Nationwide implementation program for optimal multidisciplinary management and resection of locally advanced pancreatic cancer (PREOPANC-4)

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PROJECT SUMMARY

Rationale: Non-metastasized locally advanced pancreatic cancer (LAPC) is diagnosed in 35% of all pancreatic cancer patients and is traditionally treated with palliative care. Recently, the multidisciplinary management of LAPC has evolved by the introduction of FOLFIRINOX induction chemotherapy, leading to an increased resection rate and improved outlook for five-year survival. In contrast, five-year survival after chemotherapy without surgery is virtually non-existent. In the Netherlands, the LAPC resection rate after induction chemotherapy remains low with 8% versus 25% in international centers of excellence, leading to missed opportunities for five-year survival in a selected subgroup of LAPC patients. Explanations for this large difference include the spectrum of chemotherapy use, interpretation of diagnostics, patient selection, and surgical techniques.

Objective: A safe and patient-centered implementation of the international standards of excellence for LAPC (surgery) in the Netherlands.

Study design: A prospective, nationwide, implementation program of the international standard of excellence for LAPC care in the Netherlands (2021[10]-2030[8]), including a multidisciplinary training program by the four leading international expert centers (i.e. University of Heidelberg, University of Colorado, New York University Medical Center, and MD Anderson Cancer Center). Subsequently, the three Dutch centers with the highest surgical volume and documented experience in LAPC surgery will implement this highly complex LAPC surgery in close collaboration with the other Dutch Pancreatic Cancer Group (DPCG) centers. Patients who meet the inclusion criteria will be discussed within an online (inter)national expert panel to properly select patient for surgery. In addition, the other DPCG centers can present their LAPC patients to this panel for advice about (surgical) treatment options and if these patients should be referred to the three high-volume DPCG centers for surgery. Outcomes will be compared with a historical Dutch LAPC cohort, using propensity score matching.

Study population: Adult patients with pathology confirmed non-metastasized LAPC and non-progressive disease after at least two months of (modified) FOLFIRINOX or gemcitabine-nab-paclitaxel induction chemotherapy and fit for major surgery.

Study aim: The primary study aim is to double the LAPC resection rate in the Netherlands from 8% to 16% with adequate survival and morbidity targets.

Primary targets:

(1) *Survival:* After resection, mOS of 25 months, 1-year survival >90%, and 5-year survival >20%. These outcomes will be compared to the Dutch cohort of patients (2015-2020) with RECIST non-progressive LAPC after induction chemotherapy who did not undergo surgical exploration;

(2) *In-hospital morbidity and mortality*: in-hospital/30-day mortality ≤5% and in-hospital major morbidity of <50% after resection, which will be compared with a recent Dutch cohort (2015-2020) of resected patients with borderline resectable and locally advanced pancreatic cancer after induction/neoadjuvant therapy.

Secondary targets:

(1) A non-inferior radical resection (R0) rate as compared to a recent Dutch cohort (2015-2020) of resected patients with borderline resectable and locally advanced pancreatic cancer after induction/neoadjuvant therapy; (2) non-inferior quality of life, mental and physical health status, and potential side effects on the long-term follow-up, compared to a control cohort of Dutch LAPC patients; and (3) non-inferior patients' healthcare satisfaction, compared to the Dutch historical cohort of pancreatic cancer patients.

1 BACKGROUND

Pancreatic cancer is expected to become the second cause of cancer-related deaths worldwide in 2030.[1] Pancreatic cancer is associated with a poor five-year survival rate of merely 5-10%.[2] Some 35% of patients are diagnosed with locally advanced pancreatic cancer (LAPC),[3] traditionally treated with chemotherapy or best supportive care.[4, 5] In recent years, the introduction of FOLFIRINOX (a combination of 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin) induction chemotherapy has improved the clinical outcome of these patients.[6-9] Induction FOLFIRINOX and other chemotherapeutic regimens have shown the ability to downstage LAPC to resectable disease in approximately 25% of patients,[7] with favourable 20-40 months median overall survival (mOS) and at least 20% five-year survival,[10-16] whereas five-year survival after chemotherapy without surgery is virtually non-existent.[11, 14] Therefore, this multimodality treatment for LAPC has been implemented in international centers of excellence.[6]

In the Netherlands, the LAPC resection rate after induction chemotherapy is low with 8% versus 25% in an international meta-analysis,[7, 17] leading to missed opportunities for five-year survival in a selected subgroup of LAPC patients. The difference in resection rate cannot be explained by the lower or absent use of radiotherapy only.[12, 18] Differences probably include the use of systemic chemotherapy, radiologic interpretation of tumor extension following chemotherapy, pre- and intraoperative patient selection, and surgical techniques.

