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The Dutch Pancreatic Cancer Project

*Optimization of clinical research in pancreatic cancer*

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SUMMARY, GENERAL DISCUSSION AND FUTURE PERSPECTIVES
Despite ongoing efforts, 5-year survival of pancreatic cancer remains just 6 per cent.\(^1\) Long-term survivors have been described, which may be due to specific patient and tumor characteristics.\(^2,3\) The discovery of new such biological differences among patients with pancreatic cancer results in an increasing number of disease sub-classifications.\(^4\) Therefore, smaller patient groups mandate cooperation between centers to achieve sufficiently sized study populations. These collaborations between centers have other advantages: centers may learn from each other, and identify ‘best practices’.

While studies have traditionally focused on clinical outcome parameters such as mortality or survival, patient-reported outcomes such as quality of life are now regarded as equally important.\(^5,6\) Most pancreatic cancer studies originate from several dedicated pancreatic centers treating a high number of these patients.\(^7\) Due to known volume-outcome relationships, treatment and outcomes described in literature may differ from true population based outcomes.\(^8,9\) Therefore, hampering the evaluation of (new) treatments is a paucity of data on a nationwide level.\(^10\)

There are several other important limitations to classical study designs. For example, recruitment is restricted: only 5-10% of all patients are enrolled in a clinical trial.\(^11\) Clinical trials include highly selected patient populations, which leads to low inclusion rates and limited external validity. Data collection may also be inadequate due to insufficient follow-up or the absence of patient-reported outcomes; this, in turn, results in high costs or premature termination of studies.\(^12\)

Continuing efforts to improve treatment and outcomes for patients call for novel clinical trial designs which surpass the limitations of classical study designs and new methods for data acquisition and patient recruitment.\(^13\) Furthermore, there is a need of nationwide data on the treatment and outcomes of pancreatic cancer patients to evaluate new diagnostic and treatment strategies.\(^10\) New studies should not only evaluate clinical parameters but should be comprehensive including biomaterials and patient-reported outcomes. The Dutch Pancreatic Cancer Project (PACAP) integrates all of the above through the modernization of pancreatic cancer research. PACAP provides nationwide data on the treatment and outcome of pancreatic cancer in the Netherlands including clinical parameters, biomaterials, and patient reported outcomes. A platform is created to discuss these data, initiate research, suggest potential improvements, and test improvements in clinical trials. All of this is achieved in a smart, patient-friendly, multicenter, nationwide, multidisciplinary and (cost)-effective approach. The infrastructure provided by PACAP enables the evaluation of new treatment and outcomes through innovative study designs.
FROM REGISTRY TO EVIDENCE

In the first section of this thesis we focus on the design, creation and implementation of PACAP. In Chapter 1 we evaluate nationwide compliance to three selected quality indicators from the Dutch multidisciplinary evidence based guideline on pancreatic and periampullary carcinoma. Using data from the National Cancer Registry owned by the Dutch Comprehensive Cancer Organization, and including some five-thousand patients, nationwide compliance to the three selected quality indicators was low: just over half of patients received adjuvant chemotherapy following resection of pancreatic carcinoma, two-thirds of patients were discussed in a multidisciplinary team meeting and only 40 per cent of patients initiated treatment within three weeks following the final multidisciplinary team meeting. An important limitation to our data was that we could not evaluate reasons for non-compliance. In some cases there may be legitimate reasons to deviate from guideline recommendations. For example, adjuvant chemotherapy might be omitted in older patients due to a low performance status or high burden of comorbidity, or elderly patients might refuse high-risk pancreatic surgery.

In Chapter 2 we create a nationwide evidence-based audit of pancreatic surgery in the Netherlands, including all patients who undergo pancreatic surgery because of a (suspected) pancreatic- or periampullary malignancy: the Dutch Pancreatic Cancer Audit (DPCA). There is a high amount of variation between centers and auditing is an important tool to identify practice variation and ‘best practices’. The DPCA is currently a mandatory audit in all Dutch pancreatic centers. For each procedure, 100-150 variables are obtained. After the first two registration years, we find that over 90% of all pancreatoduodenectomies performed in the Netherlands were registered and data accuracy was also more than 90%. Mortality was correctly registered in all cases. Among 1,785 pancreatic resections in-hospital mortality was 3.6%. Following pancreatoduodenectomy, mortality was 4.1%, major morbidity was 29.9%, and median hospital length of stay was 12 days. These numbers compare favorably to other nationwide reports on outcomes after pancreatic surgery.

