Impact of nationwide enhanced implementation of best practices in pancreatic cancer care (PACAP-1): a multicenter stepped-wedge cluster randomized controlled trial

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PROTOCOL TITLE

Impact of nationwide enhanced implementation of best practices in pancreatic cancer care

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ASA	American Society of Anesthesiologists
CAC	Cluster autocorrelation
DICA	Dutch Institute for Clinical Auditing
DPCA	Dutch Pancreatic Cancer Audit
DPCG	Dutch Pancreatic Cancer Group
EPI	Exocrine Pancreatic Insufficiency
ICC	Intracluster correlation
IKNL	Netherlands Comprehensive Cancer Organization
LAPC	Locally Advanced Pancreatic Cancer
MDT	Multidisciplinary team
NCR	Netherlands Cancer Registry
PACAP	Dutch PAncreatic CAncer Project
PALGA	Nationwide network and registry of histo- and cytopathology of the Netherlands
PancreasParel	Dutch Pancreatic Biobank
PD	Pancreatoduodenectomies
PERT	Pancreatic Enzyme Replacement Therapy
POC	Postoperative conclusion
PORSCH	POstopeRative Standardization of Care: THe Implementation of Best Practice After Pancreatic Resection
PROMs	Patient Reported Outcome Measures
UICC	Union for International Cancer Control
WHO	World Health Organization

SUMMARY

Rationale The Dutch Pancreatic Cancer Project (PACAP), launched in July 2014, is an initiative of the Dutch Pancreatic Cancer Group. PACAP is one of the largest nationwide collaborative outcomes registration and biobanking projects on pancreatic and periampullary cancer worldwide and includes the Dutch Pancreatic Cancer Audit (DPCA), the Patient Reported Outcome Measures (PROMs), an online expert panel, and the Netherlands Cancer Registry (NCR, Netherlands Comprehensive Cancer Organization; IKNL). During the first 3 years of PACAP, regional variation in treatment and guideline (non-)compliance were observed. These differences may lead to differences in survival and quality of life of pancreatic cancer patients throughout the Netherlands. Based on data from PACAP and recent literature, best practices for pancreatic cancer care were identified.

Objective The aim of PACAP-1 is to evaluate whether and to what extent an enhanced implementation of best practices in pancreatic cancer care in the Netherlands leads to a prolonged survival and improvement of quality of life as compared to current practice.

Study design PACAP-1 is a nationwide stepped-wedge cluster randomized controlled trial. In a per center stepwise and randomized manner, best practices in pancreatic cancer care are implemented in all 17 Dutch pancreatic centers. A regional pancreatic cancer team is identified per pancreatic center and functions as point of contact for peripheral centers in the region. Patient outcomes and compliance will be monitored by the registries founded in the PACAP initiative.

Study Population Prospective cohort of all pancreatic cancer patients diagnosed and treated in the Netherlands.

Interventions Best practices will be implemented in 3 key medical specialties in pancreatic cancer care: medical oncology, gastroenterology and surgery. Best practices will be implemented in centers during a 6 week intensive initiation period which includes monitoring, return visits, provider feedback in combination with education and reminders. The best practices follow the Dutch guideline on pancreatic cancer and the current state of the literature and can be executed without additional overall costs per center.

Main study outcomes The primary outcome is 1-year overall survival. Secondary outcomes include quality of life (first secondary outcome), 3- and 5-year overall survival, use of adjuvant and palliative chemotherapy, use of pancreatic enzyme replacement therapy (PERT), use of metal stents, synoptic reporting and participation in DPCG randomized trials.

Trial registration Trial open for accrual 22th May 2018. ClinicalTrials.gov - NCT03513705.

1. INTRODUCTION AND RATIONALE

1.1 The Dutch Pancreatic Cancer Project (PACAP)

The Dutch Pancreatic Cancer Project (PACAP) aims to improve outcomes of all stages of pancreatic cancer. Pancreatic cancer is a devastating disease. Without treatment, median survival after diagnosis is only 3-6 months. It is estimated that pancreatic cancer will be the second most frequent cause of cancer-related mortality by 2030[1]. Some 20% of patients with pancreatic cancer are amenable to potentially curative surgical resection[2]. Even after resection, the median overall survival of Dutch patients is only 16.8 months[3]. In patients in whom it is possible to perform a truly radical resection median survival increases to 3-4 years[3-5].

PACAP is an initiative of the national multidisciplinary Dutch Pancreatic Cancer Group (DPCG, www.dpcg.nl) and was officially launched in July 2014. In 6 years, PACAP aims to improve outcome and quality of life for pancreatic cancer patients in the Netherlands. This is achieved through one of the largest nationwide collaborative outcomes registration and biobanking projects on pancreatic cancer in the world, which provides unique opportunities for improving care for these patients and developing new diagnostic and treatment strategies. The PACAP registry projects have been initiated in 2014 at the start of PACAP, see www.dpcg.nl. These projects include the Dutch Pancreatic Cancer Audit (DPCA), the Netherlands Cancer Registry (NCR), the Dutch Pancreas Biobank (PancreasParel), Patient Reported Outcome Measures (PROMs) and an online expert panel. Details on PACAP registries are listed in APPENDIX 1.

1.2 The PACAP-1 trial

1.2.1. Background and rationale

In 2014 in the Netherlands, 2393 patients were diagnosed with pancreatic cancer and 1855 (78%) died within 1 year (unpublished data NCR). These numbers illustrate the severity of this disease and the need for improvement of treatment and clinical outcomes. From literature and the first 3 PACAP years, fairly straightforward points of improvement in care and guideline compliance for pancreatic cancer patients in the Netherlands were identified. Systematic reviews of guideline dissemination and implementation strategies showed that compliance by health-care workers, specifically doctors, is poor[6, 7]. Recently in the Netherlands, national compliance to 3 key items of the Dutch pancreatic cancer guideline was evaluated: the use of adjuvant chemotherapy, discussing patients within a multidisciplinary team (MDT) meeting, and waiting times between final MDT meeting and start of treatment. In general, guideline compliance was low (Figure 1)[8]. In addition, regional differences in

(type of) treatment and clinical outcomes have been identified in the Netherlands. For example, a staggering variation in the use of adjuvant chemotherapy between 5 and 55% was found in 634 patients of 70 years and older, diagnosed in 2008-2013, between the 18 Dutch pancreatic cancer centers (unpublished data NCR). Furthermore, significant differences in type of palliative chemotherapy given to 345 metastasized patients in 2015 were identified from NCR data between pancreatic centers and non-pancreatic centers (Figure 2). Also, one Dutch study showed that hospital volume was associated with improved survival for patients receiving palliative chemotherapy for metastatic pancreatic cancer[9]. Decrease in mortality was also demonstrated over the past few decades in the Netherlands after centralization of pancreatic surgery[3]. However, it is currently unclear which underlying factors associated with this centralization are responsible for the decrease in mortality. Furthermore, there is no data on the impact of centralization of pancreatic surgery on the actual care for patients, nor is it known what the consequences of centralization are for the majority of patients with unresectable or metastatic disease. To improve outcomes for Dutch pancreatic cancer patients, nationwide standardization of care is needed.

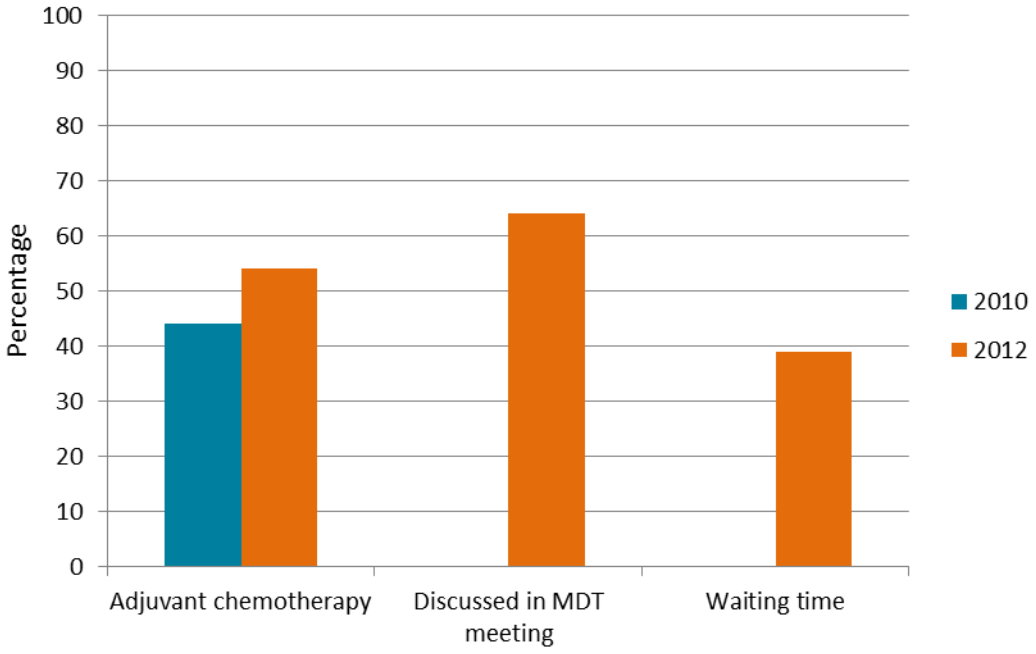

Figure 1. Guideline compliance among 2,564 patients treated for pancreatic or periampullary cancer in the Netherlands in 2010 and 2012.

To improve the overall outcome of patients with pancreatic cancer, participation in randomized clinical trials is essential. Recently, the PREOPANC-1 study was completed and it was noticed that

inclusion in this trial varied considerably between the DPCG pancreatic centers[10]. More than 60% of patients was included in only 3 of the 16 participating centers.

The PACAP-1 trial integrates current knowledge obtained by the PACAP registries and literature. Identified key best practices will be implemented in the 17 Dutch pancreatic centers and peripheral hospitals in their regions, using a stepped-wedge cluster randomized controlled trial (RCT). Since all medical specialties and hospitals treating patients with pancreatic cancer are involved in the DPCG, PACAP-1 will easily be implemented nationwide. PACAP-1 will use the registry projects described in chapter 1.1 and APPENDIX 1 to audit current practice and improve adherence to best practices and synoptic reporting in the Netherlands for pancreatic cancer patients, including the Dutch evidence-based guideline on pancreatic cancer[11]. Most importantly, with the PACAP infrastructure, the level of implementation, compliance and the effect on patients outcomes can be assessed.

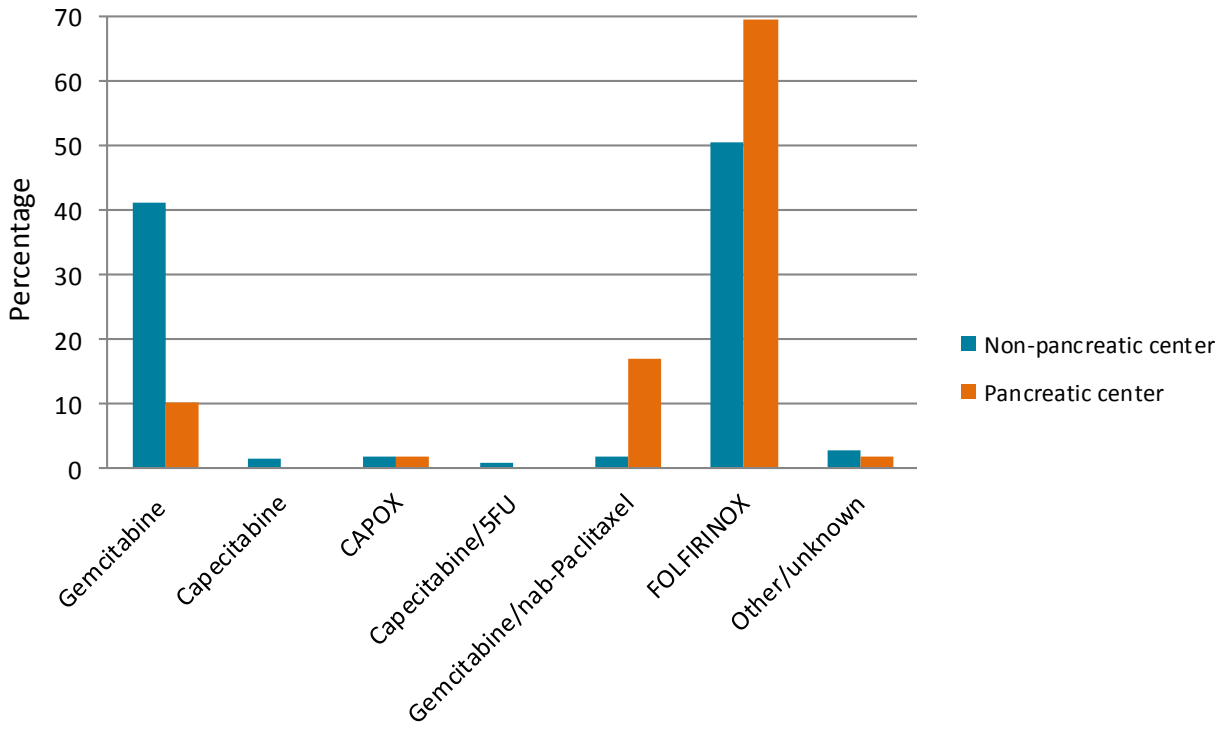

Figure 2. Type of chemotherapy given to 345 metastasized pancreatic cancer patients in 2015 in the Netherlands in pancreatic and non-pancreatic centers (NCR data).