Multidisciplinary LAPC management with expertise in patient selection and demanding high-volume surgery are essential to prevent futile surgical exploration; to resect only the tumors in patients who will benefit most probably with low morbidity and mortality from this challenging surgery.[19, 20] The value of diagnostic criteria to properly select LAPC patients for surgery is recently confirmed by the Dutch Pancreatic Cancer Group (DPCG) and others,[21-23] and subsequently stated in the international guidelines.[24, 25] Many large, highly experienced international centers of excellence currently explore all patients with non-progressive LAPC following 2-4 months of systemic chemotherapy by using these diagnostic criteria to minimize futile surgery[23] and, meanwhile, achieving LAPC resection rates of 20-30% with outlook for five-year survival.[11, 13, 26, 27]

Although the present literature about LAPC surgery is surprisingly consistent,[7, 8, 10-16, 18, 26] current data comprise only observational series from single high-volume centers of excellence and has never been translated to multicenter or nationwide settings. A nationwide multidisciplinary best-practice program is required to safely implement the international LAPC best-practice in the Netherlands. Ultimately, a randomized controlled trial will have to confirm the survival benefit from this approach but should not be performed too early in the learning curve based on recent experiences in the Netherlands.[28] The high-quality, well-organized and collaborative DPCG provides a unique platform and opportunity to carefully implement the international multidisciplinary best-practice for LAPC and, meanwhile, prospectively investigate surgical and oncological outcomes nationwide.

2 OBJECTIVES

The PREOPANC-4 project aims to safely implement the international standard of excellence for LAPC management and surgery using a multidisciplinary best-practice training program, based on the experiences of four leading international expert centers (i.e. Johns Hopkins University, University of Colorado, Heidelberg University, and MD Anderson Cancer Center). Assessments of patients' health care satisfaction, quality of life, patients' mental and physical conditions, and side effects aim to get further insight in the consequences over time of the implemented oncological (and surgical) treatment for LAPC.

We hypothesize that the PREOPANC-4 implementation project will result in the improvement in multidisciplinary patient management and selection in line with current international best-practice, leading to an increase in the LAPC resection rate in the Netherlands from 8% to 16% (NCCN definition). Hereby we have identified the follow targets.

Primary targets:

(1) *Survival:* After resection, mOS of 25 months, 1-year survival >90%, and 5-year survival >20%. These outcomes will be compared to the Dutch cohort of patients (2015-2020) with RECIST non-progressive LAPC after induction chemotherapy who did not undergo surgical exploration;

(2) *In-hospital morbidity and mortality*: In-hospital/30-day mortality ≤5% and in-hospital major morbidity of <50% after resection, which will be compared with a recent Dutch cohort (2015-2020) of resected patients with borderline resectable and locally advanced pancreatic cancer after induction/neoadjuvant therapy.

Secondary targets:

(1) A non-inferior radical resection (R0) rate as compared to a recent Dutch cohort (2015-2020) of resected patients with borderline resectable and locally advanced pancreatic cancer after induction/neoadjuvant therapy;

(2) Non-inferior quality of life, mental and physical health status, and potential side effects on the long-term follow-up, compared to a control cohort of Dutch LAPC patients;

(3) Non-inferior patients' healthcare satisfaction, compared to the Dutch historical cohort of pancreatic cancer patients.

3 MATERIALS AND METHODS

This prospective multicenter nationwide implementation program from the DPCG, executed from October 2021 until August 2030, comprises the following two phases:

(1) Phase I – Multidisciplinary best-practice training program;
(2) Phase II – Clinical implementation program.

All DPCG centers will participate in the PREOPANC-4 project. The DPCG is an experienced group of surgical and medical oncologists, radiotherapists, gastro-enterologists, radiologists, pathologists and researchers from 15 hospitals in the Netherlands. See **Appendix 1** for the participating hospitals.