In the Dutch Pancreatic Cancer Audit, complications after pancreatic operation should be defined and graded in a uniform fashion which allows for comparisons between centers and countries. The International Study Group of Pancreatic Surgery (ISGPS) is an international panel of renowned pancreatic surgeons that has already introduced various international consensus definitions and grading systems for important complications of pancreatic operation. These grading systems have been well accepted and used extensively in the comparisons of outcomes between studies, institutions and countries. In Chapter 3 we worked together with the ISGPS to review the literature and established a consensus based on this literature on the definition and classification of chyle leakage after pancreatic operation. Chyle leakage may complicate up to 10 per cent of pancreatic
resections and due to increasing numbers of extended resections being performed, the incidence of CL might increase further. A universal definition and grading allows centers to collaborate and further improve outcomes of chyle leak after pancreatic surgery in future.

For patients with unresectable disease, i.e. locally advanced or metastatic pancreatic cancer, it is equally important that studies and outcomes may be compared. Therefore, in Chapter 4 we establish the first international consensus on mandatory baseline- and prognostic characteristics to be taken into account in unresectable pancreatic cancer trials. Following a systematic review including 39 randomized controlled trials and more than 15-thousand patients to identify the most important and frequently used baseline- and prognostic characteristics in these trials, a modified Delphi panel of two rounds involving 23 leading medical-oncologists in the field of pancreatic cancer around the world was used to develop the consensus. Mandatory baseline characteristics ensure proper evaluation of a cohort and allows baseline comparisons to other studies and to patients seen in routine clinical practice. The mandatory prognostic characteristics should be included in regression analyses to adjust for their influence on treatment outcomes, or may alternatively be considered for patient stratification at randomization.

While trials have traditionally focused on clinical outcomes such as mortality or survival, patient-reported outcomes are now regarded as equally important. In chapter 5 an international two-round Delphi study among more than 500 patients and healthcare providers in the United States, Europe and Asia established the first international core set of patient-reported outcomes in pancreatic cancer. Notably, the consensus highlights the importance of the psychosocial aspects of pancreatic cancer which has traditionally been an understudied domain. Future pancreatic cancer studies should include the patient-reported outcomes identified in this study.

Another application of patient-reported outcomes is their routine, longitudinal measurement in clinical practice which may benefit both patient-centered and general quality of care. In chapter 6 we perform the first analysis with patient reported outcomes gathered through PACAP. In line with developments towards patient-centered care, patient satisfaction is increasingly recognized as an important outcome. Among a prospective cohort of 100 patients we find decreases in patient satisfaction after treatment regarding general satisfaction with care, interpersonal skills of doctors and satisfaction with the exchange of information within the care team. Decreases in satisfaction scores were larger for patients treated with curative intent, compared to patients treated with palliative intent. It was surprising to find larger decreases in satisfaction scores after curative treatment, as we hypothesized patients may appreciate ‘treatment of the disease’. Expectation
management through shared-decision making, attention to psychosocial problems, and increasing health care professionals’ communication skills may improve patients’ satisfaction with care.

In chapter 7 we demonstrate the feasibility of PACAP: a comprehensive, nationwide, multidisciplinary pancreatic cancer cohort which surpasses the limitations of classical study designs. Briefly, all patients aged ≥18 years with pancreatic cancer are eligible. Patients are asked to sign a multi-source informed consent including 1) reuse of clinical data from all medical files; 2) tissue sampling; 3) blood sampling; 4) to be informed about relevant newly identified genomic aberrations; 5) patient reported outcomes and 6) receiving information on new interventional studies and possible participation in cohort multiple randomized controlled trials (cmRCT) in the future. The cmRCT design will be addressed in more detail below. Patients can provide written informed consent for each component separately, and may retract consent for each component at any point in time. The participation rate for each informed consent item was high, demonstrating patient willingness to participation. PACAP maintains a flat hierarchy structure so that all data is easily accessible to participating centers.

FROM REGISTRY TO BEDSIDE

In the second section of this thesis we focus on the further development of PACAP. One of the strengths of PACAP is that it allows for comprehensive, nationwide evaluation of emerging concepts in pancreatic cancer and is adaptable to implement new findings. Therefore, we set out to explore some current hot topics in pancreatic cancer research.