2. OBJECTIVES

2.1 Primary objective

The primary aim of PACAP-1 is to improve 1-year overall survival in all pancreatic cancer patients in the Netherlands by enhanced implementation of key best practices.

2.2 Secondary objectives

Secondary aims are to improve quality of life (main secondary objective) and clinical outcomes (3- and 5-year overall survival, and complications) by enhanced implementation of key best practices. Another aim is to improve use of best-practice-registrations by radiologists, surgeons, pathologists, medical oncologists and gastroenterologists. Finally we aim to improve participation in DPCG randomized control clinical trials, especially those which aim to improve survival and/or quality of life.

3. STUDY DESIGN

3.1 Stepped-wedge cluster randomized controlled trial

Structured audit combined with provider feedback, education, outreach visits and reminders has shown to be the most effective implementation strategy[12]. Implementation of guidelines is not possible or desirable using 'classical' parallel-group randomized RCTs, because of contamination and the lack of actual implementation of the new strategy. Since RCTs are considered the most robust research design for establishing a cause – effect relationship, a variant of this research method is increasingly used; the stepped-wedge cluster RCT[13]. In a systematic review, where 25 studies were evaluated, it was found that the stepped-wedge cluster RCT design has mainly been applied in evaluating interventions in routine practice[13]. Data collection in such large multicenter (stepped-wedge) RCTs is often a challenge. Therefore, collection through multicenter registries has recently gained interest from researchers as it is practical and a way to significantly reduce costs for large multicenter RCTs[14].

In a stepped-wedge cluster RCT, clusters (e.g. centers) are randomly allocated a time when they are given the intervention. At the end of the study, all clusters will be receiving the intervention. Advantages of this approach, compared to parallel group or crossover cluster RCTs, are that the intervention will be rolled out to all clusters in phases. This is useful where phased implementation is preferable due to various constraints, such as logistic regional differences, and implementation in all clusters is essential, such as with guideline dissemination. Additionally, this design makes differentiation from time-effects possible. RCTs that randomize individuals cause an inevitable risk of contamination of the control patients, are difficult to implement in routine practice, and may not reflect effectiveness at a population level. Non-randomized designs, such as before-after intervention evaluations, have the tendency to overestimate the intervention effect, since the investigated intervention is usually thought to be more effective.

3.1.1 Justification for stepped-wedge design: logistical reasons and statistical efficiency

Due to cluster and regional differences in current practice, standardization of pancreatic cancer care is needed. Therefore, PACAP-1 interventions will be rolled-out nationally with regional adjustments of the implementation. For logistical reasons, it is not feasible to roll-out the interventions to all clusters and regions simultaneously, and a stepped-wedge approach is preferred. As opposed to a parallel cluster randomized design, a stepped wedge design results in an implementation of the intervention in all participating centers, which is desirable when implementing best practices.

Additionally, after calculating the statistical efficiency for PACAP-1, the power achieved from a stepped-wedge cluster RCT was considerably greater than that of a parallel cluster randomized trial. For sample size and power calculation of this trial, see chapter 4.

3.2 PACAP-1 trial design

PACAP-1 will use a combined approach to implement best practices such as stated in the Dutch multidisciplinary guideline for pancreatic cancer who provide the full range of cancer diagnostics and treatment. The PACAP-1 trial is a nationwide stepped-wedge cluster RCT which will implement best practices in all 17 DPCG hospitals and referring regional hospitals. The design of this trial was based on the CONSORT statement for cluster randomized trials[15] and draft extension for stepped-wedge trials[16].

In a step-wise manner, all clusters will transfer from control (current practice) to intervention (best practice) phase, successively. Each cluster contains 1 DPCG center and its referral region. At the first time point, all 17 centers are still in the current practice phase. At the second time point, the first cluster will be educated on best practices during the wash-in phase and subsequently continue with the best practice phase, while the other 16 centers are still in the current practice phase. As per this method, the trial continues until the 17 clusters are transferred to the intervention phase (Figure 3), during a total of 25 months.

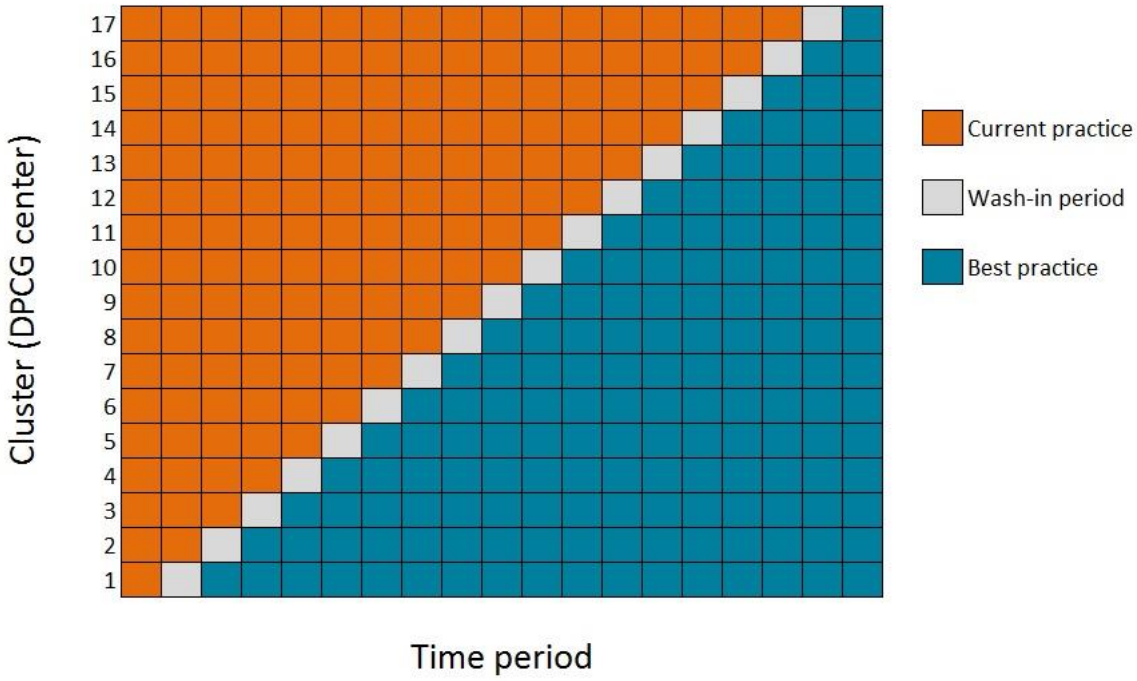

Figure 3. Schematic of PACAP-1 stepped-wedge cluster randomized controlled trial.

With this study design, the duration of the trial and inclusion time are determined by the required sample size. Details of the sample size calculation are described in chapter 4. Randomization will establish the order of clusters undergoing the transfer to intervention phase[17, 18]. Each cluster will contain one center and therefore the number of sequences is equal to the number of participating centers. Outcomes will be recorded with the anonymized DPCG registries, which includes the NCR.

The duration of the wash-in phase is 6 weeks. To achieve effective implementation of PACAP-1 best practices, a structured wash-in phase is designed (APPENDIX 2). Also, in this timeframe the study team will discuss with the local pancreatic cancer team how to implement best practices efficiently. In this trial design, avoidance of best practice contamination is important for clusters still in the control phase. Therefore, details on PACAP-1 best practices will not be shared with local clinicians before the transfer to the intervention phase. In the analysis of PACAP-1, every cluster is their own control, because of the cluster RCT design.

4. STUDY POPULATION

4.1 Population

All pancreatic cancer patients (all ages).

4.2 Patient inclusion criteria

Patients with pancreatic cancer.

4.3 Patient exclusion criteria

There are no specific patient exclusion criteria.

4.4 Participating centers

4.4.1 Center inclusion criteria

All 17 centers of the DPCG. Each performs >20 pancreatoduodenectomies (PDs) annually. Each center already has a coordinating role for pancreatic cancer for its region. It is expected that the enhanced implementation of best practices will have an impact in the entire local network.

4.4.2 Center exclusion criteria

There are no specific center exclusion criteria.

4.5 Sample size calculation

PACAP-1 is a superiority trial with 1-year overall survival as primary endpoint, which will be extracted from NCR survival data. The sample size calculation was based on the following data derived from NCR for incident cases in the year 2014:

Number of new patients per year in DPCG centers:	1075
1-year mortality rate in DPCG centers	702/1075; 65%
Number of new patients per year in the Netherlands	2393
1-year mortality rate in the Netherlands	1855/2393; 78%
Intra-cluster coefficient (95% CI) between DPCG centers for 1-year mortality	Approach A[1]: 0.0185 (0.0132-0.0575) Approach B[2]: 0.0183 (0.0131-0.0560)

[1.] Method A from the AOD library in R uses generalized linear mixed model.

[2.] Method B from the AOD library in R uses generalized linear mixed model with Monte Carlo simulations

The required sample size was calculated using the formula for stepped-wedge designs[19]. Sample sizes were calculated for different effect sizes, different intra-cluster coefficients, for 80% or 90% power, and for the DPCG centers and for all of the Netherlands separately, using a cluster autocorrelation (CAC) of 1[20] and an alpha of 0.05 (see Table 1). Subsequently, it was reversely calculated which effect sizes could be determined with 80% and 90% power given a fixed study duration (hence a fixed sample size) of 25 months for the different other assumptions (Table 1). For logistical reasons, a shorter study duration was not considered.

Currently in the Netherlands, there are 18 centers performing pancreatic surgery. However, because the St. Antonius Ziekenhuis and the UMC Utrecht are merged with regard to pancreatic cancer care, both are considered as one center in our trial, to minimize contamination.

Population	**N**	**p0**	**p1**	**RD**	**ICC**	**power**	**Interpretation**
25 months study duration (including 5.8 weeks wash-in period)							
DPCG	2142	0.65	0.550	-0.100	0.0184	0.8	80% power for true reduction of 10.0%
DPCG	2142	0.65	0.535	-0.115	0.0184	0.9	90% power for true reduction of 11.5%
All NL	4769	0.78	0.714	-0.066	0.0368	0.8	80% power for true reduction of 6.6%
All NL	4769	0.78	0.704	-0.076	0.0368	0.9	90% power for true reduction of 7.6%
All NL	4769	0.78	0.722	-0.058	0.0092	0.8	80% power for true reduction of 5.8%
All NL	4769	0.78	0.712	-0.068	0.0092	0.9	90% power for true reduction of 6.8%

Table 1. Power for effect size given fixed sample size. N = sample size, p0 = current 1-year mortality, p1 = expected 1-year mortality, RD = risk difference, ICC = intra-cluster correlation coefficient, CAC = cluster autocorrelation, DPCG = Dutch Pancreatic Cancer Group, NL = the Netherlands.

Following the PACAP-1 interventions it is expected that 1-year overall survival for all pancreatic cancer patients in the Netherlands will improve with 10%. Therefore, a 25 month study duration was chosen, which provides 80% statistical power for an absolute mortality reduction of 10.0% and 90% power for a reduction of 11.5% in the DPCG centers, with a required sample size of 2142 patients. For all of the Netherlands, assuming the ICC will be higher, the corresponding sample size provides 80% power for an absolute mortality reduction of 6.6% and 90% power for a reduction of 7.6% (Table 1).

5. TREATMENT OF PATIENTS

5.1 Intervention phase: best practices

5.1.1 Literature and PACAP: the first 3 years

To determine key best practices for implementation in PACAP-1, points of improvement for 3 key medical specialties (medical oncology, gastroenterology and surgery) involved in pancreatic cancer care in the Netherlands were identified from literature and the first 3 PACAP years (July 2014 – July 2017). These are divided in intervention and registry categories (Figure 4). Best-practice-treatments are aimed to improve survival, clinical outcomes and quality of life. Best-practice-registrations are aimed to optimize data registry with key parameter and synoptic reporting that will lead to efficient and high-quality data collection. PACAP-1 interventions are listed in APPENDIX 3 per medical specialism. An overview of PACAP-projects is presented in APPENDIX 1.

In preparation of the PACAP-1 trial a national meeting with a surgeon and/or oncologist from every DPCG center was arranged, see chapter 5.13.

Best-practice-treatments

All treatments follow the current state of the Dutch guideline on pancreatic cancer and the literature.

Treatment-1: Optimal patient information on chemotherapy (adjuvant and palliative) - concerns medical oncologists, gastroenterologists and surgeons.

Treatment-2: Pancreatic enzyme replacement therapy (PERT) in case of exocrine pancreatic insufficiency (EPI) - concerns medical oncologists, gastroenterologists and surgeons.

Treatment-3: Metal stents for biliary drainage - concerns gastroenterologists.

Best-practice-registration

Registration-1: Use of checklist for radiology reports of pancreatic cancer - concerns radiologists.

Registration-2: Use of standardized table with intra-operative events in operation report and complications of surgical treatment in discharge letters - concerns surgeons.

Registration-3: Use of nationwide PALGA standard for reporting pancreatic cancer pathology - concerns pathologists.

Registration-4: Report of World Health Organization (WHO) performance status – concerns medical oncologists, gastroenterologists and surgeons.