Initially, a limited number of centers will be trained to perform the surgical procedures conform the international best-practice for LAPC. This because surgical outcomes have previously been described to be independently associated with surgical volume.[29-32] The following criteria have been set for these centers: annual surgical volume of ≥100 pancreatic resections and documented experience in LAPC surgery (i.e. ≥20 LAPC resections). Currently, only three Dutch centers meet these criteria: Amsterdam UMC (Amsterdam), ErasmusMC (Rotterdam), and Regional Academic Cancer Center Utrecht (RAKU, Utrecht & Nieuwegein). Nevertheless, it is envisioned that other DPCG centers will also perform LAPC surgery after the PREOPANC-4 implementation project, based on these criteria and increasing experience. It is expected that UMC Groningen, Maastricht UMC+, Radboud UMC, and/or Leiden UMC will be able to fulfil the criteria for LAPC surgery regarding surgical volume and experience in LAPC in the next coming years. Subsequently, this will further increase the LAPC resection rate from 16% (aim of PREOPANC-4) to the final aim of 25% nationwide. For these reasons, the multidisciplinary teams from these centers will be present as observers during the training program. Due to the complex nature of LAPC surgery, this 'step-up approach' of introduction of the international standards for LAPC surgery in the Netherlands (i.e. starting with three centers and ultimately expanding to five centers) was chosen.

The complete collaborative structure to ensure a nationwide implementation will be further explained below. See **Appendix 2** for the project phases over time.

3.1 Phase I - Multidisciplinary best-practice training program

This preparatory phase includes both an extensive theoretical and practical training program for the Dutch multidisciplinary teams from the 3 Dutch high-volume university medical centers and the 4 observing university medical centers, executed by international leading experts in the field of LAPC.

The international experts in the field of LAPC comprise the multidisciplinary pancreatic cancer teams (e.g. medical oncologists, radiologists, radiotherapists, and hepato-pancreato-biliary [HPB] surgeons) from four of the most highly recognized centers of excellence in LAPC (surgery) worldwide: University of Heidelberg (Heidelberg, Germany), New York University Medical Center (New York, USA), University of Texas MD Anderson Cancer Center (Houston, USA), and University of Colorado (Denver, USA). The proctors for this training program include prof. T. Hackert (University of Heidelberg), prof. C.L. Wolfgang (New York University Medical Center), prof. M. Del Chiaro (University of Colorado), and dr. M.H.G. Katz (MD Anderson Cancer Center).

The multidisciplinary training program comprises three steps:

(1) Multidisciplinary training program;

(2) Surgical technique training and off-site proctoring;

(3) On-site proctoring.

See **Appendix 3** for a detailed description of the training program. Together with the Dutch and international multidisciplinary teams, the study coordinator will develop a supportive guideline, comprising all information from the training program. This supportive guideline will be used as reference during the PREOPANC-4 implementation.

Since initially the (potential) high-volume centers will be trained and only the three centers with already the highest volumes will implement the international standards of LAPC care, the remaining 8 DPCG centers have to be informed in detail about the new, best-practice possibilities for LAPC treatment via webinars once year, aiming to further raise the quality of the current Dutch standards of care in all DPCG centers

3.2 Phase II – Clinical implementation program

This phase comprises the clinical implementation of the international standard of excellence for LAPC (surgery) in the Netherlands by the trained multidisciplinary teams in the first 3 Dutch centers.

3.2.1 *Implementation design*

In all DPCG centers, patients who are diagnosed with pathology confirmed LAPC will be treated with (m)FOLFIRINOX or gemcitabine-nab-paclitaxel chemotherapy (≥2 months), according to the current Dutch guideline. Patients will undergo a diagnostic panel before and after 2 months of chemotherapy to determine the RECIST response to chemotherapy and to optimally select patients for LAPC surgery and minimizing futile surgery. After this period of induction chemotherapy, all patients who meet the inclusion criteria will be discussed within an online (inter)national expert panel. We are pleased that four international leading experts have agreed to participate in this online expert panel: prof. T. Hackert (Heidelberg University), prof. C.L. Wolfgang (Johns Hopkins Hospital), prof. M. Del Chiaro (University of Colorado Anschutz Medical Campus), and dr. M.H.G. Katz (University of Texas MD Anderson Cancer Center). Induction chemotherapy with concomitant radiotherapy will not be used in the first phase of the implementation in case of arterial tumor involvement, considering the international debate about potential severe complications.

