapeutic regimen cannot be extrapolated. However, the data suggest that combination chemotherapy results in higher response rates, which is reflected by higher resection rates at least in the group of initially non-resectable tumors. The conclusion was that patients with locally non-resectable tumors should be included in neo-adjuvant protocols and subsequently re-evaluated for resection (32). An important disadvantage is the need for pathological confirmation of pancreatic adenocarcinoma before treatment, which may be a difficult procedure. Another concern is that a subset of patients with initially resectable tumors may be progressive during neo-adjuvant therapy and tumors may become irresectable.

Two phase II/III clinical trials on neo-adjuvant therapy on initially resectable tumors are ongoing (see Table 3).

Trial nr.	Study start	Participants	Intervention/ comparison	Outcome
NCT00335543	2003 recruiting	254 pts stage I/II PAC resectable	GEM+CIS+RTx neoadjuvant *vs* no neoadjuvant therapy	1 OS 2 R0 resection rate 2 toxicity 2 QoL
NCT01150630 (SRSI-PACT-15)	2010 recruiting	370 pts stage I/II PAC resectable	GEM adj *vs* PEXG neo-adj + adj *vs* PEXG adj	1 OS 1 event-free survival 2 ORR 2 surgical resection rate 2 R0 resection rate 2 toxicity

Table 3 Ongoing trials on neo-adjuvant treatment for pancreatic cancer (33)
PAC = pancreatic adenocarcinoma; GEM = gemcitabine; CIS = cisplatin; RTx = radiotherapy; adj = adjuvant; neo-adj = neo-adjuvant; PEXG = cisplatin, epirubicin, capecitabine, and gemcitabine; QoL = quality of life; ORR = objective response rate; OS = overall survival; R0 = microscopically free resection margins

Adjuvant therapy

Radical resection is the single most important factor determining outcome in patients with pancreatic cancer. Even after radical resection, the 5-year survival is only approximately 10-20% (34). Adjuvant therapy may further improve survival.

Adjuvant chemotherapy without radiotherapy is beneficial in terms of overall survival, based on several data from phase III studies (see Table 4). 5-FU-based chemotherapy (35;36) and gemcitabine-based chemotherapy (21;22;37) both have shown longer progression-free survival and overall survival. In the ESPAC-3 trial 5-FU-based (Mayo Clinic schedule) and gemcitabine-based adjuvant chemotherapy have been compared (38). No difference in terms of overall survival (23 months), progression-free survival (14 months), or quality of life was found. However, gemcitabine appeared to be less toxic (serious adverse events 7.5% versus 14% ($p<0.01$). Six phase III trials are ongoing (see Table 5).

Since 1985 several phase III studies have been published regarding adjuvant chemoradiotherapy or adjuvant chemotherapy (see Table 4). A meta-analysis has been performed on studies including the GITSG (39), ESPAC-1(40) and EORTC (35;36) trials (41). It was shown that chemotherapy is effective as adjuvant treatment in pancreatic cancer but not chemoradiotherapy, although chemoradiotherapy seemed to be more effective in tumors with positive resection margins. However, the radiotherapy schemes used in the analyzed publications are considered to be obsolete nowadays (41). In the RTOG-9704 trial 5-FU-based chemoradiotherapy combined with gemcitabine has been compared to 5-FU prior to and after chemoradiotherapy (42). No significant difference in overall survival was found. In a recently published phase II study in patients after radical resection, adjuvant gemcitabine has been compared with gemcitabine-based chemoradiotherapy (43). Adjuvant gemcitabine-based chemoradiotherapy was feasible, well-tolerated, and not deleterious. Ongoing phase III trials including chemoradiotherapy are listed in Table 5.

Radiotherapy has been studied as intraoperative therapy, brachytherapy, three-dimensional conformal radiotherapy and intensity-modulated radiotherapy. These modulations of radiotherapy resulted in improved local control but failed to improve survival due to the development of distant metastatic disease (44).

Publication	Patients	Intervention/ Comparator	PFS/TTP (months)	OS (months)	5-year survival (%)
Adjuvant chemotherapy					
Bakkevold (45) 1993	47 patients, R0 R1 0%	A+M+5-FU *vs* observation		23 11 (p=0.02)	4 8
Takada (46) 2002	173 patients, R0-3 R1-3 42%	M+5-FU *vs* observation	(n.s.)	(n.s.)	11.5 18.0 (n.s.)
Neoptolemos (40) 2004 ESPAC1-2	289 patients, R0-1 R1 18%	5-FU+RTx *vs* 5-FU (Mayo) *vs* 5-FU+RTx, 5-FU *vs* observation		20.1 21.6 19.9 16.9[a]	7 29 13 11
Kosuge (47) 2006	88 patients, R0 R1 0%	5-FU+CIS *vs* observation		15.8 12.5 (n.s.)	26.4 14.9
Oettle (21) 2007 CONKO-001	368 patients, R0-1 R1 19%	GEM 6 cycles *vs* observation	13.4 6.9 (p<0.0001)	22.8 20.2 (p=0.005)	22.5 11.5
Ueno (37) 2009	119 patients, R0-1 R1 16%	GEM 3 cycles *vs* observation	11.4 5.0 (p=0.01)	22.3 18.4 (n.s.)	23.9 10.6
Neoptolemos (38) 2010 ESPAC-3	1088 patients, R0-1 R1 35%	GEM *vs* 5-FU (Mayo)	14.3 14.1 (n.s.)	23.6 23.0 (n.s.)	
Adjuvant CRT					
Kalser (39;48) 1985, 1987 GITSG	49 patients, R0 R1 0%	5-FU+RTx, 5-FU *vs* observation		20 11 (p=0.035)	19
Klinkenbijl (35) 1999 EORTC	114 patients, R0-1 R1 21%	5-FU+RTx *vs* observation		17 13 (n.s.)	20
Regine (42) 2008 RTOG	451 patients, R0-1 R1 >35%	5-FU, CRT, 5-FU *vs* GEM, CRT, GEM		16.9 20.5 (n.s.)[b]	22 31 (n.s.)
Van Laethem (43) 2010 EORTC	90 patients, R0 R1 0%	GEM *vs* GEM, GEM+RTx	10.9 11.8 (n.s.)	24.4 24.3 (n.s.)	
Neoptolemos (40) 2004 ESPAC1-2	289 patients, R0-1 R1 18%	5-FU+RTx *vs* 5-FU (Mayo) *vs* 5-FU+RTx, 5-FU *vs* observation		20.1 21.6 19.9 16.9[c]	7 29 13 11

Table 4 Published phase III trials on adjuvant chemo(radio)therapy for pancreatic cancer

A = doxorubicin; M = mitomycin C; GEM = gemcitabine; 5-FU = 5-fluorouracil; CIS = cisplatin; RTx = radiotherapy; CRT = 5-FU-based chemoradiotherapy (infusional 5-FU)

[a] chemotherapy *vs* no chemotherapy OS 20.1 vs 15.5 months, p=0.009

[b] In 380 patients with pancreatic head tumors only OS 20.6 *vs* 16.9 months, p=0.033

[c] chemoradiotherapy *vs* no chemoradiotherapy OS 15.9 vs 17.9 months, p=0.05

Trial nr.	Study start	Participants	Intervention	Outcome
NCT01013649 (RTOG-0848)	2009 recruiting	950 pts stage I/II post resection	GEM (1x or 5x) +/- 5-FU+RTx *vs* GEM+erlotinib (1x or 5x)) +/- 5-FU+RTx	1 OS 2 DFS 2 toxicity 2 QoL
NCT01150630 (SRSI-PACT-15)	2010 recruiting	370 pts stage I/II post resection	GEM adj *vs* PEXG neo-adj + adj *vs* PEXG adj *vs*	1 OS 1 event-free survival 2 ORR 2 surgical resection rate 2 tolerability
NCT01072981 (NLG0405)	2010 recruiting	722 pts stage I/II R0-1 resection	GEM +/- 5-FU RTx +/- *vs* Algenpantucel-L	1 OS 2 DFS
NCT00994721	2009 enrolment by invitation only	265 pts stage I/II P post resection	GEM 6x *vs* GEM 3x - RTx - GEM 3x	1 DFS 2 OS 2 QoL
NCT01077427	2011 not yet recruiting	366 pts stage I/II R0-1 resection	GEM *vs* GEM + regional hyperthermia	1 DFS 2 OS
NCT00960284 (SRSI-PACT-7)	2003 recruiting	102 pts stage IB-III R0-1 resection	PEXG/PEFG *vs* GEM	1 PFS, OS 2 toxicity, QoL

Table 5 Ongoing trials on adjuvant chemo(radio)therapy for pancreatic cancer (33)
GEM = gemcitabine; 5-FU = 5-fluorouracil; PEXG = cisplatin, epirubicin, capecitabine and gemcitabine; RTx = radiotherapy; PEXG = cisplatin, epirubicin, 5-FU and gemcitabine

Quality of life

Quality of life in patients with adjuvant chemotherapy has been evaluated in the CONKO-001 and ESPAC-3 trials (21;38). During adjuvant treatment with gemcitabine, an increase in Karnofsky performance status from 80% to 90% (no difference compared to observation) and an increase in body weight (treatment group significantly better than observation) have been shown (21). Quality of life as measured by the mean total Spitzer score (questionnaire of 5 dimensions, ie activity, daily life, health, social relations and future) improved in both treatment and observation groups from 1.4 to 1.8 (on a scale from 0 to 2) (21). No statistical difference in quality of life was shown when comparing 5-FU- to gemcitabine-based adjuvant chemotherapy (38).

Palliative chemoradiotherapy

In the absence of distant metastases, localised external beam radiotherapy may improve outcome. Some anticancer agents are known for their radio sensitizing effects, including 5-FU, gemcitabine and capecitabine. Two meta-analyses have shown that chemoradiotherapy can increase overall survival when compared with best supportive care (1 trial; 6.4 versus 13.2 months, $p<0.01$) or with radiotherapy alone (2 trials, 168 patients, HR 0.69; 95% CI 0.51–0.94) (49;50). However, chemoradiotherapy was more toxic. Chemoradiotherapy is not superior to chemotherapy in terms of survival (5 trials, HR 0.79; 95% CI, 0.32-1.95) and increases toxicity. Induction chemotherapy before chemoradiotherapy improves survival and is a promising strategy for selection of patients without early metastatic/progressing disease (49;50). Based on prospective phase II studies and observational studies, palliation of pain can be reached by chemoradiotherapy (51-53). It is important to bear in mind that there are no randomized controlled trials in which radiotherapy has been compared to chemotherapy. The randomized controlled trials that compared chemoradiotherapy, followed by chemotherapy to either best supportive care or radiation, are small. One phase III trial is ongoing (see Table 6).