Regional pancreatic cancer team

It is known from literature[3, 9], and DPCA and NCR data that there is a large regional variability in treatment and outcomes for pancreatic cancer patients. These differences will be discussed within the regional pancreatic cancer teams in each DPCG center who will act as advisory group for all regional peripheral hospitals regarding pancreatic cancer.

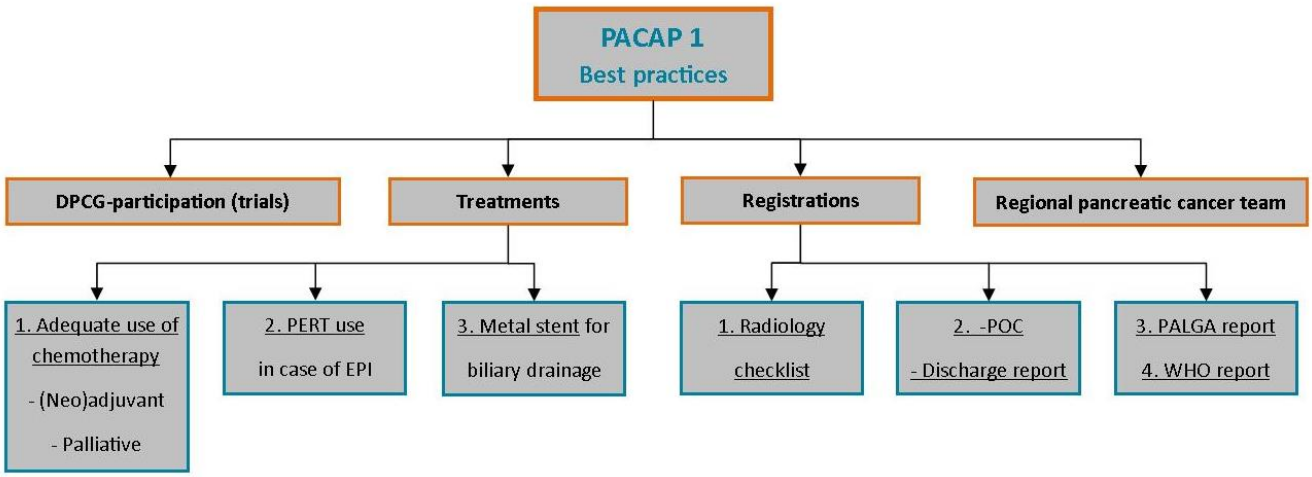

Figure 4. Schematic of PACAP-1 best practices. PERT = Pancreatic Enzyme Replacement Therapy. EPI = Exocrine Pancreatic Insufficiency. POC = Postoperative Conclusion. PALGA = Nationwide network and registry of histo- and cytopathology of the Netherlands. WHO = World Health Organization performance status.

Additional best practices

Other-1: Inclusion of pancreatic cancer patients in PACAP PROMs registry – concerns medical oncologists, gastroenterologists and surgeons.

Other-2: Participation in PancreasParel biobank – concerns medical oncologists, gastroenterologists and surgeons.

Other-3: Pathologic confirmation in patients with (suspected) metastatic and locally advanced pancreatic cancer – concerns medical oncologists and gastroenterologists.

Other-4: Participation in DPCG randomized controlled trials – concerns all healthcare providers in DPCG centers.

5.2 Treatment-1: Optimal patient information on chemotherapy

The identified points of improvement in the oncological facets of PACAP and proposed standardized treatment and information (per patient subgroup) in this chapter, were discussed and optimized with an advisory committee, containing 7 oncologists from different DPCG hospitals.

5.2.1 Background

It is widely reported that adjuvant and palliative chemotherapy for resectable, locally advanced and metastasized pancreatic cancer patients provides significant survival benefit, but also improvement in quality of life[21-27]. According to the Dutch national guidelines on pancreatic cancer all patients with good WHO performance status after pancreatic resection should receive adjuvant chemotherapy and in case of locally advanced or metastasized disease palliative chemotherapy[11]. However, national DPCA data from these 3 years showed that 36% WHO 0-1 pancreatic cancer patients did not receive adjuvant chemotherapy. NCR data from 2005-2013 showed that approximately 10-15% of pancreatic cancer patients were eligible for resection (M0-resected patients), 30-40% were M0-not resected patients and 50-55% were metastasized (M1) patients (Figure 5). Median percentage of M0 not-resected patients receiving chemotherapy was 14%, with an increase from 10% in 2005-2007 to 18% in 2011-2013 (unpublished data NCR). This group consisted of locally advanced pancreatic cancer (LAPC) patients, but also of patients that were not resected because of high age (> 80 years) and bad WHO performance status (≥ WHO 2). Still, the majority of patients were not treated according to the guideline.

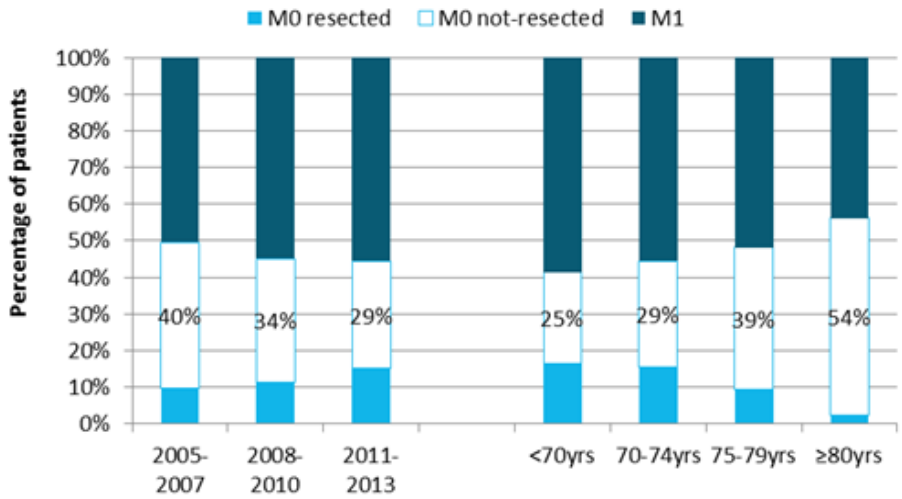

Figure 5. M0 and M1 patients from NCR data 2005-2013 (unpublished data)

The median percentage of M1 patients receiving palliative chemotherapy was 23%, with an increase from 13% in 2005 to 30% in 2013. Of these patients, 8.4% died within 30 days of start of first line chemotherapy[28]. In 2015 in the Netherlands, 10% of patients with stage 4 pancreatic cancer started with chemotherapy in the last month of life and 11% received last chemotherapy dose in the last 14 days before death (unpublished data NCR). Of all M1 patients, diagnosed between 2005-2013, 26% died within 30 days after diagnosis[28]. This can partly explain why 70% of M1 patients did not receive palliative chemotherapy, but for the majority of these patients palliative chemotherapy should be considered. In addition, a study performed in the Netherlands showed that hospital volume of palliative chemotherapy for metastatic pancreatic cancer was associated with improved survival[9]. This indicates the presence of regional differences in treatment and outcomes.

A percentage of patients will have made a grounded decision to not be treated with chemotherapy. However, other patients possibly did not receive chemotherapy due to lack of (understanding of) information or after referral back to a peripheral center after diagnosis. For this latter group it is essential to improve informing of patients in an expert center to increase the amount of patients with good WHO performance status that receive chemotherapy to not only improve time to recurrence and survival, but also quality of life. Moreover, with the aim to optimize use of chemotherapy, the percentage of patients that start new chemotherapy treatment in the last month of life and patients that receive the last dose in the last 4 weeks of life should be reduced to a minimum.

5.2.2 Best-practice-treatments – concerns medical oncologists, surgeons and gastroenterologists

Decision support tool – A information and decision support tool for 3 pancreatic cancer subgroups (see below) are designed to be used for patient and clinicians treatment decisions (https://bit.do/beslisboom). Practical patient information lines are listed in APPENDIX 4.

Resectable cancer – All resectable patients will be referred to the medical oncologist in the DPCG center they are operated in for information on adjuvant treatment options. Per DPCG center medical oncologists with focus on pancreatic cancer will see the referred patients. Treatment can be given either in the DPCG center or in a peripheral center.

Details on chemotherapy choice and guidance in treatment decisions are provided with the information and decision support tool (https://bit.do/beslisboom).

LAPC - Primary assessment of all LAPC patients will happen in DPCG center MDT meeting to establish a treatment plan. Treatment can be given either in the DPCG center or in a peripheral center.

Every LAPC patient treated in a DPCG center or peripheral center with chemotherapy will be reevaluated after 2 months of treatment in the MDT meeting of the DPCG center to assess possible treatment change and resectability.

Details on chemotherapy choice and guidance in treatment decisions are provided with the information and decision support tool (https://bit.do/beslisboom).

Metastasized disease – All metastasized patient will be discussed in the MDT meeting of a DPCG center or in a regional MDT where at least one physician of a DPCG center is present, with the exception of a predefined subgroup (by expert consensus: metastasized patients with WHO performance status 3-4, see chapter 5.13).

Details on chemotherapy choice and guidance in treatment decisions are provided with the information and decision support tool (https://bit.do/beslisboom).

5.3 Treatment-2: Pancreatic enzyme replacement therapy (PERT) in case of exocrine pancreatic insufficiency (EPI)

This best-practice has been developed with nutritional experts in the field. Standardized questions have been developed for clinicians to assess the presence of malnutrition and support the optimal use of pancreatic enzymes.

5.3.1 Background

EPI occurs in up to 90% of patients after pancreatic resection and in 25-50% with LAPC[29-31]. Steatorrhea and weight loss are the most common manifestations of EPI, with potentially large effects on quality of life and nutritional status[32]. EPI is grossly underdiagnosed and undertreated[29]. PERT is effective in treating EPI. Optimal treatment with PERT requires referral to a dietician for evaluation of individually adjusted dosages per meal or snack and patient education. A recent study showed that use of PERT was independently associated with improved survival following PD for cancer[33]. Therefore, with attention for EPI and adequate treatment, nutritional status, quality of life and survival can improve.

The reference standard for the diagnosis of EPI is the coefficient of fat absorption (CFA)[34, 35]. However, this measurement involves a specific diet with 72-hour stool collection, which is a burden for patients, logistical challenging and expensive. Literature is controversial about the fecal elastase-1 (FE-1) test as a diagnostic tool[36-39]. However, the FE-1 test is less expensive than the CFA and only requires one stool sample. This indirect pancreatic function test measures pancreatic elastase-1, a highly stable enzyme that does not degrade in the intestinal tract, in feces with highly sensitive

enzyme linked immunosorbent assay (ELISA)[40, 41]. FE1 <200 mg/g is considered as pancreatic exocrine insufficiency. In a recent systematic review, the FE-1 test is described as useful in a high prevalence population, such as patients with pancreatic cancer[38]. This is endorsed by two older prospective cohort studies[37, 40]. Not testing patients without EPI complaints is undertreatment, since early detection could have a positive effect on the nutrient and vitamin absorption and therefore could also prevent weight loss. Preventing weight loss is more profitable than gaining weight afterwards. Within the PACAP-1 trial it is advised to measure FE-1 in all pancreatic cancer patients to prevent underdiagnosis.

5.3.2 Best-practice-treatment – concerns medical oncologists, surgeons and gastroenterologists

Patients will be asked for a stool sample to measure FE-1 and about EPI symptoms at baseline. If FE1 is <200 mg/g, or if FE1 is ≥ 200mg/g, but there are ≥1 symptoms of EPI, patients will be prescribed PERT. Referral to a dietician is also advised if FE-1 is normal, but unintended weight loss is present. At every following postoperative outpatient clinic visit, patients will be asked about EPI symptoms and PERT will be prescribed if necessary. If in doubt, FE1 could be measured for a second time. A pocked sized information sheet with EPI symptoms, advise on dietician referral and start dosage of PERT is developed (APPENDIX 5).

Dieticians will be offered trainings and supportive materials, such as an online e-learning.

<u>Pancreatic enzyme-application for patients</u>

A mobile application focusing on EPI and PERT has been developed, as supportive material for patients; the *Alvleesklierenzymen*-application. Patients can daily fill out their complaints and their diet. The application gives an advice on PERT dosage and whether a patient should contact their dietician or physician. This application will be offered to all patients with EPI and PERT.

5.4 Treatment-3: Optimal biliary drainage

This best practice involves the optimal, evidence-based, strategy for biliary drainage in patients with obstructive jaundice caused by pancreatic cancer.

5.4.1 Background

Preoperative biliary drainage with metal stents is preferable over the use of plastic stents due to a lower number of stent related complications (i.e. cholangitis) and less stent dysfunction (e.g. re-obstruction and migration)[42]. Cholangitis may lead to delay in treatment, start of chemotherapy or surgery. Likewise, stent dysfunction and the resulting inadequate biliary drainage will lead to

worsened patient condition and delayed treatment with chemotherapy or surgery. However, the use of plastic stents in patients requiring preoperative biliary drainage is still frequent. During the first 3 PACAP years, 35% of placed stents in the Academic Medical Center was plastic. NCR data (unpublished) from 2015 of all patients with pancreatic cancer, show that firstly placed stents were plastic in 39% of the cases, metal in 40% and unknown in 21%. Type of stent is added as variable in the DPCA since 2017 and in this year 54% of 165 stents placed in pancreatic cancer patients that underwent resection in the Netherlands was plastic. In 2016, almost 50% of patients with a solid tumor on radiographic studies and registered in the DPCA, underwent preoperative biliary drainage[43].