If the (inter)national expert panel advises surgical exploration, this will be performed (or offered) in one of the three Dutch high-volume centers who completed the training program (i.e. RAKU, ErasmusMC, and Amsterdam UMC). The other 12 DPCG centers will be able to present patients with unresectable LAPC to the online (inter)national expert panel. If the expert panel considers surgical exploration an option, patients can be referred. These patients are not considered eligible for surgery without this implementation, therefore, the referral of these patients' will not reduce the volume of the other DPCG centers who do not undergo the best-practice training program and will therefore not negatively affect their surgical expertise.

The diagnostic panel is already standardized in all DPCG centers and includes a high-quality, multiphase computed tomography (CT) to assess the disease progression based on the Response Evaluation Criteria in Solid Tumors (RECIST) criteria and tumor markers levels, including serum cancer antigen 19.9 (CA19.9) and carcino embryogenic antigen (CEA). Optional, 2-deoxy-2-(fluorine-18)-fluoro-D-glucose positron emission tomography integrated with CT (^{18}F-FDG PET/CT) and magnetic resonance imaging (MRI) liver can be integrated in the diagnostic panel (see **Appendix 4** for the ^{18}F-FDG PET/CT protocol).

The diagnostic panel is determined before and after induction chemotherapy. Prior to LAPC surgery, a diagnostic laparoscopy has to confirm absence of peritoneal metastases. An exploratory laparotomy will be only performed in absence of peritoneal metastases. The following criteria are required for explorative LAPC surgery:

(1) Normal(ized) or decreased serum CA19.9 (and CEA);
(2) Negative diagnostic laparoscopy;
(3) Considered fit to undergo major surgery;
(4) The (inter)national expert panel recommends surgical exploration.

The first step after laparotomy is intraoperative ultrasonography (IOUS) to determine the precise extent of vascular involvement. Often, the vascular involvement is less than expected. Surgical resection will be performed when a radical resection seems feasible, typically confirmed whenever by intraoperative frozen section and biopsies. Both venous and arterial resection are performed whenever safely feasible. If resection of the (common) hepatic artery is performed in presence of high-risk conditions (e.g. small pancreatic duct and soft pancreatic parenchyma), total pancreatectomy has to be considered as alternative for partial pancreatectomy to reduce the risk of morbidity and mortality.

The diagnostics, oncological treatment (induction and adjuvant chemotherapy), and postoperative follow-up from referred patients will be executed by the local DPCG centers since this care is currently standardized, common practice in the Netherlands (see **Appendix 5** for the flow chart for nationwide care).

3.2.2 Inclusion criteria

(1) Age ≥18 years;
(2) Pathology confirmed LAPC (see **Appendix 6** for the definition);
(3) CT-based non-progressive disease in accordance with the RECIST criteria[33] after at least 2 months of systemic chemotherapy ([m]FOLFIRINOX or gemcitabine-nab-paclitaxel).

3.2.3 Exclusion criteria

(1) Metastatic pancreatic cancer prior to induction chemotherapy.

3.2.4 Sample size

The implementation results will be extensively studied, using various control groups. See **Appendix 7** for details about the control groups, patient accrual, and the sample size calculation.

In summary, the required number of patients in whom resection of LAPC performed, is at least **55** during the three-year inclusion period of the PREOPANC-4 implementation project. Striving for a 16% overall LAPC resection rate, we estimate that 344 patients will start with (m)FOLFIRINOX or gemcitabine-nab-paclitaxel. Approximately **223** patients (65%) will have non-progressive disease after at least 2 months induction chemotherapy and, therefore, included.

3.2.5 Potential burden of implementation

It is important to emphasize that the PREOPANC-4 project implements the international best practice, which is expected to lead to an increase of the resection rate amongst LAPC patients and subsequent survival benefit. On the other hand, surgical treatment is associated with risks.

Induction and adjuvant treatment with (m)FOLFIRINOX or gemcitabine-nab-paclitaxel chemotherapy, although standard of care, are associated with (mostly temporary) side effects requiring medical attention (and sometimes hospital admission) in some 60% of patients, such as neutropenia, bone marrow depression, diarrhoea, vomiting, and fatigue.[7] The extended resections with concomitant venous resection and reconstruction might be associated with an increase of major complication and mortality,[19] which could be even higher after arterial resection.[34] This project aims for mortality of ≤5% and <45% major morbidity after surgery during hospitalization, which is considerable but also largely comparable to routine pancreatic surgery in resectable disease.[11, 16, 19, 20, 34, 35]

The PREOPANC-4 project carefully selects patients with extensive shared decision-making, considering their physical and mental reserves, disease characteristics, and monitoring their healthcare satisfaction and quality of life. Only the fittest patients with a clear preference to participate in the study will be considered eligible for chemotherapy and major surgery. Hereby, we will further reduce the risk of side effects and improve survival on the long term. Thus, the premise is that the increase of survival outbalances the above-mentioned risks.