Trial nr.	Study start	Participants	Intervention	Outcome
NCT00634725	2008	820 pts	GEM *vs* GEM-erlotinib (1st randomization)	1 OS
(GERCOR	recruiting	Stage III	GEM *vs* GEM-erlotinib *vs* CAP-RTx *vs* CAP-	2 PFS
LAP07)		Unresectable	RTx-erlotinib (2nd randomization)	

Table 6 Ongoing phase III trials on locally advanced pancreatic carcinoma (33)
GEM = gemcitabine; CAP = capecitabine; RTx = radiotherapy

Palliative chemotherapy
Chemotherapy results are disappointing in metastasized pancreatic cancer. However, based on two meta-analyses chemotherapy significantly reduces the one-year mortality (odds ratio (OR) 0.37, 95% CI 0.25 to 0.57, p<0.00001) and improves quality of life when compared to best supportive care (54;55). An overview of phase III trials is given in Table 7.

Gemcitabine became the standard of care in metastatic disease in 1997, after comparison with 5-FU in a phase III trial (19). Median survival was slightly but significantly longer in the gemcitabine group (5.7 vs 4.4 months, p=0.003) and more important, gemcitabine had a clinical benefit response (i.e. improvement of pain, performance status and/or weight for at least 4 weeks) of 24% *vs* 5% for 5-FU (p=0.022). Moreover, gemcitabine had a low side effect profile, but grade 3 and 4 neutropenia was more common in the gemcitabine group (26% *vs* 5%). 5-FU was administered as weekly bolus injection. The study can be criticised because of the small sample size (n=126), the suboptimal comparator and potential bias because of no blinding and no description of randomisation (19). Different single agent gemcitabine regimens have been investigated including fixed-dose rate infusion and high-dose regimens (56;57), but the standard regimen is 1,000 mg/m2 q3/4w.

When comparing 5-FU with gemcitabine as mono-therapy regimens, there is insufficient evidence for an overall survival difference (54;55). In a meta-analysis of secondary outcomes, overall response rate appears to be better and time to progression is longer for gemcitabine than for 5-FU, but progression-free survival were not different between the drugs (58).

Combination therapy with various anticancer agents, either gemcitabine-based or fluoropyrimidine-based, has been extensively tested. Higher response rates are reported, but also more toxicity (58). In one meta-analysis, no difference in overall survival was found between gemcitabine alone and gemcitabine combinations, or 5-FU alone and 5-FU combinations (54). 5-FU-based combinations have also failed to demonstrate an overall survival benefit in phase III trials (5-FU + cisplatin) (59). In another meta-analysis, overall survival was improved in patients on gemcitabine combination therapy as compared with those on gemcitabine alone (55).
Gemcitabine combination therapy is not standard of care. When comparing different gemcitabine combination regimes, only indirect comparisons are available (60-63). Gemcitabine-based combination therapy resulted in improved overall survival when gemcitabine was combined with capecitabine (HR, 0.86; 95% CI, 0.75 to 0.98; p=0.02) (61), erlotinib (see below), and platinum analogues (HR, 0.85 (95% CI, 0.76-0.96; p=0.010) (64), as compared to gemcitabine alone (See Figure 1). However, a subgroup analysis indicated that this only accounts for patients with a good performance status (ECOG 0-1). Patients with a worse performance status (ECOG 2) did not appear to benefit from combination therapy (64). Recent phase III trial publications of gemcitabine combined with cisplatin (65) or oxaliplatin (56) have failed to demonstrate benefit in overall survival.

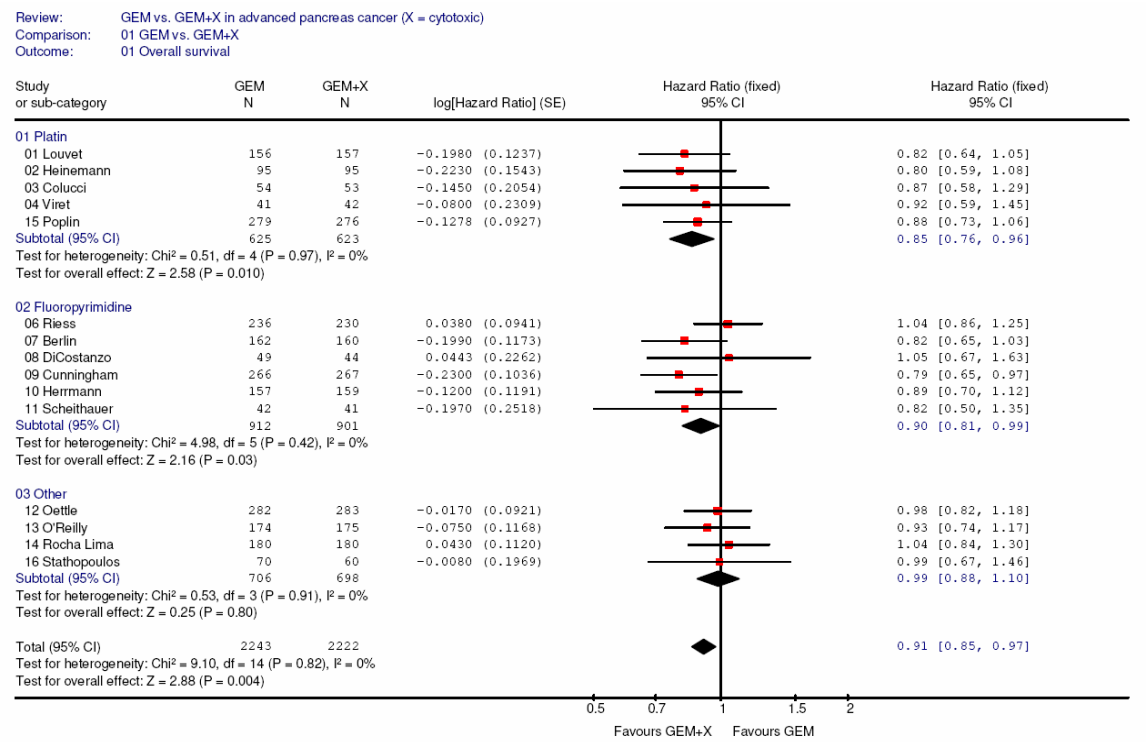

Figure 1 Meta-analysis for combination chemotherapy in advanced pancreatic cancer – overall survival with regard to combination partner (platinum analogue, fluoropyrimidine or other) for gemcitabine. Adapted from Heinemann et al (64)

Phase III studies on gemcitabine-based combination therapy with novel targeted therapies are disappointing, despite encouraging phase I/II studies, mostly because of more toxicity and no significant effect on overall survival (cetuximab (66), bevacizumab (67;68), tipifarnib (69)). However, one meta-analysis published as letter to the editor, regarding combination of gemcitabine with VEGFR or EGFR targeted therapies has pointed towards a significant effect on overall survival (pooled data from 4 studies; HR 0.89 (95% CI 0.81 to 0.98; p=0.013; heterogeneity, p=0.253; I2=26.5%)(62). In another meta-analysis on cetuximab-based therapy versus non-cetuximab therapy in advanced cancer (including other cancer types) improved PFS and OS has been demonstrated, and showed better ORR, but in the pancreatic carcinoma subgroup was no difference on PFS (HR 1.11, 95% CI 0.97–1.28), OS (HR 1.07, 95% CI 0.93–1.25), and ORR (HR 0.94, 95% CI 0.66–1.33)(70).

The only study on novel targeted therapies with positive results on overall survival up to date is the combination of gemcitabine with erlotinib, resulting in a small but significant improvement of overall survival (HR, 0.82; 95% CI 0.69 to 0.99; p=0.038)(71). This led to registration of erlotinib for the treatment of pancreatic adenocarcinoma by the FDA, despite the median gain in overall survival of approximately ten days.

Recently, promising results of the phase III trial in which gemcitabine was compared with FOLFIRINOX (5-FU, leucovorin, irinotecan and oxaliplatin) were presented (72). At the planned interim-analysis, the study was stopped because of improved median survival (10.5 months *vs* 6.9 months (HR = 0.61; 95% CI 0.46-0.81; p<0.001), better response rates (27.6% *vs* 10.9%; p=0.0008) and improved progression-free survival (6.4 months *vs* 3.4 months; p<0.0001). A concern of this regimen is the increased toxicity, with grade 3/4 diarrhoea (12.3% *vs* 1.6%), nausea (15.6% *vs* 6.3%), vomiting (17.2% *vs* 6.3%), fatigue (24% *vs* 14.3%), neutropenia (47.9 *vs* 19.2%) and febrile neutropenia (5.7% *vs* 0%) being more common in the combination arm.