Recently, effectiveness and costs were investigated for plastic and, uncovered and partially covered self-expandable metal stents for palliation of extrahepatic bile duct obstruction in a RCT. This study showed that both metal stents had longer functional time than plastic stents. Although metal stents initially were more expensive, total costs after 1 year did not differ between the different stent types[44]. In addition, a recent study investigated cost-effectiveness of metal vs. plastic stents in patients with LAPC or metastatic pancreatic cancer with a life expectancy of more than 6 months. Results showed that metal stent placement at initial onset of obstructive jaundice reduced the need for stent replacement and was a more cost-effective strategy than plastic stent placement, while improving quality of life[45].

Furthermore, an update of the European Society of Gastrointestinal Endoscopy guideline on biliary stenting is expected within months which will recommend the use of self-expandable metal stents for biliary obstruction of known etiology; preoperatively and for palliation of extrahepatic malignant biliary obstruction.

Compliance and stent related complications will be measured using the DPCA in patients requiring preoperative biliary drainage. In non-resectable patients this will be measured through the NCR.

5.4.2 Best-practice-treatment – concerns gastroenterologists

All pathologically confirmed pancreatic cancer patients requiring biliary drainage will receive a metal stent. PACAP-1 aims for a proportion of ≥75% metal stents.

Indications for biliary drainage with metal stent for extrahepatic biliary obstruction for the different patient subgroups are:

- Resectable tumor
    - Bilirubin <250 µmol/L and waiting time for surgery > 3 weeks
    - Bilirubin > 250 µmol/L
    - Cholangitis
    - Symptomatic obstructive jaundice (e.g. pruritis)
    - Before neoadjuvant chemotherapy in case of bilirubin > 25 µmol/L

- Irresectable tumor (LAPC or metastasized disease)
    - Cholangitis
    - Symptomatic obstructive jaundice (e.g. pruritis)
    - Before start of palliative chemotherapy if bilirubin > 25 µmol/L
    - Before start of neo-adjuvant chemotherapy in case of bilirubin > 25 µmol/L
    - In case elective plastic stent exchange is due it should be replaced with metal stent

Only if a metal stent is not possible due to anatomy (e.g. close relation to the hilum) or if prior severe complications after metal stent placement like cholecystitis occurred, a plastic stent is an accepted alternative.

In case of extrahepatic biliary obstruction requiring drainage, but without pathologic confirmation, either a fully covered metal or a plastic stent is an option.

5.5 Registration-1: Use of the checklist for radiology reports

5.5.1 Background

The radiology checklist for reporting pancreatic cancer imaging has been developed by the Dutch association for radiology and the DPCG. Although advised by the DPCG, DPCA data from January-June 2017 show that the CT checklist was only used in 61/143 (43%) of the cases.

5.5.2 Best-practice-registration – concerns radiologists

The radiology checklist will be used for the report of all CT-scans of pancreatic cancer patients in all DPCG centers. The checklist is reported in APPENDIX 6.

5.6 Registration-2: Use of standardized table with intra-operative events in operation report and complications of surgical treatment in discharge letters

5.6.1 Background

The standardized postoperative conclusion (POC) table for the operation report and table of complications of surgical treatment for the discharge letters are developed by the DPCG. Both tables have been tested previously and facilitate better registration of treatment and outcome. However, DPCA data from January-June 2017 showed that standardized tables are not often used, although advised by the DPCG:

(1) Standardized POC table: in 89/143 (62%) cases used
(2) Standardized complication table: 40/143 (28%) cases used

5.4.4 Best-practice-registration: Standardized postoperative conclusion – concerns surgeons

A synoptic POC has also been developed by the DPCG. This will be used in every operation report of a pancreatic resection in all DPCG centers. The synoptic POC is listed in APPENDIX 6.

5.4.5 Best-practice-registration: Standardized discharge report – concerns surgeons

A synoptic discharge report following pancreatic surgery has been developed by the DPCG. This report will be used in every discharge letter of patients that underwent pancreatic resection in all DPCG centers. The synoptic discharge report is listed in APPENDIX 6.

5.7 Registration-3: Use of nationwide PALGA standard for reporting pancreatic cancer pathology

5.7.1 Background

The use of synoptic pathology reports has been associated with an increase in the number of R1 resections[46]. A synoptic report of pancreatic pathology has been developed by the DPCG and the national society of pathology (PALGA). PACAP-1 will measure the percentage of patients receiving pancreatic resection for a suspected malignancy, in who the resection specimen is recorded according to the synoptic report and correlate this to the number of R1 resections both recorded in the DPCA. However, DPCA data from January-June 2017 showed that PALGA report is only used in 46/143 (32%) of the cases.

5.7.2 Best-practice-registration – concerns pathologists

The synoptic report by the DPCG and PALGA is advised as standardized postoperative pancreatic pathology report.

5.8 Registration-4: Report of WHO performance status

5.8.1 Background

Performance status (WHO) is an important characteristic of patients with a (suspected) pancreatic cancer. For example, the new FOLFIRINOX chemotherapy has demonstrated significant improvement in survival in patients with metastatic pancreatic cancer, however due to an increase in toxicity compared to standard gemcitabine it is reserved for patients with a maximum WHO performance status of 1. From January-June 2017, the WHO performance status was reported in the DPCA in 126/143 (88%) of the cases.

5.8.1 Best-practice-registration – concerns medical oncologists, surgeons and gastroenterologists

WHO performance status will be reported at first presentation of patients with (suspected) pancreatic cancer. WHO grading system is listed in APPENDIX 6.

5.9 Additional best practices

5.9.1 PACAP PROMs registry

Background

All patients with a pancreatic or periampullary malignancy are eligible (all tumor stages) for the PACAP PROMs. Questionnaire time points are at baseline and follow up at 3, 6, 9, 12, 18, 24, 36 months and yearly thereafter. In 18 months over 500 patients were registered for inclusion in the PACAP quality of life questionnaire study. Overall, response rates are approximately 60%. With almost 2400 newly diagnosed patients per year in the Netherlands, a significant amount of patients are not registered to participate in PACAP PROMs.

Registration for PROMS – concerns medical oncologists, surgeons and gastroenterologists

Each patient with a pancreatic malignancy is eligible for the PACAP PROMs and will be asked to participate before start of primary treatment (preferably) or before start of new treatment episode. Details in methods for this procedure are listed in APPENDIX 7.

5.9.2 Biobanking (PancreasParel)

Each patient with a pancreatic tumor is eligible for participation in the PACAP PancreasParel as described in APPENDIX 1. Currently not all Dutch pancreatic centers participate in the PancreasParel. Therefore, implementation of PancreasParel in more centers is encouraged. As biobanking is a component of PACAP and is stimulated within PACAP-1, it is reported briefly. However, because

blood and tissue samples are collected to be subjected to novel research techniques in the future, results will be reported separately from PACAP-1.

5.9.3 Pathologic analysis (PA) in patients with (suspected) metastatic and locally advanced pancreatic cancer

Background

According to the Dutch pancreatic cancer guideline, all patients with (suspected) metastatic pancreatic cancer should receive cytologic or histopathologic confirmation. This is especially important prior to palliative chemotherapy, as cytologic or histologic proof of another tumor type may impose large differences in treatment, survival and quality of life. In 10% of M1 patients[28] and 17% of M0-not resected patients (NCR data unpublished) cytologic or histopathologic confirmation is not obtained prior to palliative chemotherapy for (suspected) metastatic pancreatic cancer.

PA confirmation – concerns medical oncologists and gastroenterologists

Pathologic confirmation of all patients with (suspected) metastatic and locally advanced cancer will be performed.

5.9.4 Postoperative complication management

Approximately 20% of patients with pancreatic cancer are amenable to resection. Pancreatic resection is associated with high risk of postoperative complications of 50%[47]. A common complication is pancreatic fistula that can lead to life-threatening situations if not managed adequately[48]. Therefore, the 'POstopeRative Standardization of Care: THe Implementation of Best Practice After Pancreatic Resection' or PORSCH-trial is designed (NTR6905). The objective of this nationwide trial in the Netherlands is *to investigate if the implementation of a best practice algorithm for postoperative care focusing on early detection and step-up management of postoperative pancreatic fistula results in a lower rate of major complications and death after pancreatic resection as compared to current practice.* As the PORSCH-trial also includes all 17 DPCG centers and has the same stepped-wedge design as the PACAP-1 trial, both studies will be executed in a parallel manner. Because PORSCH aims to improve postoperative outcomes within 90 days and PACAP-1 aims to improve long-term outcomes, results will be reported separately. For detailed information on postoperative complication management, we refer to the PORSCH-trial protocol.

5.9.5 Participation in DPCG randomized controlled trials

Background

In 2017 the PREOPANC-1, a DCPG randomized clinical trial was closed after including all 244 patients. In this study, preoperative radiochemotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer was investigated[10]. This study was considered the most important oncological study of the DPCG, which could improve the outcome of pancreatic cancer patients. Although the accrual met the requirements, not all DPCG centers included sufficient eligible patients as might be expected. Just 3 centers were responsible for more than 60% of all included patients.

Participation in DPCG clinical trials – concerns all healthcare providers in DPCG centers

PACAP-1 aims to obtain a higher participation rate of eligible patients in DPCG supported randomized trials, such as the next RCT (PREOPANC-2), which will start in 2018. With the help of the DPCG, the PACAP-1 team will support better trial participation. Furthermore, together with principal investigators, the PACAP-1 team will present an overview of included patients in all DPCG centers during our return visits and will contact centers when inclusion stays behind. By these measures we aim to include more patients in a shorter period of time and a better participation of all centers in this open randomized control clinical trials with primary objective progression free and overall survival.

5.10 Support - PACAP-1 smartphone application

To support and moderate the enhanced implementation of above described best practices, a PACAP-1 smartphone application will be made available to all healthcare providers at start of the wash-in period of their cluster. This is an informative application that provides a summary of key best practices that are implemented during PACAP-1.

5.11 Control phase: current practices

Current practice will be left to the discretion of the healthcare providers in the control phase.

5.12 Future guidelines and studies

It is expected that several external factors will contribute to the outcomes of PACAP-1. Firstly, in 2018 an updated national guideline on diagnosis and treatment of pancreatic cancer and an updated European Society of Gastrointestinal Endoscopy guideline on biliary stenting are expected. Secondly, national DPCG studies will be developed and executed. For example, the PREOPANC-2 trial on

outcomes of induction FOLFIRINOX vs. upfront resection in patients with resectable pancreatic cancer is being developed. This could influence outcomes of PACAP-1 and will be taken into account in the statistical analyses.

5.13 National expert meeting

In preparation of the PACAP-1 trial a national expert meeting was organized for one oncologists and/or one surgeon per DPCG center, to prevent contamination. Oncologists and surgeons of 11 DPCG centers, and an IKNL member were present. Specialists from the other 6 DPCG centers were informed on discussed topics by email and agreed. Specific details on best practices were not shared, but extensive background and logistic information was provided, and an elaborate discussion on what best practices should entail, was conducted. Ultimately, consensus was reached on the trial design and crucial parts of the best practices were identified. The shared opinion of the experts was that with PACAP-1 the aim should be that:

1. 70% of patients with a resectabel tumor should receive adjuvant chemotherapy
2. 60% of patients with LAPC should receive chemotherapy
3. 40% of patients with metastasized disease should receive palliative chemotherapy
4. All pancreatic cancer patients should be discussed in a DPCG or regional MDT, with the exception of a small predefined subgroup (i.e. metastasized patients with WHO performance status 3-4)
5. Information transfer from DPCG to non-DPCG centers should be optimized

6. METHODS

6.1 Study endpoints

6.1.1 Primary endpoint

The primary endpoint is 1-year overall survival.

6.1.2 Secondary endpoints

Secondary study endpoints are divided in intervention, registry and other outcomes.