For pancreatic surgery, higher volume hospitals have demonstrated better postoperative results compared to lower volume hospitals.8, 9, 18 One of the main developments in pancreatic surgery in the Netherlands over the past few decades has therefore been its centralization, which was accompanied by a decrease in postoperative mortality.19 Currently 17 hospitals in the Netherlands are performing pancreatic surgery. Each hospitals performs a minimum of 20 pancreatoduodenectomies annually, as mandated by the Dutch government. In chapter 8 we analyze almost 3,500 pancreatic operations recorded in the Dutch National Cancer Registry. We find that volume-outcome relationships in pancreatic surgery extend to larger hospital volume categories than previously studied, including a volume category of ≥40 pancreatoduodenectomies annually. This includes postoperative mortality and overall survival. Ultimately, research should extend beyond solely hospital volume numbers as hospital volume is undoubtedly a proxy for numerous factors which may all contribute to a more nuanced but complex discussion regarding the volume–outcome relationships in pancreatic surgery.
Higher mortality rates have traditionally been thought to be the consequence of higher complication rates. Recent studies, however, have suggested that not the occurrence of a complication but its treatment drives differences in mortality. Failure to rescue (FTR) is defined as the death of a patient with a major postoperative complication. In chapter 9 we investigate if variation in mortality rates between centers in the Netherlands are due to more complications in some centers, or less effective treatment of (major) complications. We do this by using detailed data from the recently erected Dutch Pancreatic Cancer Audit among almost 1500 pancreatoduodenectomies during two years. Varying mortality rates between hospitals were explained to a much larger extent by varying FTR, than by varying complication rates. This was clearly illustrated by the 560% increase in FTR between the first and fourth hospital mortality quartile, compared to a 40% increased rate of major complications between these quartiles. Higher volume centers displayed lower FTR rates compared to lower volume hospitals. In this study we could not identify which factors contribute to better FTR in higher volume centers, which will be the subject of oncoming studies by the Dutch Pancreatic Cancer Group.

Risk prediction is an invaluable tool for pancreatic surgeons and can be used for counseling and shared-decision making, risk stratification, and improve intraoperative decision making. In the final chapters of this thesis we focus on several existing and emerging risk prediction models. Postoperative pancreatic fistula (POPF) is a leakage of the pancreatojejunostomy and is the most dreaded complication after pancreatic surgery which occurs in up to 20% of patients and is typically associated with prolonged hospital stay, increased re-operation and reintervention rates, and increased mortality. Various risk models for POPF have therefore been developed with varying reliability. This may be due to the subjective nature or questionable prognostic importance of some factors included in these models. In chapter 10 we develop a new risk model for POPF using over 2,500 patients from two cohorts and by external validation through an independent database. The developed risk model is based on three readily available intra-operative variables. Our model displays similar performance compared to other risk models, which are often more extensive. A strong example of the potential application of our risk model is that it may aid in individualized patient care: low risk patients may be spared certain medication (e.g. somatostatin analogues) or surgical drain placement.

A promising new prognostic tool in surgery is preoperative CT-scan derived body composition measures. Muscle mass and muscle quality derived from preoperative CT-scans have demonstrated prognostic value in various tumors. In chapter 11 we investigate these CT-scan derived measures of muscle composition in a monocentric consecutive cohort of 166 patients receiving pancreatoduodenectomy for periampullary (excluding pancreatic ductal adenocarcinoma)
carcinoma. Low muscle quality, but not low muscle mass, was independently associated with poor survival with a prognostic value equaling that of other conventional covariates determining prognosis for these patients. Our findings may provide a window for “prehabilitation” opportunities, which are subject of ongoing studies.

A novel general surgical risk model was evaluated in Chapter 12. Results of the Estimation of Physiologic Ability and Surgical Stress (E-PASS) risk model have been impressive in non-Western populations for various gastrointestinal tumors. E-PASS variables were obtained from a prospective monocentric cohort of more than 550 consecutive patients undergoing pancreateoduodenectomy for cancer. E-PASS and its modified version (mE-PASS) did not predict mortality or major morbidity after operation in this large Western cohort.