Table 7 (continued on next page)

Publication	Patients	Intervention/ Comparator	PFS/TTP (months)	OS (months)	ORR (%)	CBR (%)
Palliative chemotherapy	**GEM *vs* other agent**					
Burris (19) 1997	126 patients Symptomatic St IV 70%	GEM *vs* 5-FU (bolus)	2.3 0.9 (p=0.002)	5.7 4.4 (p=0.003)		23.8 4.8 (p=0.022)
Conroy (72) 2010 (abstract)	342 patients ECOG 0-1 St IV 100%	GEM *vs* FOLFIRINOX	3.4 6.4 (p<0.0001)	6.9 10.5 (p<0.001)	10.9 27.6 (p=0.0008)	
	GEM + platinum					
Colucci (73) 2002	107 patients St IV 58%	GEM *vs* GEM+CIS	2.0 5.0 (p=0.048)	5.0 7.5 (n.s.)	9.2 26.4 (p=0.02)	49.0 52.6 (n.s.)
Heinemann (74) 2006	195 patients St IV 85%	GEM *vs* GEM+CIS	3.1 5.3 (n.s.)	6.0 7.5 (n.s.)	8.2 10.2 (n.s.)	
Colucci (65) 2010	400 patients St IV 84%	GEM *vs* GEM+CIS	3.9 3.8 (n.s.)	8.3 7.2 (n.s.)	10.1 12.9 (n.s.)	23.0 15.1 (n.s.)
Louvet (75) 2005	313 patients St IV 70%	GEM *vs* GEM+OX	3.7 5.8 (p=0.04)	7.1 9.0 (n.s.)	17.3 26.8 (p=0.04)	26.9 38.2 (p=0.03)
Poplin (56) 2009	832 patients St IV 90%	GEM *vs* GEM FDR *vs* GEM+OX	2.6 3.5 (p=0.04) 2.7 (n.s.)	4.9 6.2 (p=0.04) 5.7 (n.s.)	6 10 (n.s.) 9 (n.s.)	
	GEM + fluoropyrimidine					
Berlin (76) 2002	322 patients St IV 90%	GEM *vs* GEM+5-FU (bolus)	2.2 3.4 (p=0.022)	5.4 6.7	5.6 6.9 (n.s.)	
Riess (77) 2005 (abstract)	473 patients	GEM *vs* GEM+5-FU (infusional)	3.5 3.5 (n.s.)	6.2 5.9 (n.s.)	7.2 4.8 (n.s.)	
Herrmann (78;79) 2007	319 patients St IV 80%	GEM *vs* GEM+CAP[a]	3.9 4.3 (n.s.)	7.2 8.4 (n.s.)	7.8 10.0 (n.s.)	19 20 (n.s.)
Cunningham (61) 2009	533 patients St IV 71%	GEM *vs* GEM+CAP[b]	3.8 5.3 (p=0.004)	7.2 8.4 (n.s.)	12.4 19.1 (p=0.034)	
Nakai (80) 2010 (abstract)	106 patients	GEM *vs* GEM+S-1	3.6 5.4 (p=0.036)	8.7 14.1 (n.s.)	9.4 18.9 (n.s.)	
	GEM + other agent					
Rocha Lima (81) 2004	360 patients St IV 81%	GEM *vs* GEM+IRI	3.0 3.5 (n.s.)	6.6 6.3 (n.s.)	4.4 16.1 (p<0.001)	
Stathopoulos (82) 2006	130 patients St IV 82%	GEM *vs* GEM+IRI	2.9 2.8 (n.s.)	6.5 6.4 (n.s.)	10 15 (n.s.)	
Oettle (83) 2005	565 patients St IV 91%	GEM *vs* GEM+ pemetrexed	3.3 3.9 (n.s.)	6.3 6.2 (n.s.)	7.1 14.8 (p=0.004)	
Abou-Alfa (84) 2006	349 patients St IV 79%	GEM *vs* GEM+exatecan	3.8 4.1 (n.s.)	6.2 6.7 (n.s.)	7.1 8.2 (n.s.)	
Reni (85) 2005	99 patients St IV 70%	GEM *vs* PEFG	3.3 5.4 (p=0.003)		8.5 33.5 (p=0.008)	

Publication	Patients	Intervention/ Comparator	PFS/TTP (months)	OS (months)	ORR (%)	CBR (%)
	5-FU *vs* 5-FU combination					
Maisey (86) 2002	208 patients St IV 60%	5-FU (infusional) *vs* 5-FU+MMC	2.8 3.8 (p=0.04)	5.1 6.5 (n.s.)	8.4 17.6 (p=0.04)	
Ducreux (87) 2002	207 patients St IV 90%	5-FU (Mayo) *vs* 5-FU+CIS	2.0 2.4 (n.s.)		0 12 (p<0.01)	
	Targeted therapy					
Bramhall (88) 2002	414 patients St IV 70%	GEM *vs* GEM+ marimastat	2.9 3.5 (n.s.)	5.3 5.3 (n.s.)	11 16 (n.s.)	
Moore (89) 2003	277 patients St IV 63%	GEM *vs* tanomastat	3.5 1.7 (p<0.001)	6.6 3.7 (p<0.001)		
Van Cutsem (69) 2004	688 patients St IV 77%	GEM *vs* GEM+tipifarnib	3.6 3.7 (n.s.)	6.0 6.3 (n.s.)	8 6 (n.s.)	
Moore (71) 2007	569 patients St IV 75%	GEM *vs* GEM+erlotinib	3.5 3.7 (p=0.004)	5.9 6.2 (p=0.038)	8.0 8.6 (n.s.)	
Kindler (90) 2009 (abstract)	632 patients St IV 80%	GEM *vs* GEM+axitinib		8.2 7.4 (n.s.)		
Van Cutsem (68) 2009	607 patients St IV 100%	GEM+erlotinib *vs* GEM+erl+bev	3.6 4.6 (p=0.0002)	6.0 7.1 (n.s.)	8.6 13.5 (n.s.)	
Philip (66) 2010	745 patients St IV 79%	GEM *vs* GEM+cet	3.0 3.4 (n.s.)	5.9 6.3 (n.s.)	14 12 (n.s.)	
Kindler (67) 2010	602 patients St IV 84%	GEM *vs* GEM+bev	2.9 3.8 (n.s.)	5.9 5.8 (n.s.)	10 13 (n.s.)	

Table 7 Published phase III trials on advanced pancreatic cancer

GEM = gemcitabine; FOLFIRINOX = 5-FU, leucovorin, irinothecan and oxaliplatin; CIS = cisplatin; OX = oxaliplatin; FDR = fixed dose rate; 5-FU = 5-fluorouracil; CAP = capecitabine; IRI = irinotecan; PEFG = cisplatin, epirubicin, 5-FU and gemcitabine; MMC = mitomycin C; PVI = protracted venous infusion; erl = erlotinib; bev = bevacizumab; cet = cetuximab

[a] capecitabine 650 mg/m2 twice daily

[b] capecitabine 830 mg/m2 twice daily

Trial nr.	Study start	Participants	Intervention	Outcome
NCT00541021	2006 recruiting	104 pts Stage IV ECOG 0-2	GEM+sorafenib *vs* GEM+placebo	1 PFS 2 toxicity 2 ORR 2 CBR 2 QoL 2 OS
NCT00425360	2006 recruiting	1110 pts Stage IV ECOG 0-2	GEM+CAP *vs* GEM+CAP+vaccination *vs* GEM+CAP, followed by vaccination	1 OS 2 TTP 2 CBR 2 ORR 2 toxicity 2 QoL
NCT00844649	2009 recruiting	630 pts metastasized ECOG 0-1	GEM *vs* GEM+abraxane (ABI-007)	1 OS 2 toxicity 2 PFS 2 ORR
NCT01231347	2011 recruiting	825 pts metastasized ECOG 0-1	GEM+AMG-479 (IGF-1R mab) 2 dosage arms *vs* GEM+placebo	1 OS 2 PFS 2 ORR 2 DCR 2 toxicity
NCT00662688	2007 recruiting	136 pts metastasized ECOG 0-2	GEM *vs* GEM+CAP *vs* GEM+dalteparin *vs* GEM+CAP+dalteparin	1 tromboembolic events 2 tromboembolic related survival 2 PFS 2 OS 2 toxicity

Table 8 Ongoing phase III trials on advanced pancreatic cancer (33)
GEM = gemcitabine; CAP = capecitabine; IGF-1R = insulin-like growth factor-1 receptor; mab = monoclonal antibody

Second-line therapy

There are limited data concerning second-line therapy after failure of gemcitabine-based therapy (see Table 9). The first phase III data were from the CONKO-003 trial, comparing 5-FU/LV+oxaliplatin (OFF) with best supportive care. A modest improvement of median overall survival was calculated (21 *vs* 10 weeks, p=0.0077). This trial was closed after inclusion of 46 out of 165 patients because best supportive care was no longer accepted by participating centers (91). Recently, new insights have come from the FFCD-0301 phase III study, in which the question was explored, whether a platinum-based regime could add to the treatment of advanced pancreatic cancer. First-line gemcitabine followed by second-line 5-FU/LV+cisplatin was compared with first-line 5-FU/LV+cisplatin followed by second-line gemcitabine (59). No difference in terms of OS or PFS was observed. Sixty percent of patients were able to receive second-line therapy after disease progression. The overall survival in the gemcitabine followed by 5-FU/LV+cisplatin arm was 8 months (59).

Publication	Patients	Intervention/ Comparator	PFS/TTP (months)	OS (months)
2nd line chemotherapy				
Oettle (91) 2005 (abstract)	46 patients GEM pre-treated	BSC *vs* OFF		7.9 9.2 (p=0.0312)
Dahan (59) 2010	202 patients St IV 100%	GEM -> 5-FU +CIS *vs* 5-FU+CIS -> GEM	3.5 3.4 (n.s.)	8.0 6.6 (n.s.)

Table 9 Published phase III trials on second line treatment in advanced pancreatic cancer
BSC = best supportive care; OFF = oxaliplatin, 5-FU and leucovorin; GEM = gemcitabine; CIS = cisplatin; 5-FU = 5-fluorouracil

Trial nr.	Study start	Participants	Intervention	Outcome
NCT01121848	2010 recruiting	128 pts After 1st line gemcitabine	CAP or 5-FU *vs* CAPOX or FOLFOX6	1 PFS 2 ORR 2 duration of response 2 OS 2 DCR
NCT00440167	2006 closed for accrual	Stage III or IV ECOG 0-2	CAP+erlotinib -> GEM *vs* GEM+erlotinib -> CAP*	Not specified

Table 10 Ongoing phase III trials on second line treatment in advanced pancreatic cancer (33) GEM = gemcitabine; 5-FU = 5-fluorouracil; CAP = capecitabine; CAPOX = capecitabine and oxaliplatin; FOLFOX = 5-FU, leucovorin and oxaliplatin; DCR = disease control rate
* Crossover design for 2nd line treatment

Subgroups
In a retrospective study of stage III/IV pancreatic cancer in elderly patients in Japan, effectiveness and safety were not different in patients aged >70 years or patients aged <70 years when treated with gemcitabine (92).