3.2.6 Project procedures

First of all, no study interventions are performed in the PREOPANC-4 project since the implementation concerns the LAPC treatment in accordance with the international best-practice, following the NCCN guideline. Therefore, this implementation concerns an optimization of the current Dutch practice.

During the first outpatient visit of LAPC patients at the surgery and/or medical oncology department in the local DPCG centers, patients are registered in the existing LAPC registry after signing informed consent for the

ongoing PACAP trial and the LAPC registry and being informed.[36, 37] Patients will receive the standard oncological (and surgical) care in a local DPCG center.

After completing ≥2 months of systemic induction (m)FOLFIRINOX or gemcitabine-nab-paclitaxel chemotherapy, those patients with subsequent non-progressive disease are discussed in the (inter)national expert panel. All patients who meet the inclusion criteria will be informed about the PREOPANC-4 project and will receive a patient information sheet. The rationale for the implementation will be explained and questions will be answered extensively.

Obtaining informed consent is necessary to guarantee the data collection. After a sufficient time for reflection, those patients who are interested to participate are asked to sign the informed consent. The written informed consent will be taken by surgeons / surgical registrars / research nurses / coordinating PhD students. The original version will be added to the study file, and patients receive a copy as by the Good Clinical Practice Recommendations. NB. If a patient is not referred to one of the 3 high-volume centers, the process of decision-making and eventually signing the informed consent will take place in the local DPCG center.

If patients are eligible for surgical exploration, they will receive a decision table (see **Appendix 8**) in order to discuss with the multidisciplinary team. Furthermore, if patients are considered suitable for surgery, the (inter)national expert panel may advice to refer the patient to one of the 3 high-volume centers if it may concern surgery that should not be performed without the PREOPANC-4 implementation.

After surgery and full recovery, patients will be referred back to their local hospital for adjuvant treatment and follow-up. Patients will be treated with up to a total of 12 courses [m]FOLFIRINOX) or 6 courses gemcitabine-nab-paclitaxel respectively (including the neoadjuvant courses), starting within 12 weeks after surgery, which is standardized care. The treating medical oncologist will assess the fitness for chemotherapy. Patients will follow the current regular scheme of follow-up at the outpatient clinic. The appointments include each 3-4 months in the first year postoperatively, after which the interval increases up to once yearly. Imaging is performed in case of clinical suspicion of tumor recurrence.

Several validated questionnaires will be used to monitor quality of life, patients' mental and physical conditions (EQ-5D-5L, EORTC QLQ-C30, HADS, WOPS and WPAI) and potential long-term side effects (EPI, EORTC QLQ-PAN26 and QLQ-CIPN20) during follow-up, as part of the nationwide PACAP project.[36, 37] In addition, patients' healthcare satisfaction will be measured in all patients who are included, using the validated EORTC IN-PATSAT32 questionnaire.[38]

Furthermore, decision-making will be evaluated, using the validated APECC decision-making self-efficacy scale,[39] together with previously used self-constructed items to measure patient involvement in decision-making.[40] Patients' healthcare satisfaction with the EORTC IN-PATSAT32 questionnaire will be evaluated at

time of diagnosis and restaging, followed by two additional (postoperative) moments at 6 and 12 months. The decision-making measures will be investigated at time of diagnosis and restaging. These questionnaires will be added to the PACAP questionnaire and included as addendum to its informed consent.

The complexities of LAPC care in the PREOPANC-4 implementation project demand continuous monitoring during the full length implementation project by analyzing preliminary results in interim meetings with the principals investigators and the (inter)national expert panel. These interim evaluations will take place each half a year during the three-year inclusion period.

3.2.7 Data collection

All patients with LAPC in the Netherlands will be registered and data will be collected using the already existing nationwide LAPC registry. Outcomes of all patients with pancreatic cancer (including LAPC) undergoing surgical exploration in the Netherlands are registered in the mandatory Dutch Pancreatic Cancer Audit (DPCA). The LAPC registry and the DPCA will be used to monitor nationwide outcomes of LAPC during the PREOPANC-4 project in all DPCG centers.