In chapter 13, by means of a systematic review including 14 studies and about 2,000 patients we found that hepatic-artery or para-aortic lymph node metastases are associated with reduced survival after pancreateoduodenectomy for malignancy. Unfortunately, included studies did not contain adequate control groups, possibly contained strong selection bias, and were of small and retrospective nature. Resection in patients with hepatic-artery LNM seems reasonable as survival times are better compared to patients with irresectable disease and this node is part of the ISGPS standard lymphadenectomy. In patients with para-aortic LNM proceeding with resection is less obvious, but due to a lack of adequate control groups and data on (neo)adjuvant therapy it remains unclear whether intra-operative detection of para-aortic LNM should automatically preclude resection in all patients.

The main results and conclusions from this thesis are:
1. Results of the treatment of pancreatic cancer in the Netherlands are good, but there is room for improvement
2. A nationwide registration of pancreatic cancer patients including clinical data, biomaterials, and patient-reported outcomes is feasible, comprehensive, accurate, and facilitates novel research designs (PACAP)
3. PACAP provides nationwide data on the treatment and the results of treatment of pancreatic cancer patients in the Netherlands
4. PACAP provides the structure to discuss these data, initiate research, suggest potential improvements, and test these improvements in clinical trials
5. PACAP facilitates international collaborations regarding pancreatic cancer care and research
6. PACAP is patient friendly, nationwide, multidisciplinary, and (cost-) effective
7. The goal of a nationwide registration of the treatment and results of the treatment of pancreatic cancer is the identification of best practices so that hospitals may learn from each other
DISCUSSION AND FUTURE PERSPECTIVES

Despite the persistent poor prognosis of pancreatic cancer there have been several recent advances in its treatment that deserve specific attention. Surgical resection currently remains the only hope for long term survival. Due to advanced technical possibilities and improvements in perioperative care,44,45 more aggressive surgical approaches have been advocated to increase resection rates. Extended resections including major artery resection are becoming a viable alternative.46 Advances in surgical possibilities should ultimately enlarge the pool of patients eligible for surgical resection, with survival times which outweigh patients with unresectable disease.

Palliative chemotherapy has been the hallmark of treatment for patients with unresectable disease.47 For patients with unresectable disease a chemotherapy combination consisting of Gemcitabine has long been regarded as the most effective agent.48 One of the greatest breakthroughs of the past decade has been the discovery of FOLFIRINOX, a chemotherapy regimen consisting of a combination of 5-fluorouracil, oxaliplatin, irinotecan and leucovorin. FOLFIRINOX improves response rate, progression-free survival and overall survival in patients with metastatic disease with a median survival of 11.1 months compared to 6.8 months in patients treated with Gemcitabine.49 Unfortunately, FOLFIRINOX is reserved for patients with a good performance status (ECOG performance score 0-1) due to an increased amount of toxicity compared to Gemcitabine.

The use of FOLFIRINOX has consequently been investigated in patient with locally advanced (i.e. unresectable) pancreatic cancer as well. While large randomized trials are eagerly awaited, aggregated evidence of smaller and retrospective studies are promising. For locally advanced pancreatic cancer median overall survival with FOLFIRINOX was 24 months in a patient-level meta-analysis.50 In comparison, median overall survival with gemcitabine for locally advanced pancreatic cancer ranged from 8 to 13 months in previous studies.51,52

The standard of care following resection of pancreatic cancer is adjuvant chemotherapy with Gemcitabine.47 Recent evidence suggests that median overall survival can be improved by adding Capecitabine to Gemcitabine in the adjuvant setting,53 or by replacing Gemcitabine with (modified) FOLFIRINOX in the adjuvant setting.54 An alternative is the administration of neoadjuvant therapy, by chemotherapy or (chemo)radiotherapy. This has several theoretical benefits. Only about half of patients receive adjuvant chemotherapy, possibly because some patients cannot tolerate adjuvant chemotherapy after surgery.55 Furthermore, a third of all patients that are deemed resectable ultimately do not undergo a resection due to metastatic or advanced disease found intraoperatively which was not detected on preoperative imaging.56 Finally, a considerable amount of patients develop metastases within the first few months following surgical resection.57 This
suggests systemic (metastatic) disease which was present during surgery but was not detected on preoperative imaging and if it had, would have precluded a resection. Studies on neoadjuvant therapy in pancreatic cancer have been scarce and their results inconsistent. Hence, two large multicenter, multidisciplinary, randomized trials are ongoing through the Dutch Pancreatic Cancer Group. These trials investigate the added value of neoadjuvant chemoradiotherapy, and neoadjuvant FOLFIRINOX in patients with (borderline) resectable pancreatic cancer.