Quality of life
Because of the limited benefit of chemotherapy on survival, quality of life is an important secondary endpoint in pancreatic cancer. No meta-analyses are available because of lack of uniformity in assessing quality of life. Clinical benefit response (CBR) is a composite endpoint of pain, performance status and weight.
In the comparative trial on gemcitabine *vs* 5-FU, CBR was 23.8% and 4.8%, respectively (p=0.022) (19). Recent trials on the evaluation of quality of life include the following:
both gemcitabine and gemcitabine+cetuximab showed palliation of both pain (successful worst pain palliation in 38% and 45% of patients, respectively) and emotional well-being (clinically significant improvement at 17 weeks in both trial arms) (93).
Both gemcitabine and gemcitabine + capecitabine resulted in a CBR of 19% and 20%, respectively (79). Quality of life, as expressed by linear-analog self-assessment indicators (including overall treatment burden, physical well-being, mood, coping effort, and functional performance), improved during chemotherapy in both treatment arms, and worsened two months before treatment failure (79). These results are consistent with the reported QoL outcomes in another trial comparing gemcitabine and gemcitabine + capecitabine (61).
When comparing gemcitabine with gemcitabine + cisplatin, CBR was 23% vs 15% (p=0.057) (65). Improvement in quality of life was modest and not statistically significant.
In the trial in which gemcitabine has been compared with the PEFG-regimen, gemcitabine alone was less effective at improving quality of life, including emotional function, fatigue, pain, and flatulence (85). No statistical comparisons were made between groups, but a clinically important change was expressed as the percentage of people with an

improved score. Response was associated with improved quality of life suggesting that effective treatment of pancreatic adenocarcinoma may have an important role in these patients (94).
In the trial comparing gemcitabine and gemcitabine + erlotinib, QoL was evaluated by questionnaires (71). There was no significant difference between the arms in global quality of life or in the individual domains with the exception of more diarrhoea in the gemcitabine + erlotinib arm ($p<0.001$).

3.3 Review of literature – cost-effectiveness

For an overview of published trials, see Table 11.

In the United Kingdom, NICE has published the Guidance on the use of gemcitabine for the treatment of pancreatic cancer in 2001. Its conclusion is that "Gemcitabine may be considered as a treatment option for patients with advanced or metastatic adenocarcinoma of the pancreas and a Karnofsky performance score of 50 or more, where first-line chemotherapy is to be used. Gemcitabine is not recommended for patients who are suitable for potentially curative surgery, or patients with a Karnofsky score of less than 50. There is insufficient evidence to support the use of gemcitabine as a second line treatment in patients with pancreatic adenocarcinoma" (95).

Three economic evaluations have been published on the basis of one sponsored trial, the Burris trial (19). These evaluations have been reviewed and summarized by Ward et al (96). Gemcitabine was considered reasonably cost-effective as compared with 5-FU-based regimens, but very sensitive to reduced estimates of survival benefit over comparators. The evidence for the quality of life benefit of gemcitabine was considered to be poor.

A Swedish economic evaluation estimated the incremental cost per life-year gained (LYG) of gemcitabine as compared to best supportive care from a societal point of view (97). The data of outcome and resource use were taken retrospectively from the Burris trial and Swedish epidemiological data. The incremental cost per LYG was estimated to be SEK 132,286 (Swedish kroner; based on 2000 exchange rates and price-level, comparable to £14,000). One-way sensitivity analysis indicated variation between £6,900 and £24,800. The cost-effectiveness ratio was particularly sensitive in upward direction to reductions in incremental survival. However, this evaluation was based on retrospective data and combined US survival results and Swedish epidemiological data (97).

The economic evaluation of Eli Lilly in the industry submission has been published in 2003 (98). From a NHS perspective with an 18-month time horizon, direct costs of treatment with gemcitabine and 5-FU, based on the regimens of the Burris trial, were estimated. Survival gain was estimated by using Kaplan-Meier curves and mean (as opposed to median) survival rates, resulting in a higher survival estimate (2.27 months) than in the Burris trial (1.24 months). Incremental cost-effectiveness ratios were presented: the central estimate of incremental cost per LYG was £12,206. Apart from the clinical benefit ratio, no quality of life data were included. The incremental cost per clinical benefit responder was £12,142. Sensitivity analysis showed cost-effectiveness ratios to be particularly sensitive to reductions in the survival and clinical benefit ratio gain assumptions.

An Italian evaluation has been published in abstract form only (99). Cost data were estimated from individual data on the use of resources and morbidity. The incremental cost of gemcitabine was estimated to be less than $20,000 as compared with the cost of 5-FU. Additional data were provided in the review of Ward et al (96), based on personal communication. The incremental LYG was estimated to be 0.22 years. The incremental cost was $10,538 and the estimated discounted cost per LYG $48,000. Based on their analysis of quality of life, the cost per QALY was $52,000. No sensitivity analysis was presented.

An economic evaluation on gemcitabine was conducted in the United Kingdom in 2001 (96). The survival gain was adapted from the Eli Lilly economic evaluation (2.27 months; 0.19 years). No QoL evidence had been identified, but an illustration using Q-TWiST analysis was provided. Direct medical costs were also taken from Eli Lilly data. Two

regimens of 5-FU were considered as comparator (De Gramont: 400 mg/m2 bolus followed by 400 mg/m2 as 22 hour infusion for which an inpatient stay is required) and PVI (protracted venous infusion; 300 mg/m2 continuously every day via an ambulatory pump). The cost of 5-FU is dependent on the mode of its delivery. The incremental cost per LYG of gemcitabine over the PVI 5-FU or De Gramont regimen was £16,543 or £7,209, respectively. Sensitivity analysis indicated variation between £8,527 and more than £25,000, and is particularly sensitive to assumptions on cost and survival. The illustration of cost per QALY gained of gemcitabine showed that the incremental QALY gained is 0.148 years, leading to an incremental cost per QALY gained of £21,088. Thus, addition of QoL adjustment is likely to reduce the survival gain. It is important to state that the clinical evidence on which the analysis is based is poor and therefore the cost-effectiveness analysis cannot be considered to be robust.

In 2003, an estimate of the direct cost of treatment has been assessed for the Swedish situation in 1997-1999. Average cost of treatment was estimated to be €18,947, 11% of which was attributable to chemotherapy (gemcitabine or 5-FU) (100).

An evaluation of the difference in treatment costs before and after the introduction of gemcitabine in Japan in 2001 was published in 2005 (101). Although direct costs of gemcitabine were an 18-fold higher than those of 5-FU, the total costs did not tend to become higher in a single institution, probably because of simplification in examinations and shorter hospitalization. However, when comparing international average costs between Sweden, Japan and the United States the cost were $19,499, $35,892 and $48,803, respectively.

Economic analyses on chemoradiotherapy in LAPC have been conducted. In 2007 an analysis based on economic modelling has been published (102). Clinical effectiveness was estimated from the SEER-Medicare database and costs were supplemented from the literature. A Markov model was developed to evaluate the cost-effectiveness of radiotherapy+5-FU relative to no treatment in elderly patients with LAPC and to determine the economic potential of radiotherapy+gemcitabine. Under the base case assumptions, with a given patient of 65 years of age without major comorbidity, the incremental cost-effectiveness ratio (ICER) per QALY was $68,724 for radiotherapy+5-FU relative to no treatment. If all the patients in this cohort would receive two cycles of gemcitabine after chemoradiotherapy, the ICER increased to $76,548 per QALY. Because the effectiveness of radiotherapy+gemcitabine is unknown, a hazard ratio for death of 0.85 or less for the gemcitabine-based chemoradiotherapy relative to the 5-FU-based chemoradiotherapy corresponded with an ICER of less than $100,000 per QALY. In the perspective of a threshold of $100,000 per QALY, these treatments were considered to be cost-effective.

In 2010, in another economic evaluation in LAPC treated with gemcitabine alone, gemcitabine plus conventional radiotherapy, gemcitabine plus intensity modulated radiotherapy and gemcitabine plus stereotactic body radiotherapy have been compared by construction of a Markov model (abstract only, (103)). Clinical effectiveness data were obtained from literature, costs were derived from US Medicare data. The ICER of gemcitabine plus stereotactic body radiotherapy as compared to that of gemcitabine alone was $80,131 per QALY, whereas the ICERs of gemcitabine plus conventional radiotherapy or intensity modulated radiotherapy compared to gemcitabine alone were $134,965 and $2,083,882 per QALY, respectively. Probabilistic sensitivity analysis demonstrated that the probability of cost-effectiveness (at a willingness to pay of $100,000 per QALY) for the four treatment strategies was 31%, 12%, 0.3% and 56%, respectively.

An economic evaluation concerning neo-adjuvant and adjuvant therapies is available in abstract only (104). A model was constructed to evaluate four regimens: neoadjuvant gemcitabine-based chemoradiotherapy (50.4 Gy), the same regimen with a different radiotherapy dose (30 Gy), adjuvant chemoradiotherapy (per RTOG 9704 protocol) and

adjuvant gemcitabine (per ESPAC-3 protocol). Effectiveness data were obtained from literature, costs were derived from Medicare in 2009 US dollars. The estimated cost of the adjuvant gemcitabine regime was $74,649. The incremental cost of adding radiotherapy was >$5,000 without survival benefit. Median survival benefit of neo-adjuvant therapy over adjuvant chemotherapy was 4 months, with incremental costs of $30,028 (50,4 Gy) and $15,566 (30 Gy). Therefore the authors conclude that neo-adjuvant therapy as compared to adjuvant therapy is cost-effective.