This already existing infrastructure is unique and will be clearly instrumental for the PREOPANC-4 implementation project to create a registration cohort of whom a subgroup of patients will be eligible for inclusion and subsequently asked for participation in this project. The existing infrastructure will demonstrate the impact of PREOPANC-4 on a nationwide scale.

In addition, when an included patient will undergo surgical exploration with intention for resection, the surgeon will register details about decision-making, intraoperative findings, and procedural details in an electronic case report form (eCRF), using Castor EDC. This will be done in a pseudo-anonymized manner. Only the study coordinator will have access to the registered data and is able to identify the patients with a unique study number.

Quality of life, patients' physical and mental status, and potential adverse events will be monitored by validated questionnaires, using the PACAP project; a recently started nationwide multicenter stepped-wedge cluster randomized controlled superiority trial that implements the best practices for pancreatic cancer care in the DPCG.[36, 37] Research nurses who are affiliated to the PACAP project will submit these questionnaires to the included patients on the mentioned moments. The study coordinator will supervise this process.

3.2.8 Data storage and privacy

The central data management and analyses will be executed by the study coordinator, supervised by the statistician (S. van Dieren). In close collaboration with the local study coordinators, the study coordinator will monitor the patient inclusion and complete execution of the diagnostic panel and data registration in the LAPC

registry and DPCA. The continuous data monitoring and collection with the LAPC registry and DPCA will guarantee complete and timely recording, handling, and storage of data and documents.

Data will be managed and stored according to the FAIR principles. Data will be available for verification and re-use for at least fifteen years. All research data will be retained and stored in a study database at the central network server, and can only be accessed by those specifically granted access to the database involved. Permission for third persons to access the data is possible and can be easily requested by contacting the principal investigator.

Participant-derived data will always be handled confidentially and coded using an identification code. The key to this code will be kept separately from the dataset. Personal identifying data will not be made available to other persons. Any data storage and handling procedures will ensure participant data protection and confidentiality, and will be performed under the direct responsibility of the principal investigator. Results of research will be published without any reference to individual subjects.

3.2.9 Statistical analyses

Next to the regular evaluations of the implementation results, the outcomes of the implementation will be evaluated and published after completing the three-year follow-up considering the challenging multimodal LAPC care. Thereafter, patients' survival status will be evaluated and published after completing the five-year follow-up.

To analyse the benefit of the implemented international best-practice for LAPC, surgical and oncological outcomes of the included patients will be compared with a propensity-matched historical Dutch patient cohorts. See **Appendix 7** for the control groups and patient accrual. See **Appendix 9** for the definitions and analyses of variables of interest.

3.2.10 Ethics & privacy

The medical ethical committee from all 15 DPCG centers will be asked if ethical approval is required.

3.2.11 Authorships

Authorships will be based on the recommendations from the international committee of medical journal editors (ICMJE). Here, the authorships regarding the surgical-oncological papers are further explained:

Thomas F. Stoop, MD[1^]; Leonard W.F. Seelen, MD[2*]; Freek van 't Land, MD[3*]; Eran van Veldhuisen, BSc[1]; Susan van Dieren, MSc, PhD[1]; << participating DPCG centers >>; Bas Groot Koerkamp, MD, PhD[3]; J. Sven D. Mieog, MD, PhD[4], MD, PhD[4]; Chris L. Wolfgang, MD, PhD[5]; I. Quintus Molenaar, MD, PhD[2]; Marcel den Dulk, MD, PhD[6]; Marco Del Chiaro, MD, PhD[7]; Marion B. Stommel, MD, PhD[8]; Matthew H.G. Katz, MD, PhD[9]; Olivier R.C. Busch, MD, PhD[1]; Thilo Hackert, MD[10]; Maarten W.

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The PREOPANC-4 implementation project will be performed on behalf of the Dutch Pancreatic Cancer Group. The shared last authorships are reserved for the supervisors J.W. Wilmink, H.C. van Santvoort, C.H.J. van Eijck, and M.G. Besselink.

The study coordinator (T.F. Stoop) will be the first author, followed by the shared coordinators of the ErasmusMC and RAKU as shared second authors. E. van Veldhuisen (post-doc Amsterdam UMC) and S. van Dieren (statistician Amsterdam UMC) will become third and fourth author, respectively.