Recent evidence suggests that neoadjuvant FOLFIRINOX treatment may downsize 10-20% of locally advanced pancreatic tumors to such an extent, that they become eligible for surgical resection. Unfortunately, current state-of-the-art CT-imaging is very poor in determining the resectability of locally advanced pancreatic cancer after chemotherapy, including FOLFIRINOX. So, currently it is unclear whether all patients after FOLFIRINOX should undergo surgical exploration when, in fact, only 10-20% are indeed resectable. More accurate imaging would improve the selection process for explorative laparotomy. While the exact mechanisms explaining the discrepancy between radiological (i.e. CT-imaging) and the intraoperative determination of pancreatic cancer resectability remain to be elucidated, several studies have demonstrated that chemotherapy induces a ring of fibrosis at the outer borders of the cancer, which at CT-imaging is indiscernible from cancer tissue. Currently, we are performing a study using diffusion weighted imaging (DWI) on MRI; DWI represents the random diffusion of water molecules on MRI. Because the diffusion of water molecules is altered by the density of intracellular and extracellular structures, DWI is able to differentiate accurately between various intra- and extracellular constituents, for example edema or fibrosis. Therefore, with DWI it may be possible to improve the differentiation between fibrosis versus viable pancreatic tumor after chemotherapy, and therefore improve the accuracy of imaging local (viable) tumor extension, after chemotherapy compared to current state-of-the-art CT-imaging.

Patients in whom resection is not feasible during explorative laparotomy after chemotherapy due to locally advanced disease might benefit from local ablation strategies. Two examples include irreversible electroporation (IRE) and radiofrequency ablation (RFA). IRE is a non-thermal ablation technique creating short pulsed high-voltage current fields. The electrical pulses permeabilize the cell membrane, causing a disruption of intracellular homeostasis and thereby inducing apoptosis. RFA involves the implantation of one or more electrodes directly into the tumor. These needles produce a high frequency alternating current, producing heat and thus tissue destruction. In patients with locally advanced pancreatic tumors, IRE has been associated with a median overall survival of up to 27 months. Median survival rates following RFA reported in recent observational non-randomized cohort studies range from 19 to 25.6 months with an increase of survival of a maximum of 20 months compared to palliative chemotherapy. A randomized
controlled trial is now underway by the Dutch Pancreatic Cancer Group investigation the role of RFA in the treatment of patients with locally advanced pancreatic cancer.

Through PACAP, emerging treatment strategies such as those described above can be formally evaluated in a nationwide, prospective, multidisciplinary, and comprehensive manner. PACAP will serve as a basis for multiple new studies with the aim to establish a continuous source of data for a variety of research purposes, and address the limitations of traditional study designs. The research database created in PACAP will contain a large variation of prospective observational data that can be used to investigate what (intrinsic and environmental) factors are associated with survival and patient-reported outcomes, to find new predictive markers for treatment outcome and side-effects, and to develop more accurate diagnostic tests and efficient follow-up surveillance strategies.

Next to research, PACAP has the ability to audit pancreatic cancer care. The goal of measuring outcomes is usually to determine optimal treatment by comparing interventions. Clinical auditing, however, aims at measuring and comparing outcomes of doctors or hospitals for a specific patient population. These results can then be used to improve current practice and increase transparency, which is increasingly demanded by society. Auditing may be seen as a PDCA (plan-do-check-act) cycle. First, quality of care is defined, for example an evidence-based guideline. Second, care is evaluated, i.e. is there compliance to various guideline recommendations and what are the patient related outcomes. Third, areas of lagging compliance are identified and changes are implemented to increase compliance.

Monitoring quality of care is increasingly being implemented throughout the medical landscape. Surgeons have played a key role regarding the initiation and implementation of clinical auditing in clinical care. Prominent initiatives such as the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) have already improved outcomes for patients.\textsuperscript{75, 76} Auditing is relevant especially to areas of surgery where there is much inter-hospital variation: in pancreatic surgery, differences in mortality between hospitals are among the largest.\textsuperscript{8} Fair comparison of performance indicators across hospitals (i.e. benchmarking) requires adjustment for differences in baseline characteristics. Therefore, baseline characteristics associated with performance indicators (e.g., tumor stage when comparing survival) should also be collected in PACAP.\textsuperscript{77, 78} Due to the success of clinical auditing, other medical disciplines such as medical-oncology are rapidly developing clinical audits to implement in clinical care as well.