Three studies have evaluated the economic impact of adding erlotinib to gemcitabine in palliative chemotherapy for advanced pancreatic cancer.
The cost-effectiveness from a societal point of view was evaluated in 2006 (abstract only, (105)). Effectiveness parameters were obtained from literature and costs from Medicare. When using wholesale sources of erlotinib costs, incremental costs per LYG were $364,680 upon addition of erlotinib for 6 months. The authors concluded that adding erlotinib to gemcitabine does not approach cost-effectiveness at even the highest year per life gained.
Other investigators, with author disclosures related to the manufacturer of erlotinib, have determined the budget impact of adding erlotinib in a model of a hypothetical managed care plan, consisting of 500,000 members (106). In this model, 43 newly diagnosed pancreatic cancer cases per 500,000 persons were estimated each year. Assuming that erlotinib would be added to the treatment regime in 10 patients for a duration of 15.7 weeks, the incremental costs were $120,000, or $0.020 per health care plan member per month. This result is relatively insensitive to factors affecting direct costs in sensitivity analyses. However, the model relies on the low incidence (8.6 per 100.000) and the assumption of treating only 23% for 15.7 weeks of these patients.
The cost per QALY of adding erlotinib to gemcitabine was estimated by a post-hoc, informal cost-effectiveness analysis (107). The only significant QoL domain was time spent with diarrhoea. Costs were presented in 2007 US dollars. The incremental costs per LYG of adding erlotinib to gemcitabine were $410,000. When adjusted to quality of life impact of diarrhoea, the ICER per QALY was between $430,000 and $510,000 (107).

Study	Type of economic evaluation	Perspec-tive used	Time frame	Unit cost data	Source of effectiveness data	Source of resource use data	Comparator/ Intervention	Effectiveness (Mean survival)	Total costs	Cost-effectiveness results (ICER per LYG)	Remarks
Ragnarson (97) 1999	Cost-effectiveness	Sweden; societal	lifetime	1996 SEK; direct medical costs and transportation, no discounting	Burris (US) (19) Retrospective Swedish data 1994-95	Burris (US) (19)	BSC GEM+BSC	- 0.104 years (incremental)	- € 1,549 (SEK 13,771) (incremental)	- € 14,880 (SEK 132,286)	Sensitivity analysis: (survival, additional care, nr of cycles) € 7,297 to 26,362 (SEK 64,870 to 234,361)
Trippoli (96;99) 1999 (abstract)	Cost-utility	Not reported	Not reported	Individual data, annual discount 3%	Burris (19), Q-TWiST analysis	Individual data	5-FU GEM	- 0.22 years QALY 0.20 (incremental)	- € 7,636 ($ 10,538) (incremental)	- € 37,681 / QALY ($ 52,000)	No sensitivity analysis
Aristides (98) 2003	Cost-effectiveness	United Kingdom, NHS	18-month horizon	2000 UK£; direct medical costs, annual discount 6%	Burris (19)	Burris (19)	5-FU GEM	0.377 years 0.565 years (0.189 incremental)	€ 1,484 (£ 1,261) € 4,199 (£ 3,569)	- € 14,360 (£ 12,206)	Sensitivity analysis: (costs) € 11,764 to 29,764 (£ 10,000 to 25,300) ICER is very sensitive to reductions in survival
Ward (96) 2001	Cost-effectiveness and -utility	United Kingdom, NHS	Not reported	2000 UK£, direct drug and health service costs, discounting?	Burris (19), illustration QoL with Q-TWiST analysis	Ross (108)	5-FU (PVI) 5-FU (GRA) GEM	0.377 years 0.377 years 0.565 years (0.189 incremental) QALY 0.148	€ 2,018 (£ 1,715) € 4,092 (£ 3,478) € 5,693 (£ 4,839)	- - € 19,462 (PVI) (£ 16,543) € 8,481 (GRA) (£ 7209)	Sensitivity analysis: € 10,032 to >29,411 (£ 8,527 to >25,000; PVI) € 24,809 / QALY (PVI) (£ 21,088)
Grubbs (109) 2006 (abstract)	Cost-effectiveness	US	Not reported	2006 US$ retail costs	Moore (71)	Not reported	GEM GEM+ERL	6.0 months 6.4 months	- € 12,038 ($ 16,613)	- € 361,144 ($ 498,379)	Sensitivity analysis: (therapy duration) € 240,372 ($ 332,252)
Miksad (107) 2007	Cost-effectiveness	US; third party payer	lifetime	2007 US$ wholesale prices and Medicare reimbursement rates, no discounting	Moore (71)	experts	GEM GEM+ERL	- Incremental 7.98 or 9.36 days (adjusted for impact of diarrhoea)	- € 11,010 ($ 15,194)	- € 297,101 ($ 410,000)	ICER per QALY € 311,594-369,565 ($ 430,000-510,000)

Table 11 Cost-effectiveness gemcitabine in pancreatic cancer

1 € = 0.85 UK£ = 1.38 US$ = 1.36 CAN$ = 8.89 SEK (currency rates February 2011, www.xe.com)

SEK = Swedish Kroner; BSC = Best supportive care; ICER = incremental cost effectiveness ratio; QALY = Quality-adjusted life year; GEM = gemcitabine; 5-FU = 5-fluorouracil; PVI = protracted venous infusion; GRA = de Gramont regimen; NHS = National Health Service (UK); Q-TWiST = quality-adjusted time without symptoms or toxicity

3.4 Daily practice in the Netherlands

Six medical oncologists were interviewed, representing 3 academic centres and 3 peripheral hospitals spread over the Netherlands. The total annual count of new patients with pancreatic cancer treated in these hospitals is 445 (range per hospital: 15-300 patients). One representative of the Dutch pancreatic cancer patient alliance was interviewed. This representative conducts 50% of fellow-patient contacts in the Netherlands, which is estimated by this representative to be 20 contacts per year.

Gemcitabine is the mainstay of chemotherapy in pancreatic cancer and preferred over 5-FU. Treatment with gemcitabine is well tolerated. Hospital admission because of toxicity of gemcitabine is rare. Dose adjustments are infrequent.

Adherence to Dutch clinical guidance seems to be high.
In resectable disease, radical resection and adjuvant chemotherapy are the standard of care in all interviews. Neo-adjuvant therapy is only considered in borderline resectability. However, neo-adjuvant chemoradiotherapy in borderline resectable pancreatic carcinoma is not considered in one academic and one peripheral hospital.
Locally advanced disease and metastasized disease are treated with gemcitabine in 5 out of 6 hospitals. In one hospital, gemcitabine-based chemoradiotherapy is given for LAPC and gemcitabine for metastasized disease.
Despite limited evidence, erlotinib added to gemcitabine is given as standard treatment by some, including one of the interviewed medical oncologists. Because of the palliative nature of treatment in advanced pancreatic cancer, toxicity is an important factor in treatment. Therefore, toxic regimens like gemcitabine-based combination therapy are not yet incorporated in the Netherlands. Limited experience in the field indicates that treatment with the novel FOLFIRINOX regimen might be an alternative for patients in good clinical condition.
Second-line therapy after gemcitabine is not routinely offered to patients; if so, participation in a phase I trial is offered in 5 out of the 6 hospitals.
In all hospitals, patients are informed on the treatment by the medical oncologist and by a specialized nurse as well.

Whenever possible, treatment in study protocols is preferred. It is estimated by the interviewed oncologists that this is offered to 40 to 70% of patients.

The representative of the Dutch pancreatic cancer patient alliance emphasized the importance of objective, reliable and complete information. Preferably, the information is provided by both the medical oncologist and a specialised oncology nurse, supplemented with written information. The most common reason for consulting the patient alliance is lack of information. Treatment decisions are preferably made by counselling. There are no signals of impaired availability of chemotherapy in the Netherlands.

A group of patients is seeking a second-opinion. No structured information is available of optional clinics where second opinions can be obtained. A subgroup of patients will obtain a second-opinion abroad, generally in Belgium or Germany. The reasons for a second-opinion include uncertainty about the advice and patients preference for alternative therapy, including gemcitabine-based combination therapy.

Illustration
Obtaining reliable absolute numbers of pancreatic cancer patients and how they are treated per hospital is difficult and time consuming. Therefore, an illustration is provided of the results of one academic centre. In 2010, 27 patients were referred to the

medical oncology department with the diagnosis pancreatic adenocarcinoma. Preferred treatment strategies are adjuvant therapy after gross resection of resectable tumor, consisting of six cycles of gemcitabine (gemcitabine 1000 mg/m2 weekly on days 1, 8, 15 followed by one week rest). For borderline resectable disease neo-adjuvant treatment is considered, which is the same treatment as given for LAPC. Patients with LAPC are treated with chemoradiotherapy (radiotherapy on days 1-34, total dose 50,4 Gy), combined with weekly gemcitabine 300 mg/m2 for 6 weeks, followed from week 8 by gemcitabine 1000 mg/m2 weekly on day 1, 8, 15 followed by one week rest). LAPC is also treated in a phase II clinical trial with conventional chemoradiotherapy combined with panitumumab. Palliative treatment consists of gemcitabine (gemcitabine 1000mg/m2 weekly on day 1, 8, 15 followed by one week rest) or FOLFIRINOX, which is only considered in good clinical condition. Baseline and follow-up information of one patient was missing. In Table 11 a summary is given.

Distribution of tumor stages is consistent with literature. Of 27 patients, 17 patients (63%) were actually treated, including 2 patients who were treated in other hospitals. Dose reductions were necessary in 7 of 15 patients (46%). Of patients who were not treated (37%), 4 patients declined chemotherapy themselves, and 5 patients were in bad clinical condition and therefore were not offered chemotherapy. No neo-adjuvant treatment was given.