Intervention outcomes:

- Quality of life at baseline and all follow-up moments (see APPENDIX 7 for details)
    - EQ-5D-5L
    - EORTC QLQ-C30
    - EORTC QLQ-PAN26
    - EPI questionnaire
- 3- and 5-year overall survival
- Complications will be measured during the complete duration of the PACAP-1 trial:
    - Chemotherapy (palliative or (neo)adjuvant)
        - Toxicity grade 3-4
        - Type of toxicity (hematological, gastrointestinal, neurological, other)
    - Stent placement (metal or plastic)

Process measure outcomes

- Proportion of post-pancreatectomy patients receiving adjuvant chemotherapy
- Proportion of patients receiving neoadjuvant chemotherapy
- Proportion of LAPC patients that underwent pancreatic resection
- Proportion of unresectable patients receiving palliative chemotherapy
- Proportion of patients that received palliative chemotherapy in last month of life
- Proportion of patients with suspected or confirmed EPI receiving PERT
- Proportion of patients with suspected or confirmed EPI that visited a dietician
- Proportion of patients requiring biliary drainage receiving a metal stent
- Proportion of (suspected) metastasized patients undergoing PA

Registry outcomes:

- Proportion of diagnosed pancreatic cancer patients registered for PROMs
- Proportion of diagnosed pancreatic cancer patients registered in DPCA
- Proportion of post-pancreatectomy patients with synoptic discharge letter
- Proportion of post-pancreatectomy patients with POC
- Proportion of patients with (suspected) unresectable pancreatic cancer with documented WHO performance status at first presentation
- Proportion of post-pancreatectomy patient with synoptic resection specimen report
- Proportion of patients diagnosed with a solid pancreatic tumor with CT-scan checklist
- Proportion of patients registered for biobanking in participating PancreasParel centers
- Proportion of LAPC patients discussed in regional Multidisciplinary Team meeting during diagnostic period
- Proportion of treated LAPC patients that underwent resection after chemotherapy
- Proportion of LAPC patients discussed in Multidisciplinary Team meeting 2 months after start of chemotherapy
- Use of smartphone application

6.1.3 Other study parameters

Baseline patient characteristics:

- Age
- Sex
- Height in cm
- Weight in kg
- Smoking status
- WHO performance status
- Relevant medical history
    - Disease requiring medical treatment, such as cardiovascular disease, renal failure, pulmonary disease, diabetes
- American Society of Anesthesiologists (ASA) classification
- Pre-treatment pathology diagnosis
- Tumor stage at diagnosis

6.2 Randomization, blinding and treatment allocation

PACAP-1 will follow the identical randomization order as in the PORSCH trial, because both studies are executed in the 17 DPCG centers and for the current study PORSCH best practices (see below) will be considered the standard of care for postoperative complication management in the Netherlands.

The PORSCH trial focusses on optimal detection and management of complications of pancreatic surgery. Randomization is performed at the start of the PORSCH trial by an independent statistician. As described in the PORSCH trial protocol: *Centers will be randomized using R statistics software to determine the timing of cross-over from current practice to best practice*[49]. *Stratification at randomization is applied for center volume (>45 vs. ≤45 pancreatic resections a year, median value based on data from the DPCA 2014-2015).*

Because of the design of PACAP-1, it is not feasible to blind healthcare providers to the best practice treatments and registrations. All PACAP-1 research data is obtained from existing encoded PACAP registries (NCR, DPCA and PROMs), warranting (pseudo-)anonymization of patients (see chapter 10.1).

6.3 Study procedures

No new study procedures are introduced. PACAP-1 aims to assess the impact of enhanced implementation of current best practices. Therefore, the aim is to improve standard of care compliance by informing, stimulating and reminding local clinicians per cluster to follow best practice interventions outlined by PACAP-1.

Best practice procedures, identified from literature and PACAP, include all interventions documented in Chapter 5 and APPENDIX 3.

6.4 Withdrawal centers

Because of the stepped-wedge cluster RCT design of PACAP-1, it is crucial that all randomized DPCG hospitals complete the trial, so an unequal distribution of patients between current and best practice arms is prevented. However, if a center drops out of the study the randomization order will be maintained. Patients treated in a dropout center during this trial will still be accounted for in the final analysis, according to intention-to-treat analysis.

6.5 Replacement centers after withdrawal

All 17 DPCG hospitals participate in PACAP-1 and therefore hospitals cannot and will not be replaced after withdrawal.

6.6 Study duration

Planning of the PACAP-1 trial started in PACAP year 3 (November 2016) and the aim is to start implementation in May of 2018 after obtaining local approval in all participating centers. The trial will run for 25 months.

7. SAFETY REPORTING

With PACAP-1 best practice interventions, current practice interventions are not changed, but stimulated to be executed adequately. Therefore, this trial will not introduce any additional safety or health risk for patients compared to regular care.

8. STATISTICAL ANALYSIS

Outcomes of all patients with pancreatic cancer in the Netherlands will be evaluated before and after wash-in period (i.e. current practice vs. best practice). Patients will be assigned to current or best practice based on the date of first treatment (i.e. biliary stent placement, chemotherapy or primary resection). In case of no treatment or best-supportive care, date of diagnosis will determine assignment to current or best practice. Follow-up time is based on date of diagnosis for all patients. For patients diagnosed in a non-DPCG center, the assignment to current or best practice will depend on the affiliated DPCG center, which will be determined prior to the start of the study. Primary analysis will be performed with an intention-to-treat analysis according to the randomization order and cross-over dates. If implementation is not performed as scheduled, secondary analysis will be performed according to a per protocol analysis. Patients diagnosed during the wash-in period will be described but will be excluded from the analysis. The primary comparison between current and best practice will be performed for patients from all hospitals in the Netherlands. If relevant, 95% confidence intervals (CI) will be reported. All p-values will be based on a 2-sided test. P-values of less than 0.05 will be considered statistically significant.

8.1 Handling of missing data

Missing data on baseline characteristics will be imputed by multiple imputation techniques. Outcome data will not be imputed, patients which are lost to follow-up within 1 year will be censored at the date of loss to follow-up. Complete and multiple imputed data analysis will be performed to check for inconsistencies.

8.2 Baseline characteristics

Descriptive statistics will be used for analysis and reporting of baseline characteristics. Chi-square or Fisher's exact test will be used to compare categorical variables between patients in current practice and those in best practice. Parametric continuous variables will be reported as mean with standard deviation (SD) and will be compared using the Student's T-test. Non-parametric continuous variables will be reported as median with interquartile range (IQR) and will be compared using the Mann-Whitney-U test.

8.3 Primary outcome

One year overall survival will be analyzed with mixed-effects Cox proportional hazards regression models using a random intercept for hospital and a random slope on intervention effect for hospital. The analysis will be adjusted for (calendar) time and for the following baseline characteristics: age at

diagnosis and tumor stage at diagnosis using the Union for International Cancer Control (UICC) tumor/node/metastasis (TNM) 8th edition (2018) classification and staging system for pancreatic cancer.

8.4 Secondary outcomes

Quality of life will be analyzed using mixed-effects linear regression models, with a random effect per DPCG center. Primary analysis will be performed with Area Under the Curve (AUC) for the time points at baseline and follow-up 3, 6, 9 and 12 months or until death or dropout. Exploratory analysis will be performed with AUC for time points until 3- and 5-year follow-up (see APPENDIX 7) or until death or dropout, delta analysis, Quality Adjusted Life Years (QALY) and for 1 time point. Adjustment for random and fixed effects will be performed similar to the primary analysis. Model assumptions will be checked and, if violated, appropriate measures will be taken to derive unbiased standard errors.

3- and 5-year overall survival will be analyzed similar to the primary endpoint with mixed-effects Cox proportional hazards regression models.

Complication rates will be determined using competing events analysis for time to first complication, corrected for the competing event death. Analyses will be performed for any of all complications and for each type of complication separately. Both cause-specific hazard ratios (reflecting the effect per day alive) and sub-distribution hazard ratios (reflecting the overall effect) will be determined.

Other secondary outcomes will be descriptive in nature, e.g. the proportion of patients in the intervention vs. the control arm using PERT or receiving metal stents.

8.5 Subgroup and sensitivity analyses

Subgroup analyses will be performed for 3 patient subgroups (i.e. patients with resectable, locally advanced and metastatic pancreatic cancer), hospital volume (>40 vs. ≤40 PDs per year[3]) and trial participation in prospective DPCG trials (e.g. PREOPANC-2, PORSCH).

Also, subgroup analysis will be performed for outcomes pancreatic centers versus referring centers. Patients are allocated to the center in which the primary treatment (e.g. pancreatectomy or first line chemotherapy) has been given.

Sensitivity analyses will be performed for time before and after implementation of the updated national guideline on pancreatic cancer and European Society of Gastrointestinal Endoscopy guideline on stenting.

8.6 Interim analysis

Evaluation of study outcomes will not be performed with an interim analysis. However, interim analysis will be performed to assess number of inclusions at the time point that half of the inclusions is expected. In the case that <47,5% of inclusions is acquired at that time point, the length of the steps as described in chapter 3 will be increased for the remaining time of PACAP-1. As a result, sample size will be reached and statistical power will be maintained. Furthermore if necessary, when PORSCH increases the length of the steps, PACAP-1 will do so too, to maintain a minimum time difference of 5 months between wash-in phases of both studies in the same cluster.

9. ETHICAL CONSIDERATIONS

9.1 Regulation statement

This trial is designed and will be conducted in accordance to the requirements of the Helsinki Declaration and Good Clinical Practice. The aim of PACAP-1 is to evaluate the effect of enhanced implementation of best practices for pancreatic cancer care. The interventions proposed are currently standard of care according to literature and guidelines, and for participation in PROMs only completing questionnaires is required. The focus of this trial was to educate and stimulate local clinicians to follow known best practice and optimize data registry. As patients in PACAP-1 are not subject to novel treatment and no precepts for behavior are imposed, this research does not fall under the Medical Research Involving Human Subjects Act (WMO).

9.2 Recruitment and consent

As this trial introduces nationwide implementation of best practices at cluster level, all pancreatic cancer patients presented in the DPCG centers will participate. Time of inclusion will increase and therefore more patients will be treated according to best practice while superiority over current practice is not established. Thus, informed consent of individual patients will not be asked in PACAP-1. Furthermore, the necessity for informed consent has been waived by local medical ethical committees in several studies that evaluated cluster level education of clinicians[17, 50] (CAP-PACT trial NCT02604628). In addition, collection of PACAP-1 data will happen through existing encoded PACAP registries (i.e. DPCA, NCR and PROMs) for which no informed consent is required (see chapter 10.1). However, cluster consent of the pancreatic cancer team from every DPCG center will be obtained[51].

10. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

10.1 Handling and storage of data and documents

Data will be collected through DPCA, NCR and PROMs.

Nationwide DPCA registration, containing mostly surgical data, is completed by local clinicians through an online survey supported by Medical Research Data Management (MRDM). MRDM secures privacy and safe data management and complies to the requirements of information safety with NEN 7510:2011 and ISO 27001:2013 certifications. An opt-out procedure is in place by which patients can refuse the use of their data. Coded DPCA data is securely send to the PACAP project leader every 3 months. MRDM is the only one with access to the coding key.

NCR data, containing mostly survival, oncological, chemo- and/or radiotherapy information, is collected from local medical records by trained IKNL registration employees. An opt-out procedure is in place by which patients can refuse the use of their data. Coded NCR data will be obtained from IKNL by the PACAP-1 research team at request. NKR is the only one with access to the coding key.

PROM questionnaires are completed by patients either on paper or online with the first quality of life evaluation at baseline before index treatment. After that, questionnaires will be send out every 3 months in the first year, every 6 months in the second year, and every 12 months for subsequent years. After collection of paper questionnaires at the AMC, storage and digitalization happens at Profiel (subdivision of IKNL focusing on quality of life). Online completed questionnaires are primarily collected at Profiel. Patients sign an informed consent form for participation. Coded data will be obtained from Profiel by the PACAP-1 research team at request. Profiel and the PACAP-coordinating investigators are the only ones with access to the coding key.

10.2 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion. All substantial amendments will be notified to the METC and to the competent authority. Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

10.3 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first patient, numbers of

patients included and numbers of patients that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

10.4 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit. The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action. In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination. Within 1 year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

10.5 Public disclosure and publication policy

10.5.1 Final manuscript and co-authorship

PACAP-1 was registered at ClinicalTrials.gov (NCT03513705). The results of PACAP-1 will be submitted to a peer-reviewed journal regardless of study outcome. Co-authorship will be based on the international guidelines. Beside the key authors (coordinating investigators as first authors and principal investigators as senior authors), each participating DPCG center will be offered 3 authorships. Each center will determine internally who these authors are, but it is advised to include a surgeon, medical oncologist and gastroenterologists. Additional involved researchers per center can be listed as collaborator.

10.5.2 Publications during the trial

Best practices are based on the current standard of care and literature, and identified improvement points from the first years of PACAP. Publications on treatment of pancreatic cancer during PACAP-1-trial will be reviewed by the PACAP-1 research team. All "practice changing" evidence publications that conflict with the proposed best practices of this trial will be reviewed by the DPCG stakeholders. The DPCG stakeholders and PACAP-1 research team will decide together whether best practices should be adjusted based on the new evidence.

11. REFERENCES

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APPENDIX 1: Overview of PACAP projects

The Dutch Pancreatic Cancer Audit (DPCA) - A clinical audit focusing on surgical patients in all 17 pancreatic cancer centers in the Netherlands. Clinical variables (>100 per patient) of all pancreatic resections performed in 1 of the 17 pancreatic centers in the Netherlands are prospectively registered in the DPCA. In 2014-2015 >1600 and in 2016 almost 1000 pancreatic resections were registered nationwide. Cross-checks have demonstrated >90% and >99% case ascertainment and >99% and >99% data accuracy after 1 year and in registry year 2016, respectively.

The Netherlands Cancer Registry (NCR) in collaboration with the Netherlands Comprehensive Cancer Organization (IKNL) – A clinical audit focusing on all Dutch patients with pancreatic cancer in which they are registered from diagnosis until death. Including in all DPCG centers, detailed clinical data of patients receiving chemotherapy, radiotherapy or no treatment is obtained by trained IKNL registration employees.