In the first section of this thesis, we establish the need for a dedicated pancreatic cancer registry. We discover that nationwide compliance to selected quality indicators from the Dutch guideline
on pancreatic and periampullary carcinoma was low. As there may be valid reasons to deviate from guideline recommendations, a dedicated pancreatic cancer registry can identify patient and tumor characteristics which may contribute to deviation from guideline recommendations, identify practice variation and best practices between centers, and improve compliance in future.

The Dutch Pancreatic Cancer Audit is the first registry launched by PACAP. By including more than 90 per cent of all pancreatic resections performed in two years in The Netherlands, the DPCA at this time already empowered us to provide nationwide data on treatment and outcomes, and improve transparency. Each year, nationwide data is presented in the annual DPCA report which is available to all. Multiple analyses will follow to investigate current quality of care of pancreatic surgery in the Netherlands and identify areas for improvement. Because the DPCA can serve as an online ‘Case Record Form (CRF)’ (i.e. study variables), adding a few variables for research purposes can easily enable nationwide, multicenter, multidisciplinary research. To ensure high quality data, a data verification project has been launched to avoid bias in the DPCA. Once a year, specially trained registration employees perform at random cross-checks between registered data and medical charts in hospitals on important parameters such as mortality, complications etc. Registration burden will be reduced by implementation of nationwide synoptic reports which we have developed for operation note, discharge letter, and pathology and radiology reports. Synoptic reporting has the additional benefit to ensure that all critical data which is important for (shared) decision making is always recorded and available to all involved medical specialists.

The DPCA is unique because it covers all pancreatic cancer patients in the Netherlands. Other noticeable population based registries originate mainly from the U.S. including the Surveillance, Epidemiology, and End Results (SEER), Medicare, and NSQIP programs. While each includes a greater absolute number of patients and hospitals, coverage is far below 100%. For example, the SEER program includes only 28% of the total population.

A collaboration between the DPCG and the Dutch Comprehensive Cancer Organization (IKNL) has resulted in a data sharing collaboration, allowing the DPCA to be linked to the Dutch National Cancer Registry (NCR). In the NCR, approximately 200 clinical items are recorded for each patient with pancreatic cancer irrespective of disease stage. Therefore, the recorded items significantly differ but complement the DPCA items. Consequently, for each 2000-3000 new patients diagnosed with pancreatic cancer in the Netherlands each year PACAP has achieved that 200-400 various clinical items are gathered.
In order to create a comprehensive registry which allows for the identification of best practices, recorded data should adhere to a universal language which also allows for comparisons between centers and countries. Therefore, definitions used should be identical. Ideally, patients and health care providers should agree on these definitions to maximize the potential influence of comparative studies. Through three chapters, we standardized three important aspects of pancreatic cancer care and research. First, we developed international consensus on the definition and grading of chyle leak after pancreatic surgery, a treatable but common and potentially serious complication after pancreatic operation. Second, we defined mandatory baseline- and prognostic characteristics in trials for unresectable pancreatic cancer. Future studies should include these baseline- and prognostic variables to allow adequate baseline comparisons and risk adjustment, respectively. Finally, we identified a core set of patient-reported outcomes which should guide future studies on patient-reported outcomes, may serve as a guideline for those wanting to initiate longitudinal registries of patient-reported outcomes, and draw attention to the psychosocial aspects of pancreatic cancer in clinical care.

A second registry within PACAP includes the longitudinal patient-reported outcomes registry. As a proof of concept, we describe patient-reported outcomes of the first 100 patients included. In coming years, the patient-reported outcome registry will further expand. To optimize response rates intensive patient contact is needed. Next to the automated electronical reminders that are in place additional PACAP staff will maintain close personal contact with all patients to answer questions etc. Furthermore, this additional staff will aid in managing the expected high number of patient inclusions. Next to data on nationwide outcomes regarding patient-reported outcomes, PACAP aims to provide doctors and patients with patient-level feedback which may be used in the consultation room.