Stage	**Preferred treatment strategy**	**Patients**	**%**	**Treated**	**Not treated**
Stage I Stage IIA Stage IIB	resection + adjuvant gemcitabine	4 patients	15	2 patients (1 dose reduction) 1 patient treated elsewhere	1 patient declined adjuvant therapy
Stage III	chemoradiotherapy	6 patients	22	2 patients in clinical trial 3 patients standard therapy (1 dose reduction)	1 patient declined therapy
Stage IV	palliative gemcitabine	15 patients	55	7 patients (4 dose reduction) 1 patient treated elsewhere	2 patients declined therapy 5 patients bad condition
	palliative FOLFIRINOX	1 patient	4	1 patient (1 dose reduction)	
Unknown		1 patient	4		1 unknown
Total		27 patients	100	17 patients	10 patients

Table 11 Illustration: Referred patients to medical oncologists in one academic centre

3.5 Cost assessment

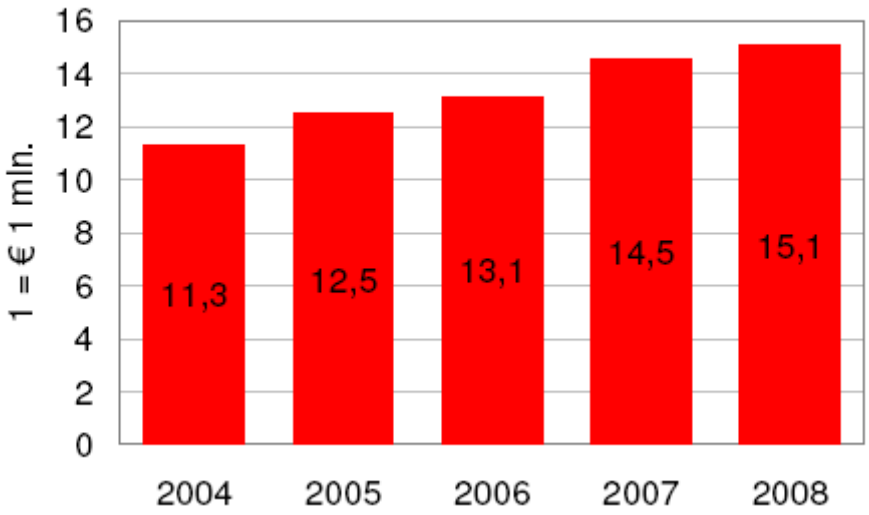

Figure 2 Total costs gemcitabine for all indications, all hospitals in the Netherlands, 2004-2008 (Adapted from Stichting Farmaceutische Kengetallen, april 2010)

The Dutch Foundation for Pharmaceutical Statistics (Stichting Farmaceutische Kengetallen, SFK) has been evaluating data concerning the use of pharmaceuticals in the Netherlands since 1990 (110). Since 2006, SFK monitors costs of expensive drugs in hospitals. Expensive drugs in hospitals has been defined as drugs that are incorporated in the 'Beleidsregel Dure Geneesmiddelen', which in practice are drugs that cost more than €2.5 million. In 2008, total costs of expensive drugs in Dutch hospitals were €379.5 million, with an increase of 19.5% compared to 2007 (111).

Total costs of gemcitabine for all indications in the Netherlands have been steadily increasing from 2004 to 2008 (see Figure 2). Since the introduction of generic preparations of gemcitabine in 2009, the direct costs of gemcitabine (200 mg vial) have dropped from €47 in 2008 to €37.50 in 2010. Therefore, a decrease in total costs is expected (111). For actual costs, see Table 12.

	Manufacturer	Presentation	Price (€)
Gemcitabine	Eli Lilly (Gemzar)	1000 mg	186,22
		200 mg	43,04
	SUN	1000 mg	186,22
		200 mg	41,00
	Accord	1000 mg	186,22
		200 mg	41,00
	Actavis	1000 mg	186,21
		200 mg	43,03
		1000 mg = 25 ml	186,21
		2000 mg = 50 ml	372,42
		200 mg = 5 ml	43,03
	CF	38 mg/ml; 26,3 ml	193,68
		38 mg/ml; 5,26 ml	41,00
	Ebewe	1000 mg	175,92
		200 mg	32,40
		1000 mg = 100 ml	195,00
		200 mg = 20 ml	41,00
		500 mg = 50 ml	97,50
	Fresenius	1000 mg	180,00
		2000 mg	360,00
		200 mg	41,00
	Hospira	1000 mg	185,00
		2000 mg	370,00
		200 mg	42,50
	PCH	1000 mg	91,03
		200 mg	20,90
	Sandoz	1000 mg = 25 ml	195,00
		2000 mg = 50 ml	390,00
		200 mg = 5 ml	41,00
5-FU	PCH	5000 mg = 100 ml	33,44
		500 mg = 10 ml	3,88
		1000 mg = 20 ml	6,89
		250 mg = 5 ml	1,94
	Accord	5000 mg = 100 ml	33,44
		500 mg = 10 ml	3,28
		1000 mg = 20 ml	6,89
		250 mg = 5 ml	1,72
	Ebewe	5000 mg= 100 ml	29,52
	Sandoz	500 mg = 10 ml	3,28
		1000 mg = 20 ml	6,89
		250 mg = 5 ml	1,53
Erlotinib	Fisher farma (Roche)	100 mg	1756,00*
		150 mg	2180,00*
	Roche	25 mg	510,86*
		100 mg	1767,99*
		150 mg	2189,34*
	Delphi (Roche)	150 mg	2143,08*

Table 12 Direct costs of gemcitabine, 5-FU and erlotinib in the Netherlands, based on G-standaard handelsproducten January 2011

* 30 tablets

An illustrative calculation on actual direct costs of gemcitabine in the treatment of pancreatic cancer per annum is provided below.

Assumptions on incidence rates and stage grouping are based on epidemiological data from the Netherlands (See Section 1.2.1; (7)). Direct costs of gemcitabine are provided in Table 12. No value-added tax was included. We assumed 2,000 new pancreatic cancer patients per annum, with 15% initially resectable tumors, 75% advanced, irresectable tumors (stage III and IV) and 10% locally advanced/borderline resectable tumors. For this illustration, we assumed 100% of patients treated per standard protocol and 0% in clinical trials. Chemoradiotherapy with weekly gemcitabine 500 mg/m2 for 6 weeks combined with radiotherapy to a total dose of 50.4 Gy, was considered standard therapy for locally advanced/borderline resectable tumors (31). Standard adjuvant therapy is 6 cycles of gemcitabine 1,000 mg/m2 according to the CONKO-001 trial (21). Standard palliative therapy in irresectable tumors is gemcitabine 1,000 mg/m2 according to the Burris trial (19). We assumed that the average body surface area is 1.8 m2.

In Table 13 an overview of total costs of gemcitabine based on our calculation is provided.

Treatment	Patients	Cost per treatment	Total costs	Sensitivity analyses
Adjuvant	270 patients (180-270)	€4,824	€1,302,480	€868,320 to €1,890,000
Chemoradiotherapy	200 patients	€1,116	€ 223,300	
Palliative	750 patients (600-1200)	€2,412	€1,809,000	€1,286,400 To €5,880,000
Total	1230 patients (980-1670)		€3,334,780	

Table 13 Calculation on total costs of gemcitabine in pancreatic cancer in the Netherlands

Adjuvant therapy is indicated in 300 patients (2,000 patients * 15%). Resource use was derived from the CONKO-001 trial (21). The treatment protocol included 6 cycles, with every cycle consisting of 3 weekly infusions of gemcitabine 1,000 mg/m2 followed by one week of rest. In the trial 10% of patients received no therapy and 62% completed the treatment protocol. The average dose of gemcitabine was 700 mg/m2 per infusion (due to dose reductions).
We assume that 270 patients (300 patients * 90%) will actually receive adjuvant therapy, consisting of 18 infusions (6 cycles * 3 infusions). The average dose is assumed to be 700 mg/m2, and therefore 1,260 mg per infusion (700 mg/m2 * 1.8 m2). Direct costs of one infusion of gemcitabine is calculated at €268 (1 vial of 1,000 mg (€186) and 2 vials of 200 mg (2 * €41 = €82)). One adjuvant treatment is calculated at €4,824 (18 infusions * €268). When treating 270 patients, total direct costs of gemcitabine are calculated at €1,302,480.

Sensitivity analyses
When varying the percentage of patients treated from 60% to 100%, the total direct costs of gemcitabine range from €868,320 to €1,447,200.
When increasing the average dose to 1000 mg/m2, one adjuvant treatment is calculated at €6,300. The total direct costs of gemcitabine when treating 270 patients increase to €1,701,000.
When increasing both percentage of patients and average dose to 100%, total direct costs of gemcitabine increase to €1,890,000.

Chemoradiotherapy treatment is indicated in 200 patients (2,000 patients * 10%). We assumed that all patients receive 6 weekly infusions of gemcitabine 500 mg/m2 without dose reductions. Thus, direct costs of one infusion of gemcitabine is calculated at €186

(500 mg/m2 * 1.8 m2 = 900 mg). The costs of gemcitabine in one chemoradiotherapy treatment is calculated at €1,116 (6 infusions * €186). When treating 200 patients the costs of gemcitabine are €223,300. A subset of these patients will eventually have progressive disease and receive palliative therapy.

Palliative therapy is indicated in 1,500 patients (2,000 patients * 75%), however we assume that only 50% actually receives therapy due to poor clinical condition (ECOG >2) or denial of chemotherapy. This is based on our experience and the structured interviews (see Section 3.4). Resource use was derived from the Burris trial (19). The treatment protocol included cycles of gemcitabine until disease progression or toxicity. The first cycle of gemcitabine consists of 7 weekly infusions of gemcitabine 1,000 mg/m2 followed by one week of rest. Every following cycle consists of 3 weekly infusions of gemcitabine 1,000 mg/m2 followed by one week of rest. The median PFS on gemcitabine treatment in the Burris trial was 2.3 months (=10 weeks). However, only symptomatic patients were included in that trial. The median PFS on gemcitabine treatment ranged from 2.0 to 3.9 months (9 to 17 weeks) in the trials listed in Table 7. We assumed that 750 patients (1,500 patients * 50%) will actually receive palliative therapy, consisting of 9 infusions. The average dose is assumed to be 700 mg/m2, and therefore 1,260 mg per infusion (700 mg/m2 * 1.8 m2). Direct costs of one infusion of gemcitabine is calculated at €268 (1 vial of 1,000 mg (€186) and 2 vials of 200 mg (2 * €41 = €82)). One palliative treatment is calculated at €2,412 (9 infusions * €268). When treating 750 patients, total direct costs of gemcitabine are calculated at €1,809,000.

Sensitivity analyses:
When varying the range of infusions from 8 to 14, the total direct costs of gemcitabine range from €1,608,000 to €2,814,000.
When varying the percentage of patients treated from 40% to 80%, the total direct costs of gemcitabine range from €1,447,200 to €2,894,400.
When increasing the average dose to 1000 mg/m2, one palliative treatment is calculated at €3,150. The total direct costs of gemcitabine when treating 750 patients increase to €2,362,500.
When increasing the number of infusions to 14, the percentage of patients treated to 80% and average dose to 100%, the total direct costs of gemcitabine increase to €5,880,000.