The international advisors and proctors (M. Del Chiaro, C.L. Wolfgang, M. Katz, and T. Hackert) are included as authors.

Three authors will be listed as co-authors from each trained center. If a DPCG center (other than the three trained centers) contributes at least five resected patients to this study, an additional co-authorship will be allocated. All other authors will be listed in alphabetical order.

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APPENDIX 1. PARTICIPATING CENTERS

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APPENDIX 2. PROJECT SCHEDULE	2021		2022				2023				2024				2025 <...> 2028				2029				2030	
	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2
WP1 - Multidisciplinary best-practice training program																								
1.1 Multidisciplinary training program (step 1)	M1																							
1.2 Surgical training program and off-site proctoring (step 2)	M2																							
1.3 On-site proctoring (step 3)		M3																						
1.4 Data collection & data management		M4																						
WP2 - Clinical implementation program																								
2.1 Diagnostic and treatment pathways																								
2.2 Patient inclusion						M5								M6										
2.3 Data collection & management																						M7		
2.4 Data analyses, evaluation & dissemination				M8		M8		M8		M8		M8		M8									M9	
																							M10	M11

Legend

Work package 1: Multidisciplinary best-practice training program

M1: The three Dutch multidisciplinary teams have completed the webinars (step 1), together with the observing centers.

M2: All participating HPB surgeons have completed the technical skills training and off-site proctoring program (step 2).

M3: All participating HPB surgeons have completed the on-site proctoring program (step 3).

M4: Achieved when the supportive guideline is completed.

Work package 2: Clinical implementation program

M5: Achieved when the first 50 patients have been discussed in the online (inter)national expert panel.

M6: Achieved when 55 of 223 included LAPC patients after induction chemotherapy underwent resection in the three centers during the three-year implementation period.

M7: Achieved when the follow-up is completed and all data from the included patients are completely registered in the LAPC registry and Dutch Pancreatic Cancer Audit.

M8: Achieved when each half-yearly interim meeting during the three-year inclusion period is executed together with the principal investigators and the (inter)national expert panel to evaluate the preliminary results.

M9: Achieved when the data analyses are completed.

M10: Achieved when the surgical, oncological, quality of life, and patients' healthcare satisfaction outcomes are evaluated in the Dutch Pancreatic Cancer Group, project group, and Living with Hope Foundation (see chapter 'Dissemination plan').

M11: Achieved when the publications are submitted and further dissemination of outcomes is started (see chapter 'Dissemination plan').

APPENDIX 3. MULTIDISCIPLINARY TRAINING PROGRAM

The multidisciplinary training program comprises three steps:
Step 1 Multidisciplinary training program;
Step 2 Surgical technique training and off-site proctoring;
Step 3 On-site proctoring.

Step 1. Multidisciplinary training program
The multidisciplinary teams from the international expert centers will educate the Dutch multidisciplinary teams (involving medical and radiation oncologists, radiologists, gastro-enterologists, pathologists, and HPB surgeons) from the selected Dutch centers about (1) chemo(radio)therapeutic regimens and related patient selection; (2) the interpretation of diagnostic tests (i.e. conditional factors, tumor markers, imaging); (3) the requirements for proper patient selection and pitfalls; and (4) indications and contra-indications for LAPC surgery, based on scientific evidence and expert opinion. These webinars are supported by cases, imaging, and videos from live operations, illustrating clinical cases and (surgical) proceedings step-wise per situation. The international proctors will organize additional webinars, including (1) radiological webinars for abdominal radiologists and surgeons to focus more in detail on modalities, techniques, and disease characteristics at time of restaging after induction chemotherapy; and (2) surgical webinars for HPB surgeons to discuss intraoperative patient selection and surgical techniques among others.

Subsequently, the trained multidisciplinary teams will organize webinars (at least one per year) for the multidisciplinary teams for all 15 DPCG centers about the pros and cons of the best-practice, aiming to further raise the quality of the current Dutch standards of care in all DPCG centers.