Vital to the success of PACAP is an infrastructure which allows easy multidisciplinary collaboration between centers. In the final part of the first section of this thesis, we describe the logistics and governance surrounding PACAP. All eligible patients give separate informed consent for the various aspects of PACAP. All data is stored in secure online databases. Centers may at any time access their own data. Through the scientific committee of the Dutch Pancreatic Cancer Group centers may request the full set of comprehensive data for research purposes. They may also file proposals for large, multicenter, multidisciplinary studies to be implemented within PACAP.

In the second part of this thesis, we focus evaluating several hot topics in pancreatic cancer which may be eligible for formal evaluation or implementation in PACAP. First, we further examine previously established volume-outcome relationships which have led to centralization of pancreatic
surgery in the Netherlands and was accompanied by reduced postoperative mortality.\textsuperscript{91} This has resulted in a volume cut-off installed by the Dutch government, requiring each hospital to perform a minimum of 20 pancreatoduodenectomies annually.\textsuperscript{92} Compared to larger countries, in the Netherlands transferring patients to a high volume center is logistically far less demanding due to smaller travelling distances. While we find that volume-outcome relationships transfer to even higher volume categories than previously studied, we are limited by the fact that we cannot conclude what it is that these centers are doing better. As we base our results on averages, some lower volume hospitals may be performing equally well and displaying similar characteristics to some of the higher volume centers.

We continue to investigate what may drive differences in mortality between centers and volume categories. Much effort has previously been put into the prevention of complications. While important, we identify that in the Netherlands failure to rescue is much more responsible for differences in mortality between centers and volume categories, compared to differences in the incidence of complications. Defined as the number of patients passing with a major complication, failure to rescue may be a multifactorial process but good complication management in high-volume centers seems to be responsible for lower mortality.\textsuperscript{93} Various factors responsible for better failure to rescue have been studied such as staffing numbers, technology status, infrastructure between centers, the ratio of nurses/staff, intervention radiology, timing of CT scanning etc.\textsuperscript{22, 94-96} However, it could be that just volume itself, treating many complications, could be responsible for lower FTR in these centers. In the Netherlands, the Dutch Pancreatic Cancer Group has recently launched a nationwide study investigating such factors between centers.

Risk stratification is an invaluable tool for pancreatic surgeons. The most dangerous complication after pancreatic surgery is postoperative pancreatic fistula (POPF).\textsuperscript{14, 25} Various risk models have been developed, and their accuracy has been subject of ongoing investigations.\textsuperscript{26, 27, 97} Limiting some models for the prediction of POPF is their extensiveness, subjective nature, or inclusion of parameters with questionable prognostic significance. We developed a new risk model for POPF with three intra-operatively, readily available variables.\textsuperscript{98} In future, the DPCA may serve as a tool to investigate the effectiveness of this new risk model, and its clinical applicability.

The general surgical risk model E-PASS (and its modified form mE-PASS) displayed disappointing results in our large Western cohort, while results had been promising in Asian populations with various gastrointestinal tumors.\textsuperscript{41, 99} Some differences in our findings compared to those found in Asia may be explained by differences in populations and ethnicity, or differences in surgical volume. There are some factors further limiting the clinical utility of general risk models such as E-PASS.
For example, most models focus on postoperative morbidity and mortality but do not consider the survival benefits that are gained by the operation. Furthermore, unfavorable preoperative conditions may also be attenuated by improved surgical performance. The most dangerous complication after pancreatoduodenectomy is POPF. Therefore risk scores for POPF seem to be preferred among pancreatic surgeons.

Attention to CT-scan derived body composition measures which may be of prognostic significance have exponentially increased over the past years. Strong independent prognostic values have been identified for a wide array of tumors. We find that muscle quality measured on preoperative CT scanning may be more important than muscle quantity. Currently hampering the routine application of these measurements in preoperative (shared) decision making is the lack of treatment for decreased muscle mass or quality. Training programs may take several months which abolishes their application in the preoperative setting. However, 'prehabilitation' strategies which are currently under investigation may increase the clinical utility of CT scan derived body composition measures in future.