4. Discussion and conclusion

Discussion and conclusion

In the Netherlands, the annual incidence of pancreatic cancer is approximately 2000 patients (7). Pancreatic cancer can be grouped in resectable, locally advanced and metastasized disease. Gemcitabine is used in neo-adjuvant, adjuvant and palliative regimen in pancreatic cancer, and gemcitabine-based therapy should therefore be considered in the course of disease of all newly diagnosed pancreatic cancer patients. However, in the past two decades, no important advances have been made in improving overall survival (see Figure 4).

If possible, curative resection is the treatment of choice. Neo-adjuvant therapy in resectable disease is not standard of care. The benefit of neo-adjuvant chemoradiotherapy in borderline resectable tumors has to be established in a phase III trial with well defined eligibility criteria. Whether neo-adjuvant therapy will expand its role beyond borderline-resectable tumors remains questionable.

Recent advances have been made in resected pancreatic cancer, with improved overall survival following adjuvant gemcitabine-based chemotherapy. However, improved overall survival does not usually translate into cure, and most patients will eventually die from recurrent disease or metastases (5-year survival after radical (R0) resection and adjuvant chemotherapy is approximately 20-25%, see Table 4).

Since the Burris-trial in 1997 (19), gemcitabine is the mainstay of therapy in advanced pancreatic cancer. This is based on improvement of quality of life and a small survival improvement. However, the validity of this trial is open to question. Because of the low toxicity profile, the possibility to administer gemcitabine in an outpatient clinic and the lack of an alternative, gemcitabine remains the mainstay of therapy. Combination therapy of gemcitabine with other anticancer agents (platinum-based or fluoropyrimidine-based) resulted in a small additional improvement of survival in patients with a good performance status, but also in more toxicity and some schedules need hospital admission to administer cisplatin or 5-FU (but not capecitabine) (58;64). Combination therapy of gemcitabine with targeted therapy is disappointing; however combination of gemcitabine with erlotinib was the first to show a statistically significant improvement of survival, albeit questionable if this improvement is clinically relevant (71). Promising results of the FOLFIRINOX regimen may lead to further improvement of survival for patients with a good performance status, at the cost of more toxicity and the need of a hospital admission to administer the chemotherapy (72).

Because of limited data on second-line therapy, treatment in clinical trials is preferable.

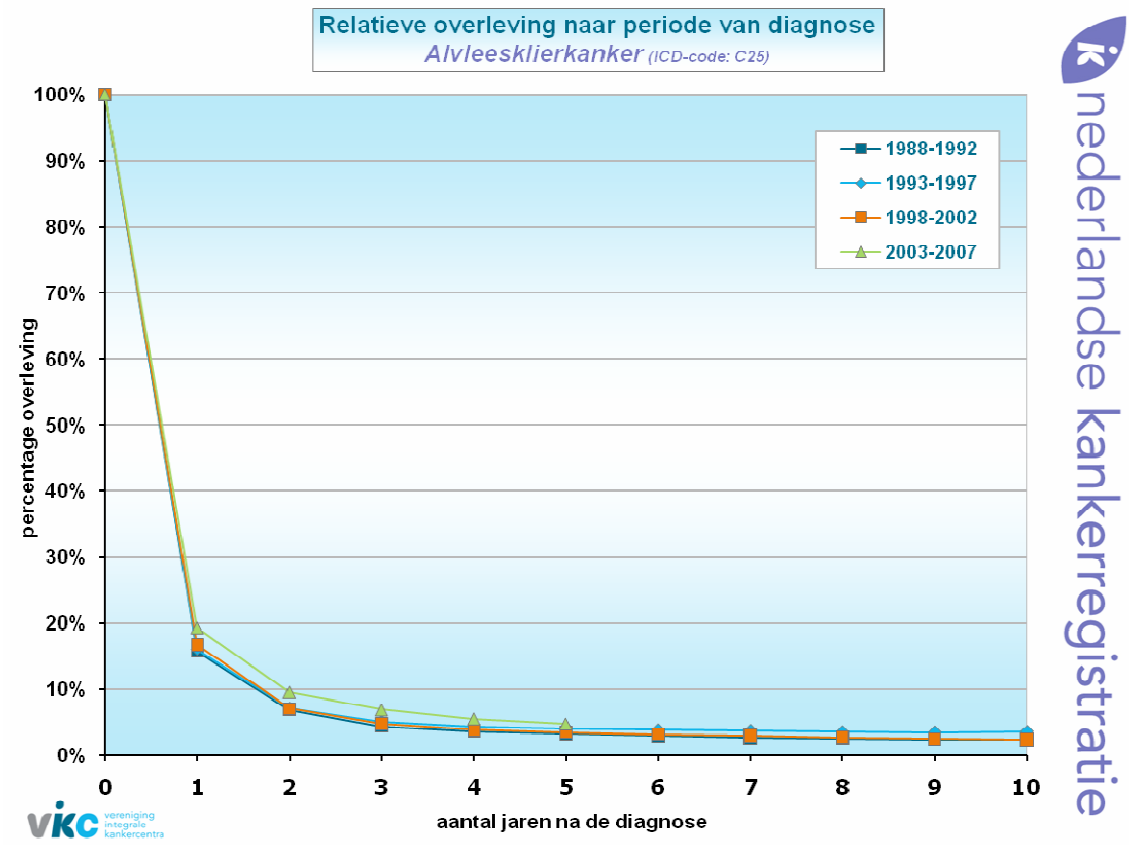

Figure 4 Relative survival to the period of diagnosis of pancreatic cancer in the Netherlands (7).

Cost-effectiveness data of gemcitabine-based treatment options in advanced pancreatic cancer are limited and based on one clinical trial. These data are very sensitive to estimates of survival benefit. The presented data are not representative for the Netherlands and outdated (96-99). Quality of life data are insufficient, and thus no robust cost-utility evaluation is known. One illustrative analysis has indicated that the addition of quality of life data is likely to reduce the survival gain and thus a higher cost per quality-adjusted life-year (96). In order to determine the cost-effectiveness of gemcitabine in the Netherlands, there is need for an economic evaluation including a cost-utility analysis of currently available treatment options. Until then, based on extrapolation of the NICE evaluation in the United Kingdom, gemcitabine is cost-effective when the society is willing to pay approximately € 25,000 per QALY (96). The combination of gemcitabine + erlotinib is cost-effective when the society is willing to pay approximately € 350,000 per QALY (105;107).

Guidelines in the Netherlands (Oncoline), Europe (ESMO) and the United States (NCCN) have been updated recently (4;11;12). The most important differences in these guidelines are listed here. The guidelines agree in treating initially resectable tumors with resection followed by adjuvant chemotherapy (either gemcitabine or 5-FU). The role of adjuvant chemoradiotherapy is controversial. Borderline resectable tumors can be treated with neo-adjuvant chemoradiotherapy. Locally advanced tumors can be treated with chemoradiotherapy according the NCCN guideline and the ESMO guideline. However, In the Dutch guideline, chemoradiotherapy in this stage is considered for pain palliation or in clinical trials. Locally advanced and metastasized tumors can be treated with gemcitabine. The Dutch and ESMO guidelines do not recommend to use combination-therapy. However, in the NCCN guideline combination of gemcitabine with erlotinib, cisplatin, oxaliplatin or a fluoropyrimidine can be considered. The BOM committee judged positively for gemcitabine as adjuvant therapy, but not for gemcitabine as palliative therapy. However, because of low toxicity and no alternative treatment, gemcitabine can be considered in this situation (20;24).

The data provided from daily practice in the Netherlands are subject to several limitations. Obtaining reliable absolute numbers of pancreatic cancer patients per hospital and how they are treated is difficult and time consuming. Therefore, structured interviews were conducted to obtain an overview of current daily practice in the Netherlands. Despite the low number of interviewed medical oncologists, they represent approximately 20% of patients with pancreatic cancer in the Netherlands. Input from patients was obtained by an interview of one representative of pancreatic cancer patients. An illustration on daily practice in one academic centre was obtained by reviewing medical files and pharmacy data.

Adherence to the Dutch clinical guideline seems high, according to interviews with a selection of medical oncologists in the Netherlands. However, some patients are treated with combination regimens despite low incremental effectiveness and high costs (gemcitabine + erlotinib), or abroad because of different optional treatments offered (combination therapy in Belgium). These indications of non-adherence to guidelines in the Netherlands raise questions of the reasons, quantity and costs of non-adherence. If the non-adherence is relevant in terms of reduced cost-effectiveness, strategies to improve adherence can be developed.

In an illustration on daily practice in one academic centre, 63% of all pancreatic cancer patients were treated and 37% received best supportive care. Of all patients, 15% of tumors were primarily resected (of which 75% received adjuvant chemotherapy), 19% received chemoradiotherapy for LAPC and 33% received palliative chemotherapy. Apart from the high rate of adjuvant chemotherapy, these percentages are consistent with literature. However, adjuvant chemotherapy has only recently been established in pancreatic cancer. In a population-based study in Ireland (1994-2003), 7.2% of all patients were treated with a surgical resection, 4.6% with chemoradiotherapy and 7.1% chemotherapy (112). In the cohort 2002-2003, chemotherapy in resected patients was given in 39%, whereas chemotherapy in unresected patients was given in 20%. Best supportive care was given in 42% of patients. In a retrospective cohort study in Australia (2002-2003), 6% received chemoradiotherapy and 24% of all patients received palliative chemotherapy, whereas 48% received best supportive care (113). In two other publications on treatment patterns, surgery was done in 11.3% (France, 2001-2005) and 14.1% (USA, 1998) and best supportive care was given in 38.7% (France, 2001-2005) (114;115). Chemotherapy was given in 41.8% (France, 2001-2005) 42.1% (USA, 1998) and radiotherapy in 8.8% (France, 2001-2005) and 20.4% (USA, 1998) (114;115). In our illustration, chemotherapy was refused by patients in 15%, in comparison with 8.0% in the USA in 1998 (114).