The Dutch Pancreas Biobank (PancreasParel) – PancreasParel obtains blood and tissue samples of all patients with pancreatic and periampullary cancers. The biobank is part of the Parelsnoer Institute (www.parelsnoer.org). Preoperative blood samples, perioperative tissue samples (tumor tissue and normal tissue) and postoperative blood samples are collected. Since its official launch in February 2015, over 488 patients have been included. Currently, 13 centers participate in the biobank; 4 academic centers and 1 teaching hospital are actively including. IRB approval has been obtained in 6 more centers; logistic facilities are currently being established in these hospitals.

Patient Reported Outcome Measures (PROMs) - PROMs are prospectively registered for all patients with pancreatic and periampullary cancer; starting in the winter of 2015, after 7 months, 7 academic and 11 peripheral centers in the Netherlands had joined this initiative. Within 18 months, 517 patients were included and 308 patients returned quality of life (QoL) questionnaires (i.e. response rate 60%).

An online expert panel - The PACAP expert panel received 180 patients from 9 centers, referred between April 2015 and July 2017. Sub-analysis of the first 79 referrals identified locally advanced pancreatic cancer (LAPC) in 100% of cases and in 51% (40/79) of patients there was an additional treatment or a change in the planned treatment strategy. Of these patients, a resection with curative intention was performed in 8 patients (10%) and 28 patients (35%) were included in a clinical trial, investigating local ablative therapies. In all cases the expert panel advice was provided within 1 week.

APPENDIX 2: Methods of implementation of PACAP-1 best practices

To achieve effective implementation of PACAP-1 best practices, a structured wash-in phase is designed.

1. At the start of the wash-in phase, a regional "kickoff" evening is organized by the PACAP-1 research team at the DPCG-center with presentations on details of the interventions and logistics of PACAP-1. All involved physicians and nurses from the DPCG-center and peripheral hospitals in that region are invited.
2. At this evening, the regional pancreatic cancer team is introduced as central group to implement the best practices, PACAP-1 interventions and logistics in that region.
3. Also, all PACAP-1 support materials will be made available. They include the detailed protocol, the PACAP-1 smartphone application, decision support tools, pocketsize PACAP-1 overview and access to protected parts of www.pacap.nl.
4. In the first and second week of the wash-in phase, introductory presentations will be given to each medical specialty. The PACAP-1 research team will also participate in a local MDT meeting in which pancreatic cancer patients are discussed.
5. In week 3-6 of the wash-in phase, the PACAP-1 research team will discuss the progress of the implementation with the regional pancreatic cancer team and involved clinicians and nurses from peripheral hospitals. With this approach, identified points of improvement in the implementation strategy will be adjusted if necessary.

Once a DPCG-center and that region is in best practice phase, reminder visits will be scheduled and stimulating reminder emails will be send.

1. A 2-monthly update will be send via email to the involved clinicians and nurses with a graph that show the "scores" for compliance to PACAP-1. Other DPCG-centers will be anonymized in the graph.
2. Four-six months after wash-in phase, a reminder visit will be scheduled with presentations on the progress of PACAP-1. This provides local clinicians and nurses the opportunity to ask questions.
3. If necessary, more update and reminder visits will be scheduled.

Throughout PACAP-1, the regional pancreatic cancer teams or the PACAP-1 research team will be available for questions from anyone involved in this study.

APPENDIX 3: List of PACAP-1 interventions per medical specialty

MEDICAL ONCOLOGY				
	Intervention	**Definition**	**Outcome**	**Measurement**
1	Standard information and decision support tool	Use of standard information and decision support tool for all pancreatic cancer patient subgroups (e.g. via https://bit.do/beslisboom)	Survival	NCR
2	Discussion on chemotherapy (resectable patients)	Percentage of resectabel pancreatic cancer patients with whom chemotherapy options are discussed in DPCG center	Survival Quality of Life	NCR PROMs DPCA
3	Diagnostics LAPC patient established in DPCG center	Percentage of LAPC patients in the diagnostic phase that are discussed in DPCG MDT meeting	Survival Quality of Life	NCR PROMs DPCA
4	Post-induction chemotherapy discussion of LAPC patient in DPCG center	Percentage of LAPC patients treated with chemotherapy that are discussed in DPCG MDT meeting after 2 months of therapy	Survival Quality of Life	NCR PROMs DPCA
5	PERT	Percentage of patients with EPI who receive PERT	Quality of Life	NCR PROMs
6	Key parameter WHO performance status reporting	Percentage of patients with a (suspected) pancreatic malignancy, in who the WHO performance status is noted at first presentation.	-	NCR DPCA
7	Pre-treatment pathology confirmation	Percentage of patients with (suspected) locally advanced and metastatic pancreatic cancer, with histological or cytological proof of pancreatic adenocarcinoma	-	NCR
8	PROMs	Percentage of patients with a (suspected) pancreatic malignancy, who are registered for the PACAP PROMs	-	PROMs
9	Biobanking	Percentage of patients receiving pancreatic resection for suspected malignancy, who	-	PancreasParel

		are registered for the PancreasParel		

SURGERY				
	Intervention	**Definition**	**Outcome**	**Measurement**
1	Medical oncology referral	Percentage of patients with pancreatic cancer referred to medical oncologist for consultation on adjuvant chemotherapy	Survival Quality of Life	NCR PROMs
2	PERT	Percentage of patients with EPI who receive PERT	Quality of Life	NCR PROMs
3	Synoptic discharge letter	Percentage of patients receiving pancreatic resection for a (suspected) malignancy, in whom the synoptic complication table is used in the discharge letter	-	DPCA
4	Synoptic POC	Percentage of patients undergoing pancreatic resection in whom the synoptic POC is used in the operation report	-	DPCA
5	PROMs	Percentage of patients receiving pancreatic resection for (suspected) malignancy, who are registered for the PACAP PROMs	-	PROMs
6	Biobanking	Percentage of patients receiving pancreatic resection for (suspected) malignancy, who are registered for the PancreasParel	-	PancreasParel
7	Standardized complication management	Standardized approach to early detection and treatment of pancreatic fistula (PORSCH trial)	Postoperative complications	DPCA PROMs PORSCH

GASTROENTEROLOGY				
	Intervention	**Intervention**	**Outcome**	**Measurement**
1	Metal stent	Percentage of patients with a (suspected) pancreatic malignancy requiring biliary drainage, receiving a metal (rather than a plastic) stent.	Complications	NCR DPCA
2	PERT	Percentage of patients with EPI who receive PERT	Quality of Life	NCR PROMs
3	Pre-treatment pathology confirmation	Percentage of patients with (suspected) locally advanced and metastatic pancreatic cancer, with histological or cytological proof of pancreatic adenocarcinoma	-	NCR

PATHOLOGY				
	Intervention	**Definition**	**Outcome**	**Measurement**
1	Synoptic reporting	Percentage of patients receiving pancreatic resection for a suspected malignancy, in who the resection specimen is recorded according to the PALGA/Dutch Society of Pathology nationwide synoptic report	Number of R1 resections	DPCA

RADIOLOGY				
	Intervention	**Definition**	**Outcome**	**Measurement**
1	Synoptic reporting	Percentage of patients with a (suspected) pancreatic, in who the Computed Tomography (CT) is recorded according to the Dutch Society of Radiology CT-checklist.	-	DPCA

APPENDIX 4: Chemotherapy patient information for the outpatient clinic (in Dutch)

CHEMOTHERAPIE BIJ ALVLEESKLIERKANKER

Hieronder wordt de waarde van chemotherapie bij alvleesklierkanker weergegeven voor drie verschillende situaties (zie onder). Het is belangrijk dit onderscheid te maken, omdat voor elk van de drie situaties andere behandelopties mogelijk zijn. Deze informatie is samengesteld door een landelijke commissie van internist-oncologen en chirurg-oncologen van de Dutch Pancreatic Cancer Group. Waar mogelijk zijn hier Nederlandse gegevens gebruikt maar ook de belangrijkste internationale studies.

Drie mogelijkheden voor patiënten met alvleesklierkanker

1. PATIENTEN NA EEN OPERATIE WAARBIJ ALVLEESKLIERKANKER IS VERWIJDERD

1a. NA ALVLEESKLIEROPERATIE: WEL OF GEEN CHEMOTHERAPIE?

Alvleesklierkanker komt vaak weer terug in de eerste jaren na een alvleesklieroperatie ondanks dat de tumor volledig is verwijderd. De kanker kan dan niet opnieuw met een operatie verwijderd worden. De kans om 5 jaar na een operatie voor alvleesklierkanker nog in leven te zijn is 8% zonder chemotherapie (*ESPAC-1 studie, NEJM 2004*[24]), 16% met gemcitabine alleen en is 29% met de combinatie chemotherapie gemcitabine-capecitabine (*ESPAC-4 Lancet 2017*[52]).

ESPAC-1 STUDIE[24]*:* *www.pubmed.com/15028824*
ESPAC-4 STUDIE[52]*:* *www.pubmed.com/28129987*

1b. NA ALVLEESKLIEROPERATIE: WELKE SOORT CHEMOTHERAPIE?

De beste chemotherapie na een operatie voor alvleesklierkanker is de combinatie van gemcitabine en capecitabine. Met deze combinatie leven patiënten langer dan patiënten die alleen gemcitabine ontvangen (mediane overall survival: 28 vs. 25,5 maanden, *ESPAC-4 Lancet 2017*[52]).

ESPAC-4 STUDIE[52]*:* *www.pubmed.com/28129987*

1c. NA ALVLEESKLIEROPERATIE: BIJWERKINGEN?

De combinatie chemotherapie van gemcitabine en capecitabine is intensiever dan gemcitabine alleen. Het chemotherapie schema bestaat in principe uit 8 kuren in totaal.

Ernstige bijwerkingen (“Graad 3-4”) komen vaker voor bij de combinatietherapie: in totaal bij 63% van de patiënten met de combinatietherapie, tegenover 54% bij gemcitabine alleen. De patiënt zal

echter niet van al deze bijwerkingen klachten ervaren. Bij combinatietherapie rapporteert 7% van de patiënten ernstige bijwerkingen van hand-voet syndroom (klachten van handen en/of voeten zoals jeuk, pijn, roodheid, blaren of infecties), 6% vermoeidheid, 5% diarree, 3% infecties en 2% koorts. Bij gemcitabine alleen was dit 5% vermoeidheid, 2% diarree, 7% infecties en 2% koorts (geen hand-voet syndroom) (*ESPAC-4 Lancet 2017*[52]).

De kans te moeten stoppen door bijwerkingen voor de 6e kuur is 8% groter bij de combinatietherapie. Bij de combinatietherapie stopt 22% van de patiënten met chemotherapie vs. 14% die gemcitabine alleen gebruiken (*ESPAC-4 Lancet 2017*[52]).

ESPAC-4 STUDIE[52]*:* www.pubmed.com/28129987

1d. NA ALVLEESKLIEROPERATIE: VERSLECHTERT DE KWALITEIT VAN LEVEN DOOR CHEMOTHERAPIE?

De kwaliteit van leven verslechtert niet door gebruik chemotherapie, maar verbetert juist iets. Patiënten die chemotherapie gebruiken rapporteren langer een goede kwaliteit van leven dan patiënten zonder chemotherapie (9,6 vs. 8,6 Quality-Adjusted Life Months) (*QoL data ESPAC-1 Int J Cancer 2009*[21]).

De door patiënten gerapporteerde kwaliteit van leven verschilt niet tussen de combinatietherapie en gemcitabine alleen groep (*ESPAC-4 Lancet 2017*[52]).

QoL data ESPAC-1[21]*:* www.pubmed.com/19330830
ESPAC-4 STUDIE[52]*:* www.pubmed.com/28129987

2. PATIENTEN MET NIET-OPERABELE ALVLEESKLIERKANKER ZONDER UITZAAIINGEN

2a. GEEN OPERATIE, GEEN UITZAAIINGEN: WEL OF GEEN CHEMOTHERAPIE?

In 30-40% van de gevallen is alvleesklierkanker lokaal uitgebreid met ingroei van de tumor in omliggende grote bloedvaten, waardoor geen operatieve verwijdering kan plaatsvinden. In deze situatie is chemotherapie de standaardbehandeling. Tot enkele jaren geleden werd alleen gemcitabine chemotherapie gegeven (*Burris et al. J Clin Oncol 1997*[53]), soms in combinatie met radiotherapie. Deze behandeling vermindert soms klachten en geeft een kleine kans op langere overleving. Zonder chemotherapie leven patiënten gemiddeld 6 maanden (mediane overall survival, *IMPALA Ann Surg Oncol 2017*[26]), met gemcitabine 6-13 maanden (mediane overall survival *Burris et al. J Clin Oncol 1997*[53]*, Chauffert et al. Ann Oncol 2008*[54]).
Uit twee recent verschenen studies is gebleken dat de gemiddelde overleving van patiënten die FOLFIRINOX* chemotherapie kregen 16-24 maanden is (mediane overall survival, *Suker et al. Lancet Oncol 2016*[25]*, Rombouts et al. Ann Surg Oncol 2016*[55]). Daarnaast lijkt uit (kleinere) studies dat chemotherapie, met name FOLFIRINOX, de tumor kan verkleinen en daarmee de kans vergroot om alsnog een operatie te kunnen ondergaan. Uit een Nederlandse studie blijkt dat bij 11% van de patiënten de tumor alsnog met een operatie kon worden verwijderd (*IMPALA Ann Surg Oncol 2017*[26]*, Rombouts et al. Ann Surg Oncol 2016*[55]). Lastig hierbij is dat het effect van FOLFIRINOX chemotherapie op een CT- of MRI-scan niet te zien is en beoordeling door een ervaren centrum

nodig is, waar onder andere een combinatie van serum CA19.9 en intraoperatieve echografie worden gebruikt.