In our systematic review on the prognostic importance of intraoperatively detected lymph node metastases we find ourselves limited by retrospective and small studies. Resection in patients with hepatic-artery LNM seems reasonable as survival times are better compared to patients with irresectable disease. In patients with para-aortic LNM proceeding with resection is less obvious, but due to a lack of adequate control groups and data on (neo)adjuvant therapy it remains unclear whether intra-operative detection of para-aortic LNM should automatically preclude resection in all patients. Through PACAP, PANODE is a nationwide prospective study on intraoperatively detected lymph node metastases with the potential to include each patient receiving pancreatoduodenectomy in the Netherlands. To this extent, several PANODE study variables were added to the Dutch Pancreatic Cancer Audit, but most are already standardly collected.

While offering the ability to provide nationwide multicentric multidisciplinary research through classical study designs including clinical parameters, biomaterials, and patient-reported outcomes, PACAP is geared towards the facilitation of novel trial designs. A strong example of the possibilities of PACAP is the ongoing PANODE study (see above). Two other prominent examples are discussed. First, the cohort multiple Randomized Controlled Trial (cmRCT) is a novel alternative design for evaluation of new interventions. The basis of the cmRCT design is an observational cohort consisting of patients with the condition of interest, who undergo standard treatment and for whom clinical and patient-reported outcome measures are captured at predefined intervals – as
is the case in PACAP. When a new intervention is ready for formal evaluation, all patients within the cohort who are eligible for this treatment are identified. From this sub cohort, a group of patients are randomly selected and offered the experimental intervention. Outcomes of these patients will be compared to the systematically measured outcomes of those patients that were in the sub cohort (i.e. were eligible to receive the treatment) but who were not randomly selected to be offered the experimental intervention. As soon as another experimental intervention is introduced for a similar (partially or completely overlapping) group of patients, the same process may be repeated. The cmRCT design is one of the novel research designs empowered by PACAP which will expand research possibilities in future.90

In confirmation with the original PACAP project plan, the full capabilities of PACAP will be demonstrated through a cluster randomized stepped wedge trial, which will implement best practices identified through its own data in a nationwide manner. This form of implementation is not possible using ‘classical’ parallel-group randomized controlled trials.105 In a stepped wedge cluster randomized trial, clusters (i.e. hospitals) are randomly allocated a time when they are given the intervention. The intervention is in this case implementation of the identified best practices. At the endpoint, all clusters will be receiving the intervention. Advantages of this approach, compared to parallel group or crossover cluster randomized controlled trials, are that the intervention will be rolled out to all clusters in phases, it is useful where phased implementation is preferable by various constraints, and it makes differentiation from time-effects possible. Randomized controlled trials that randomize individuals are difficult to implement in routine practice, and may not reflect effectiveness at a population level. Nonrandomized designs as pre- and post-intervention evaluations have the tendency to overestimate the intervention effect, since the investigated intervention is usually thought to be more effective. In a systematic review, including 25 studies, it was found that the cluster randomized stepped wedge controlled trial design has mainly been applied in evaluating interventions in routine practice, particularly for interventions that have been shown to be effective in more controlled research settings.106 Outcomes will be recorded by PACAP. The use of multicenter registries to provide baseline data and outcomes needed in RCTs has recently gained interest from researchers as it is a way to significantly reduce costs for large multicenter RCTs.13

In this thesis, we describe the design, creation, implementation and future directions of PACAP. PACAP provides nationwide data on the treatment and outcome of pancreatic cancer in the Netherlands including clinical parameters, biomaterials, and patient-reported outcomes. A platform is created to discuss these data, initiate research, suggest potential improvements, and test improvements in clinical trials. All of this is achieved in a smart, patient-friendly, multicenter,
nationwide, multidisciplinary and (cost-) effective approach. The structure provided by PACAP enables the evaluation of new treatment and outcomes through innovative study designs. The ultimate goal of PACAP is to be implemented within standard care. PACAP may provide all relevant parties such as doctors, patients, healthcare inspectorate, government, insurance bodies, etc. with detailed nationwide information on the treatment and outcomes of pancreatic cancer. At this moment the PACAP projects described are not standard care and are therefore dependent on external funding to achieve its projects and goals.
REFERENCES

17. Chen J, Ou L, Hollis SJ. A systematic review of the impact of routine collection of patient reported outcome measures on patients, providers and health organisations in an oncologic setting. BMC Health Serv Res 2013; 13:211.


82. Dutch Comprehensive Cancer Organization. Available at: www.iklnl.nl.
92. Duth Healthcare Inspectorate.