An illustrative economic evaluation was conducted to obtain actual yearly gemcitabine costs on pancreatic cancer in the Netherlands. The other direct medical costs, including co-medication (e.g., anti-emetics), therapy of adverse events and outpatient clinic visits were not included in this evaluation. The calculations were limited due to assumptions. If possible, assumptions were based on literature. One assumption was that no patients were treated in trial protocols. However, it is estimated by the interviewed medical oncologists that 40% to 70% of patients are treated in clinical trials. In one aforementioned publication (USA, 1998) 5% of patients were treated in a clinical trial protocol (114). Gemcitabine-based chemoradiotherapy for locally advanced or borderline resectable pancreatic cancer is given in several treatment strategies, with different dosing regimens of gemcitabine, ranging from 300 mg/m2 to 1000 mg/m2 weekly for 6 weeks. We arbitrarily have chosen the regimen (gemcitabine 500 mg/m2) as described in the ECOG 1200 trial (31). Because of a low number of treatments in this group, this choice is not likely to have a significant effect. Other assumptions, concerning percentages of patients treated, dose reductions and number of cycles given, have been tested in sensitivity analyses. Our assumptions may limit the results. However, more accurate data on direct costs of gemcitabine in pancreatic cancer are not available. Our calculations suggest that approximately 20% of total costs of gemcitabine in the

Netherlands are for account of pancreatic cancer.

Gemcitabine monotherapy is generally well tolerated and can be administered in the outpatient clinic. Experience has increased since its registration in 1995. Dose adjustments are infrequent. Since 2009 generic preparations are available and reductions in costs are therefore expected.

Drug development in pancreatic cancer is ongoing. Despite promising phase I and phase II trial results, the results in phase III trials are disappointing. It is suggested that the discrepancy between phase II and III studies originate from the better clinical performance of patients enrolled in phase II studies (116). Overall response rates of chemotherapy in metastasized disease are only 10-25%. Efficacy may be further improved by better allocation of therapy, using factors that predict the response of therapy. Because of the relatively small trials and slow recruitment, variance is introduced by less strict inclusion criteria (e.g. both locally advanced and metastasized disease) and thereby detection of a statistically significant difference may be more difficult. Moreover, uniform and sensitive measurements of quality of life in trials are still lacking (117). Because of the palliative character of the treatment, patient-reported quality of life measurements should be included.

In future trials, improvement of cost-effectiveness should be emphasized. Evaluation and interventions on improving effectiveness/allocation (drug development, adequate selection of patients), cost-lowering strategies (pooling of chemotherapeutic agents, outpatient clinic treatments instead of hospital admission, oral regimens (e.g. capecitabine in adjuvant treatment)), measurement and improvement of quality of life are needed.

From a patient's point of view, objective, reliable and complete information is pivotal. Evaluation of patient satisfaction and reasons for seeking second opinion in the Netherlands or even abroad could direct strategies to improve information provision for patients.

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Conflict of interests: none

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Appendices

Appendix A: Dutch epidemiological data of subgroups

vereniging integrale kankercentra

ICD-code: C25 PANCREAS

Relative survival of pancreatic cancer patients (18 years and older) in the Netherlands											
	tumor count	Years after diagnosis									
		0	1	2	3	4	5	6	7	8	9	10
Year of diagnosis*	**25325**											
1988-1992	3510	100%	16%	7%	4%	4%	3%	3%	3%	3%	2%	2%
1993-1997	5950	100%	16%	7%	5%	4%	4%	4%	4%	3%	3%	4%
1998-2002	7425	100%	17%	7%	5%	4%	3%	3%	3%	3%	2%	2%
2003-2007	8440	100%	19%	10%	7%	5%	5%					
2003	1504	100%	19%	10%	7%	6%	5%					
2004	1679	100%	19%	10%	8%	6%						
2005	1802	100%	20%	8%	6%							
2006	1705	100%	17%	10%								
2007	1750	100%	20%									
Age group (1998-2007)												
18-44 years	407	100%	32%	20%	15%	15%	14%	13%	12%	10%	9%	9%
45-54 years	1488	100%	24%	13%	9%	8%	6%	6%	6%	5%	5%	4%
55-64 years	3430	100%	21%	9%	6%	5%	4%	4%	3%	3%	3%	3%
65-74 years	4732	100%	16%	7%	4%	3%	3%	3%	2%	2%	2%	2%
>75 years	5808	100%	11%	4%	3%	2%	2%	2%	2%	2%	1%	1%
Sex (1998-2007)*												
Male and female	15865	100%	18%	8%	6%	5%	4%	4%	4%	3%	3%	3%
Male	7892	100%	18%	8%	6%	5%	4%	4%	4%	3%	3%	2%
Female	7973	100%	18%	8%	6%	5%	4%	4%	3%	3%	3%	3%
TNM-stadium 5th edition; 1999-2002												
I	237	100%	41%	22%	18%	15%	12%	12%	12%	12%	11%	11%
II	299	100%	32%	13%	8%	6%	6%	5%	6%	5%	6%	6%
III	413	100%	38%	16%	9%	6%	5%	4%	3%	3%	2%	2%
IVA	452	100%	24%	9%	6%	4%	3%	3%	2%	2%	2%	2%
IVB	1734	100%	5%	2%	1%	1%	1%	1%	1%	1%	0%	0%
unknown	171	100%	15%	7%	4%	3%	3%	3%	3%	3%	3%	0%
6th edition; 2003-2007												
IA	97	100%	64%	45%	37%	33%	30%					
IB	258	100%	43%	25%	16%	13%	11%					
IIA	354	100%	35%	19%	13%	10%	10%					
IIB	690	100%	46%	23%	14%	10%	7%					
III	660	100%	26%	8%	5%	3%	2%					
IV	2797	100%	7%	3%	2%	1%	1%					
unknown	134	100%	19%	11%	8%	8%	8%					

* standardised to age group

Table 2 derived from (7)

Appendix B: Performance scales (Karnofsky, ECOG-WHO-Zubrod)*

Status	Karnofsky	Grade	ECOG
Normal, no complaints	100	0	Fully active, able to carry on all pre-disease performance without restriction
Able to carry on normal activities. Minor signs or symptoms of disease	90	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
Normal activity with effort	80		
Care for self. Unable to carry on normal activity or to do active work	70	2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
Requires occasional assistance, but able to care for most of his needs	60		
Requires considerable assistance and frequent medical care	50	3	Capable of only limited self-care, confined to bed or chair 50% or more of waking hours
Disabled. Requires special care and assistance	40		
Severly disabled. Hospitalization indicated though death nonimminent	30	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
Very sick. Hospitalization necessary. Active supportive treatment necessary	20		
Moribund	10		
Dead	0	5	Dead

* Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982. The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

Appendix C: Literature search protocol

Pubmed/Medline (4 November 2010)

Search	Query	Result
#72	Search #66 AND #64	27
#71	Search #69 OR #70	114
#70	Search (#25 AND #28 AND #33) NOT medline[sb]	73
#69	Search #25 AND #28 Limits: Humans, Clinical Trial, Meta-Analysis, Practice Guideline, Randomized Controlled Trial, English, Dutch, Publication Date from 2010 to 2011	41
#66	Search #25 AND #28	2077
#64	Search "Costs and Cost Analysis"[Mesh] OR cost*[tiab] OR economic*[tw] OR cost[tiab] OR costs[tiab]	591598
#28	Search #26 OR #27	7165
#27	Search 122111-03-9[EC/RN Number] OR 103882-84-4[EC/RN Number] OR 95058-81-4[EC/RN Number]	5116
#26	Search gemcitabin*[tw] OR gemzar[tw] OR "ly 188011"[tw] OR ly188011[tw]	7159
#25	Search #21 OR #22 OR #24	61507
#24	Search #3 AND #23	23418
#23	Search (pancreas[tiab] OR pancreatic[tiab])	153238
#22	Search (pancreas[tiab] OR pancreatic[tiab]) AND (cancer*[tiab] OR carcinoma*[tiab] OR neoplas*[tiab] OR tumour*[tiab] OR adenoma*[tiab] OR incidentaloma*[tiab])	38812
#21	Search "Pancreatic Neoplasms"[Mesh]	44868
#3	Search Tumor[tiab] OR tumora*[tiab] OR tumorb*[tiab] OR tumorc*[tiab] OR tumord*[tiab] OR tumore*[tiab] OR tumorf*[tiab] OR tumorg*[tiab] OR tumorh*[tiab] OR tumori*[tiab] OR tumorj*[tiab] OR tumork*[tiab] OR tumorl*[tiab] OR tumorm*[tiab] OR tumorn*[tiab] OR tumoro*[tiab] OR tumorp*[tiab] OR tumorq*[tiab] OR tumorr*[tiab] OR tumors*[tiab] OR tumort*[tiab] OR tumoru*[tiab] OR tumorv*[tiab] OR tumorw*[tiab] OR tumorx*[tiab] OR tumory*[tiab] OR tumorz*[tiab]	786427

Embase (4 November 2010)

Search	Query	Result
#24	#16 AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim) AND [2010-2011]/py	53
#19	#16 AND #17	63
#17	'cost benefit analysis'/exp OR 'cost effectiveness analysis'/exp OR 'cost utility analysis'/exp	118819
#16	#11 AND #15	4705
#15	#12 OR #13 OR #14	20105
#14	'122111-03-9':rn OR '103882-84-4':rn OR '95058-81-4':rn	18549
#13	gemcitabin*:mn,tn,ab,ti OR gemzar:mn,tn,ab,ti OR 'ly 188011':mn,tn,ab,ti OR ly188011:mn,tn,ab,ti	8906
#12	'gemcitabine'/exp OR 'gemcitabine triphosphate'/exp	19567
#11	#9 OR #10	78936
#10	pancreas:ab,ti OR pancreatic:ab,ti AND (cancer*:ab,ti OR carcinoma:ab,ti OR neoplas*:ab,ti OR tumor*:ab,ti OR tumour*:ab,ti OR adenoma*:ab,ti OR incidentaloma*:ab,ti)	53410
#9	'pancreas tumor'/exp	63366

Cochrane (4 November 2010)

ID	Search	Hits
#1	(pancreas OR pancreatic):ti,ab,kw and (cancer* OR carcinoma OR neoplas* OR tumor* OR tumour* OR adenoma* OR incidentaloma*):ti,ab,kw	1158
#2	(gemcitabin* OR gemzar OR ly188011):ti,ab,kw or (ly 188011):ti,ab,kw	1010
#3	(#1 AND #2)	217
#4	(#3), in 2010	10