De combinatietherapie gemcitabine + nab-paclitaxel kan mogelijk de kans vergroten op langere overleving, maar er zijn nog niet veel studies verricht met deze behandeling bij patiënten zonder uitzaaiingen (*Kasi et al. JCO 2017*[56]*, Heinemann et al. Ann Oncol 2013*[57]).

* FOLFIRINOX is een combinatietherapie van leucovorine, fluorouracil, oxaliplatin en irinotecan

Burris et al.[53]*:* www.pubmed.com/9196156
IMPALA studie[26]*:* www.pubmed.com/28560601
Chauffert et al.[54]*:* www.pubmed.com/18467316
Suker et al.[25]*:* www.pubmed.com/27160474
Rombouts et al.[55]*:* www.pubmed.com/27370653
Kasi et al.[56]*:* http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.e15744
Heinemann et al.[57]*:* www.pubmed.com/23852311

2b. GEEN OPERATIE, GEEN UITZAAIINGEN: WELKE SOORT CHEMOTHERAPIE?

Afhankelijk van de conditie van de patiënt, zijn FOLFIRINOX of gemcitabine (+ nabpaclitaxel) de beschikbare chemotherapie schema's. FOLFIRINOX en gemcitabine (+ nab-paclitaxel) zijn niet onderling vergeleken in studies. Wel zijn er studies naar beide middelen apart uitgevoerd. Hieruit lijkt FOLFIRINOX de meest effectieve chemotherapie (*systematic reviews: Suker et al. Lancet Oncol 2016*[25]*, Rombouts et al. Ann Surg Oncol 2016*[55]). Deze behandeling is echter wel intensiever en zwaarder dan gemcitabine (+ nab-paclitaxel) chemotherapie. Doordat de dosis van de chemotherapie heel vaak (circa 90% van de gevallen) wordt verlaagd, kunnen de meeste mensen met een gemiddelde conditie deze chemotherapie verdragen (*Rombouts et al. J Cancer 2016*[58]).

Gemiddeld leven patiënten in deze situatie 16-24 maanden na FOLFIRINOX en 6-13 maanden na gemcitabine (+ nab-paclitaxel) chemotherapie (*systematic reviews: Suker et al. Lancet Oncol 2016*[25]*, Rombouts et al. Ann Surg Oncol 2016*[55], en *Kasi JCO 2017*[56]*, Von Hoff et al. NEJM 2013*[59]*, Heinemann Ann Oncol 2013*[57]).

Uit een Nederlandse studie blijkt dat na chemotherapie (FOLFIRINOX, of gemcitabine afhankelijk van de conditie van de patiënt) bij 11% van deze patiënten de alvleesklierkanker alsnog verwijderd kan worden met een operatie (*IMPALA Ann Surg Oncol 2017*[26]*, Rombouts et al. Ann Surg Oncol 2016*[55]).

Suker et al.[25]*:* www.pubmed.com/27160474
Rombouts et al.[55]*:* www.pubmed.com/27370653
Rombouts et al.[58]*:* www.pubmed.com/27698926

2c. BIJWERKINGEN?

Ernstige bijwerkingen ("Graad 3-4") zijn gerapporteerd na FOLFIRINOX bij 52% van patiënten met en zonder uitzaaiingen (*Rombouts et al. J Cancer 2016*[58]). Na gemcitabine bij patiënten zonder uitzaaiingen was dit 37% (*SCALOP Lancet Oncol 2013*[60]). U zult echter niet van al deze bijwerkingen

klachten ervaren. De meest gerapporteerde ernstige bijwerking bij FOLFIRINOX was misselijkheid of overgeven (10%), en daarnaast buikpijn (8%), diarree (6%), vermoeidheid (6%) en koorts door verslechtering van afweer (5%) (*Rombouts et al. J Cancer 2016*[58]*, Peddi et al JOP 2012*[61]*, Marthey et al. Ann Surg Oncol 2015*[62]). Bij gemcitabine was dit vermoeidheid (11%), en daarnaast diarree (8%), misselijkheid of overgeven (8%), gewichtsverlies (8%) en koorts door verslechtering van afweer (3%) (*SCALOP Lancet Oncol 2013*[60]).

De meeste ernstige bijwerkingen na FOLFIRINOX verdwijnen na verlaging van de dosering chemotherapie zonder dat dit ten koste gaat van de effectiviteit *(Rombouts et al. J Cancer 2016*[58]*, Rombouts et al. Ann Surg Oncol 2016*[55]*, Karim et al. Clin Oncol 2018*[63]*).*

Rombouts et al.[58]*:* www.pubmed.com/27698926
SCALOP studie[60]*:* www.pubmed.com/23474363
Peddi et al.[61]*:* www.pubmed.com/22964956
Marthey et al.[62]*:* www.pubmed.com/25037971
Rombouts et al.[55]*:* www.pubmed.com/27370653
Karim et al.[63]: www.pubmed.com/29137884

2d. GEEN OPERATIE, GEEN UITZAAIINGEN: VERSLECHTERT DE KWALITEIT VAN LEVEN DOOR CHEMOTHERAPIE?

Over kwaliteit van leven na chemotherapie in deze situatie is helaas geen informatie beschikbaar. Wel is het bekend dat patiënten met uitgezaaide alvleesklierkanker die worden behandeld met FOLFIRINOX langer een goede kwaliteit van leven hebben dan met gemcitabine chemotherapie. In dat geval wordt achteruitgang op kwaliteit van leven na 6 maanden chemotherapie twee keer zo vaak gerapporteerd bij gemcitabine dan bij FOLFIRINOX (66% vs. 31%, *PRODIGE 4 NEJM 2011*[64]*)*

PRODIGE 4 studie[64]*:* www.pubmed.com/21561347

3. PATIENTEN MET UITGEZAAIDE ALVLEESKLIERKANKER

3a. UITGEZAAIDE ALVLEESKLIERKANKER: WEL OF GEEN CHEMOTHERAPIE?

In ongeveer 40% van de gevallen is alvleesklierkanker uitgezaaid en is het daarom niet zinvol om de tumor operatief te verwijderen. In deze situatie verbetert chemotherapie de kans op langere overleving en verbetert chemotherapie de kwaliteit van leven. Zonder chemotherapie is de overleving gemiddeld 2 maanden *(Bernards et al. Acta Oncol 2015*[65]*)*, met gemcitabine 6,8 maanden *(PRODIGE 4 NEJM 2011*[64]*)*, met gemcitabine + nab-paclitaxel 8,7 maanden *(MPACT long-term survival analysis J Natl Cancer Inst 2015*[66]*)* en met FOLFIRINOX* 11,1 maanden *(PRODIGE 4 NEJM 2011*[64]*)*.

* FOLFIRINOX is een combinatietherapie van leucovorine, fluorouracil, oxaliplatin en irinotecan

Bernards et al.[65]*:* www.pubmed.com/25263080
PRODIGE 4 studie[64]*:* www.pubmed.com/21561347
MPACT long-term survival analysis[66]*:* www.pubmed.com/25638248

3b. UITGEZAAIDE ALVLEESKLIERKANKER: WELKE SOORT CHEMOTHERAPIE?

FOLFIRINOX of gemcitabine + nab-paclitaxel zijn de twee meest effectieve chemotherapie schema's. Deze zijn echter wel intensiever en zwaarder dan gemcitabine alleen en zijn daardoor gereserveerd voor mensen met een gemiddelde tot goede conditie. Door de dosis FOLFIRINOX te verlagen kunnen veel mensen met een gemiddelde conditie (in staat om huishoudelijk werk te verrichten) deze chemotherapie wel verdragen *(Rombouts et al. J Cancer 2016[58])*.

Rombouts et al.[58]: www.pubmed.com/27698926

FOLFIRINOX en gemcitabine + nab-paclitaxel zijn nog niet onderling vergeleken in klinische studies, maar allebei wel met gemcitabine alleen:

FOLFIRINOX vs. gemcitabine

Gemiddelde/mediane overleving van patiënten behandeld met FOLFIRINOX is 11,1 maanden en na gemcitabine is dit 6,8 maanden *(PRODIGE 4 NEJM 2011[64])*.
Het aantal patiënten waarbij de tumor zichtbaar reageert op chemotherapie is 32% bij FOLFIRINOX en 9% bij gemcitabine *(PRODIGE 4 NEJM 2011[64])*.

PRODIGE 4 studie[64]: www.pubmed.com/21561347

Gemcitabine + nab-paclitaxel vs. gemcitabine

Patiënten die combinatietherapie gemcitabine en nab-paclitaxel krijgen, leven ruim 2 maanden langer dan patiënten met alleen gemcitabine. Dit is 8,7 maanden na de combinatietherapie en 6,6 maanden na alleen gemcitabine *(MPACT long-term survival analysis J Natl Cancer Inst 2015[66])*.

Patiënten die langer dan 3 jaar overleven waren alleen aanwezig in de combinatietherapie gemcitabine en nab-paclitaxel groep, niet in de groep met alleen gemcitabine. In de combinatietherapie groep was 4% na minstens 3 jaar nog in leven *(MPACT long-term survival analysis J Natl Cancer Inst 2015[66])*.

MPACT long-term survival analysis[66]: www.pubmed.com/25638248

3c. UITGEZAAIDE ALVLEESKLIERKANKER: BIJWERKINGEN?

FOLFIRINOX vs. gemcitabine

Ernstige bijwerkingen ("Graad 3-4") worden vaker gezien bij FOLFIRINOX dan bij gemcitabine alleen *(PRODIGE 4 NEJM 2011[64])*. In totaal krijgt ongeveer 52% van patiënten met en zonder uitzaaiingen na FOLFIRINOX ernstige bijwerkingen *(Rombouts et al. J Cancer 2016[58])*. De patiënt zal echter niet van al deze bijwerkingen klachten ervaren. De meest gerapporteerde ernstige bijwerking bij FOLFIRINOX was misselijkheid of overgeven (10%), en daarnaast buikpijn (8%), diarree (6%), vermoeidheid (6%) en koorts door verslechtering van afweer (5%) *(Rombouts et al. J Cancer 2016[58], Peddi et al. JOP 2012[61], Marthey et al. Ann Surg Oncol 2015[62], PRODIGE 4 NEJM 2011[64])*.

PRODIGE 4 studie[64]*: www.pubmed.com/21561347*
Rombouts et al.[58]*: www.pubmed.com/27698926*
Peddi et al.[61]*: www.pubmed.com/22964956*
Marthey et al.[62]*: www.pubmed.com/25037971*

Gemcitabine + nab-paclitaxel vs. gemcitabine
Ernstige bijwerkingen ("graad 3-4") zijn vergelijkbaar tussen gemcitabine + nab-paclitaxel en gemcitabine alleen. Dit is 50% bij de combinatietherapie en 43% bij gemcitabine alleen. De patiënt zal echter niet van al deze bijwerkingen klachten ervaren. Bij de combinatietherapie rapporteert 17% van de patiënten vermoeidheid, 17% perifere zenuwklachten (zoals gevoelsstoornissen), 6% diarree en 3% koorts door verslechtering van afweer. Bij gemcitabine alleen was dit 7% vermoeidheid, 1% perifere zenuwklachten, 1% diarree en 1% koorts door verslechtering van afweer.
Haarverlies trad op bij 50% van de patiënten met gemcitabine + nab-paclitaxel, tegenover 5% bij alleen gemcitabine *(Von Hoff et al. NEJM 2013*[59]*)*.

Von Hoff et al.[59]*: www.pubmed.com/24131140*

3d. UITGEZAAIDE ALVLEESKLIERKANKER: VERSLECHTERT DE KWALITEIT VAN LEVEN DOOR CHEMOTHERAPIE?
Patiënten met FOLFIRINOX registreren langer een goede kwaliteit van leven dan patiënten met gemcitabine. Achteruitgang op kwaliteit van leven 6 maanden na chemotherapie wordt twee keer zo vaak gerapporteerd door patiënten die gemcitabine krijgen in vergelijking met FOLFIRINOX patiënten (66% vs. 31%, *PRODIGE 4 NEJM 2011*[64]*)*.
Over kwaliteit van leven bij gemcitabine en nab-paclitaxel bij uitgezaaide alvleesklierkanker is helaas geen informatie beschikbaar.

PRODIGE 4 studie[64]*: www.pubmed.com/21561347*

4. ALGEMENE VRAGEN

4a. STOPPEN MET CHEMOTHERAPIE?
De patiënt kan altijd stoppen met de chemotherapie, er is geen verplichting om de behandeling af te ronden. Bijwerkingen kunnen overigens vaak verholpen of voorkomen worden door medicijnen of door de dosering aan te passen.

4b. IN WELK ZIEKENHUIS?
Meestal kan de begeleiding van en behandeling met chemotherapie in het dichtstbijzijnde ziekenhuis plaatsvinden. De oncoloog in het alvleesklierkanker-expertisecentrum ('pancreas-centrum') kan met de oncoloog in het voor de patiënt dichtstbijzijnde ziekenhuis bellen om te overleggen of dit mogelijk is.

4c. BEHANDELING IN STUDIEVERBAND?
Overweeg of een patiënt in aanmerking komt voor therapie in studieverband. Zie de bijlage voor een overzicht van de lopende studies namens de DPCG (zie ook www.dpcg.nl).

APPENDIX 5: Schematic EPI and PERT strategy (in Dutch)

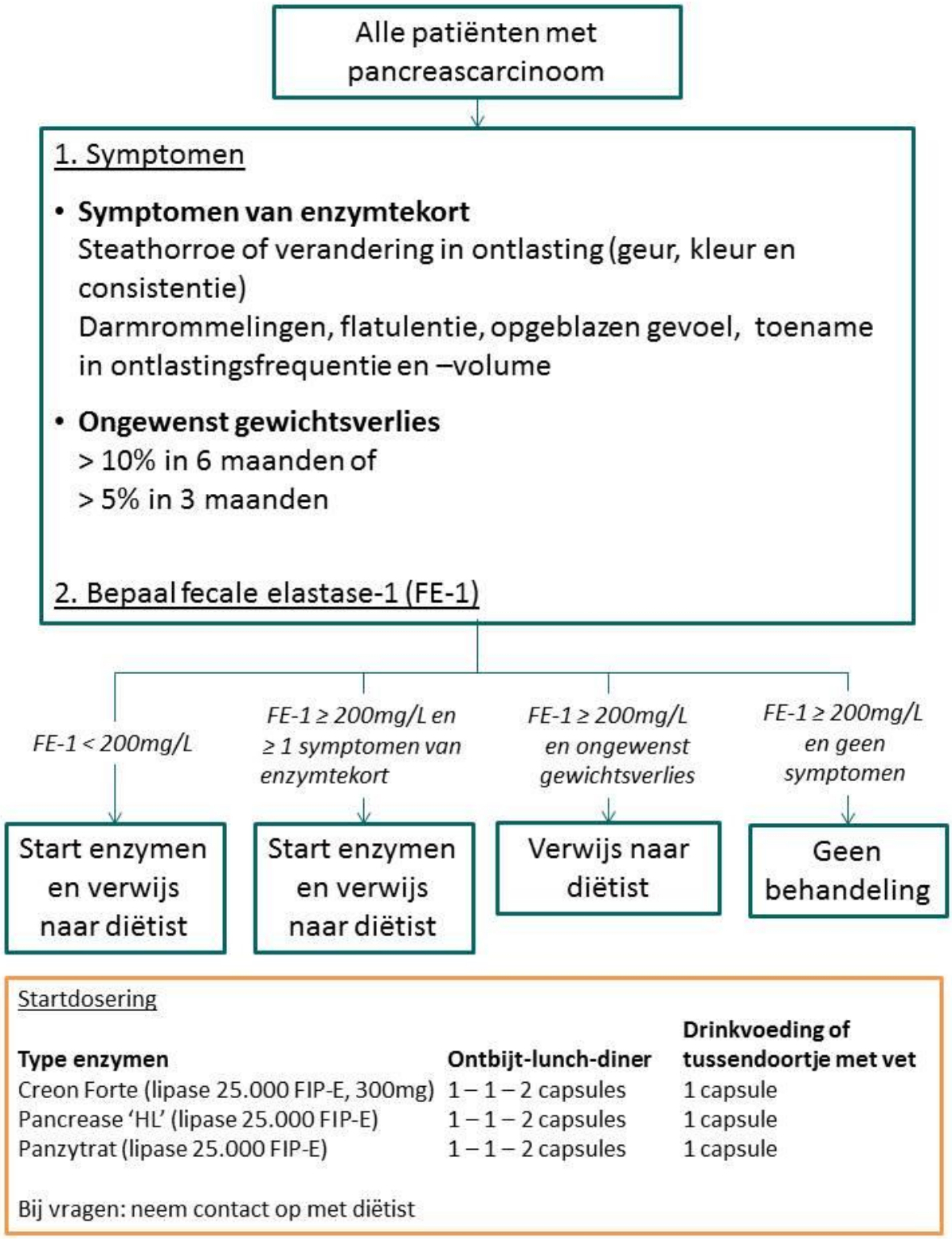

Figure 6. Schematic EPI and PERT strategy (in Dutch).

APPENDIX 6: Synoptic reporting templates

Radiology: CT-checklist for solid pancreatic tumor (in Dutch)

Pancreas tumor

- Locatie (periampullair / kop / corpus / staart)
- Grootste doorsnede (any plane): mm / niet te meten
- Aankleuring (hyper- / iso- / hypodens)
- Cysteuze partijen?
- Max diameter ductus pancreaticus: Max diameter CBD: Intrahepatische galwegdilatatie:
- Stent in situ: nee / ja [metaal of plastic]
- Pancreasparenchym: normaal/ atrofie en/of acute pancreatitis en/of chronische pancreatitis
- Aard: zeker maligne / waarschijnlijk maligne / onzeker / waarschijnlijk benigne / zeker benigne
- Adenocarcinoom/ andere diagnose, nl:

Uitbreiding tumor en relatie tumor met vaten

- Arteriële anatomie: normaal / accessoire tak (replaced LHA uit LGA) / accessoire tak (replaced RHA uit AMS) / replaced CHA uit AMS / vroege splitsing CHA met posterieur verloop RHA / anders, nl:
- Doorgankelijkheid truncus coeliacus en/of AMS: normaal / onzeker / stenose truncus coeliacus [lig arcuatum / atherosclerose] en/of AMS
- Contact AMS: geen / <90° / 90°-≤180° / 180°-≤270° / >270°
  Lumenreductie AMS: nee / ≤50% / >50% / occlusie
- Contact truncus coeliacus: geen / <90° / 90°-≤180° / 180°-≤270° / >270°
  Lumenreductie truncus coeliacus: nee / ≤50% / >50% / occlusie
- Contact a. hepatica (communis of propria): geen / <90° / 90°-≤180° / 180°-≤270° / >270°
  Lumenreductie a. hepatica: nee / ≤50% / >50% / occlusie
- Contact accessoire/replaced/dorsale tak: nvt / geen / <90° / 90°-≤180° / 180°-≤270° / >270°
- Contact met andere arteriën: geen / ja [welke + mate van contact]
- Contact Vena Portae: geen / <90° / 90°-≤180° / 180°-≤270° / >270°
  Vervormd: ja / nee. Lumenreductie Vena Portae: nee / ≤50% / >50% / occlusie
- Contact VMS: geen / <90° / 90°-≤180° / 180°-≤270° / >270°
  Vervormd: ja / nee. Lumenreductie VMS: nee / ≤50% / >50% / occlusie
- Lengte porto-mesenteriale betrokkenheid: mm (as the crow flies)
- Collateralen: nee/ ja [locatie] [typeer]
- Radiologische TNM: [T] / [N] / [M]
- Indien post-chemo: RECIST-respons tov pre-inductiescan [d.d. - -]: complete response / partial response / stable disease / progressive disease
- Ingroei omliggende organen: nee / ja
  Indien ja: peripancreatisch vet *[richting AMS / mesocolon transversum / betrokkenheid eerste jejunale venen / richting cava-aorta / craniaal richting truncus coeliacus / dorsaal van*

pancreascorpus-staart / hepatoduodenale ligament (rond CHB/CBD, AH, porta) / anders, nl:] / duodenum / maag / anders, nl:

Suspecte lymfklieren

- Regionaal: nee / ja [locatie en grootte]
- Niet-regionaal (M klieren): nee / ja [locatie]

Metastasen

- Nee / ja / onzeker
  Indien ja: lever / peritoneaal / long / anders, nl:

Relevante nevenbevindingen:

CONCLUSIE:

- Verwachte aard van de tumor (zowel vwb kwaadaardigheid als veronderstelde PA)
- Locatie en grootte tumor:
- Anatomische variant
- Vasculaire betrokkenheid:
  - Relevante arteriële structuren: geen, <90°, 90°-180°, 180°-270°, >270° contact
  - Portoveneus: <90°, 90°-180°, 180°-270°, >270° contact én lengte betrokkenheid
- Doorgankelijkheid truncus coeliacus en AMS:
- Metastasen op afstand: M klieren en/of M overig

Relevante nevenbevindingen:

<u>Oncology:</u> WHO performance status

Grade 0 - Able to carry out all normal activity without restrictions.

Grade 1 - Restricted in physically strenuous activity but ambulatory and able to carry out light work.

Grade 2 - Ambulatory and capable of all self-care but unable to carry out any work; up and more than 50% of waking hours.

Grade 3 - Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.

Grade 4 - Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

Grade 5 – Death.

<u>Surgery:</u> postoperative conclusion report after PD (in Dutch)

Ten behoeve van de Dutch Pancreatic Cancer Audit (PPPD/PRPD/Klassieke Whipple):

Diameter ductus pancreaticus tpv porta: ***mm

Consistentie pancreas: ***zacht/hard

Peroperatief octreotide toegediend: ***ja/nee/preoperatief al somatuline

Veneuze resectie vena portae e/o VMS en type: ***Nee/wedge/segment

Arteriele resectie: ***Nee/a. hepatica communis of propria of dextra/ tr. coeliacus/AMS/anders

Aanvullende resectie: ***nee/milt/mesocolon transversum/colon segment resectie/hemicolectomie rechts/maagresectie/anders

Pancreas anastomose: ***PJ/PG ***duct-to-mucosa/dunking of invaginatie/voortlopend enkelrijig ***Doorlopend/losgeknoopt ***enkelrijig/dubbelrijig

Overige maatregelen: ***nee/intra-abdominale drain(s)/voedings-jejunostomie/nasojejunale voedingssonde/stent in pancreas anastomose/stent in biliodigestieve anastomose

Bloedverlies: ***ml

Korte conclusie procedure: ***Open/laparoscopische ***PPPD/PRPD/klassieke Whipple ***met/zonder vasculaire resectie

<u>Surgery:</u> postoperative conclusion report after pancreatic central/distal resection (in Dutch)

Ten behoeve van de Dutch Pancreatic Cancer Audit (pancreas corpus/staart resectie):

Diameter ductus pancreaticus tpv porta: ***mm

Consistentie pancreas: ***zacht/hard

Peroperatief octreotide toegediend: ***ja/nee/preoperatief al somatuline

Veneuze resectie vena portae e/o VMS en type: ***Nee/wedge/segment

Arteriele resectie: ***Nee/a. hepatica communis of propria of dextra/ tr. coeliacus/AMS/anders

Aanvullende resectie: ***nee/milt/mesocolon transversum/colon segment resectie/hemicolectomie rechts/maagresectie/anders

Overige maatregelen: ***nee/intra-abdominale drain(s)/voedings-jejunostomie/nasojejunale voedingssonde/stent in pancreas anastomose/stent in biliodigestieve anastomose

Behandeling pancreas stomp: ***overhechten stomp/onderbinden d. pancreaticus/stapler zonder matje/stapler met matje/tachosyl/weefselpatch/anastomose met dunne darm of maag/weefsellijm

Bloedverlies: ***ml

Korte conclusie procedure: ***Open/laparoscopische ***corpus/staart resectie ***met/zonder milt resectie

Surgery: synoptic discharge report (in Dutch)

Classificatie chirurgische complicaties (Clavien-Dindo)

Graad: I/II/III/IV/V

Classificatie Post-Operatieve Pancreatics Fisteula (POPF, ISGPS 2016)

Graad: 0/Biochemical leak (= geen POPF)*/B/C

* Indien Biochemical Leak: poli postoperatief bepalen 0/B/C

Classificatie Vertraagde Maagontlediging Delayed Gastric Emptying na after pancreastic surgerychirurgie (DGE, ISGPS 2007)

Graad: 0/A/B/C

Classificatie Post-Pancreatectomyie Hemorrhage Bloeding(PPH, ISGPS 2007)

Graad: 0/A/B/C

Classificatie Bile LeakageGal Lekkage (ISGPS 2011)

Graad: 0/A/B/C

Classificatie Post-Operatieve Chyleus Leakkage (POCL, ISGPS 2016)

Grade: 0/A (=no POCL)/B/C

(Voor definities: http://dpcg.nl/images/ISGPS-definities-uitgebreid.pdf)

APPENDIX 7: PACAP inclusion method

- All new patients with a pancreatic or periampullary malignancy are eligible (all tumor stages).
- Preferably inclusion before primary treatment. However, inclusion before new treatment episode is also relevant.
- Type of follow-up program (treatment, no treatment) is no exclusion criterion
- Diagnostics should be finished. However, pathology confirmation is not required.
- Registration of a patient:
    - Inform patient on PACAP and invite for participation. Make note in medical record.
    - Register patient by filling out the online application form at www.pacap.nl or call the PACAP-registration telephone (06-31383590) and mention patient name, local patient number and telephone number.
- The PACAP research team will contact patient with additional information and includes the patient if the patient is willing to participate.
- PACAP follow-up is coordinated completely by PACAP research team, including:
    - Three-monthly quality of life questionnaires
    - Clinical data capture
- Questionnaire time points:
    - Baseline: before primary treatment or new treatment episode (e.g. before adjuvant chemotherapy, but after operation, or before second line chemotherapy)
    - Follow-up: 3, 6, 9, 12, 18, 24, 36 months and yearly thereafter, until death or drop out

Figure 7. Schematic PACAP procedures and contents (in Dutch).