Step 2. Surgical training program – Off-site proctoring
International proctors and highly experienced Dutch vascular and transplant surgeons (i.e. prof. H. Verhagen [ErasmusMC], dr. M. Idu [Amsterdam UMC], and drs. R. van de Mortel [RAKU]) will organize training sessions for the six HPB surgeons from the three selected, high-volume Dutch centers in the Skills lab & Simulation Center (ErasmusMC, Rotterdam). These training sessions consist of lectures and practical skills training on the (1) approach of major peripancreatic vasculature; (2) (contra-)indications for and techniques of vascular dissection/divestment; (3) pitfalls and (contra-)indications for portomesenteric venous and arterial resections (and reconstructions); and (4) postoperative monitoring and anti-coagulants regimens. Cadavers will be used for the practical skills training.

The involvement of both international proctors and vascular and transplant surgeons in this skills training program results in the required full range of attention for the technical as well as the oncological aspects of complex LAPC surgery. However, the aim is not that arterial reconstructions will be done by HPB surgeons since a short-term training program is not expected to provide sufficient experience. Rather, the aim is to improve knowledge, communication and interaction between these vascular surgeons and the (transplant) HPB surgeons regarding dissection and, if needed, resection and reconstruction and to discuss common clinical scenarios.

A total of 6-9 surgeons from the 3 high-volume Dutch centers will be surgically trained by proctoring during several live LAPC resections with concomitant arterial resection at the four international sites during two-week visits. Every visit will include at least a combination of surgeons from all three Dutch centers. The live operations will be recorded and evaluated with the whole group of surgeons and proctors.

Step 3. Surgical training program – On-site proctoring
Finally, each trained Dutch surgeon performs LAPC resections at his own institution (Amsterdam UMC / ErasmusMC / RAKU), proctored by one of the advisory surgeons (on-site proctoring; **step 3**) during a one-week visit. This system of on-site proctoring will ensure the safety of LAPC surgery during the PREOPANC-4 project.

If feasible, HPB surgeons from the 4 observing centers (i.e. Maastricht UMC+, UMC Groningen, Leiden UMC, and Radboud UMC) will join these sessions.

Despite this surgical training program, the close involvement and consultation of the Dutch vascular and transplant surgeons remains of vital importance during the three-year implementation project if complex arterial resections and reconstructions could be needed (see **WP2**).

Together with the Dutch and international multidisciplinary teams, the study coordinator will develop a supportive guideline for the PREOPANC-4 project, comprising all information from the webinars and live operations. This supportive guideline will be used as reference during the PREOPANC-4 implementation project.

Data collection & management
The multidisciplinary training program will be developed and prepared in close collaboration between the international multidisciplinary teams and the multidisciplinary teams from the participating Dutch centers. The study coordinator will control this process and will develop the supportive guideline in close collaboration with the (inter)national multidisciplinary teams.

The international experts will work closely together with the study coordinator to collect and share materials for the supportive guideline. Data for the supportive guideline will be transferred via the protective software program 'FileSender' (https://filesender.surf.nl). Subsequently, these data will be stored in a highly protective digital work environment of the Amsterdam UMC, protected with QR-code and finger print verification. Patient cases, imaging, and surgical (training) videos remain completely anonymized in the supportive guideline.

APPENDIX 4. ^{18}F-FDG PET/CT PROTOCOL

This supplementary document provides advices for the use and investigations of the ^{18}F-FDG PET/CT scans as optional part of the diagnostic panel, both prior to and after completing the induction chemotherapy.

Procedure:
The ^{18}F-FDG PET/CT procedure including patient preparation, image acquisition (and reconstruction) will be performed in accordance with the FDG PET/CT EANM procedure guidelines for tumour imaging (version 2.0).[1]

In case of quantitative analyses (i.e. assessment of uptake values such as maximum, mean and/or peak standardized uptake [SUV], total lesion glycolysis [TLG], and/or metabolic active tumor volumes [MATV]), reconstruction will be performed in accordance with the EARL protocol. SUVs will corrected for body weight and/or lean body mass.

Non-diabetic patients are required to fast for six hours before the scan and diabetic patients are required to fast for four hours. If the serum glucose levels will be >11 mmol/l, the ^{18}F-FDG PET/CT scan will be postponed until the levels are below this cut-off.

All ^{18}F-FDG scans will be controlled for image-quality and visually interpreted by experienced nuclear medicine physicians. The ^{18}F-FDG PET has to be combined with a low dose CT scan for proper quantification.

Timing:
Two ^{18}F-FDG PET/CT scans will be performed as standard of care. The first scan will be performed up to 2 weeks before the start of FOLFIRINOX induction chemotherapy, and the second will follow after at least two months of induction chemotherapy (after approximately 2 weeks).

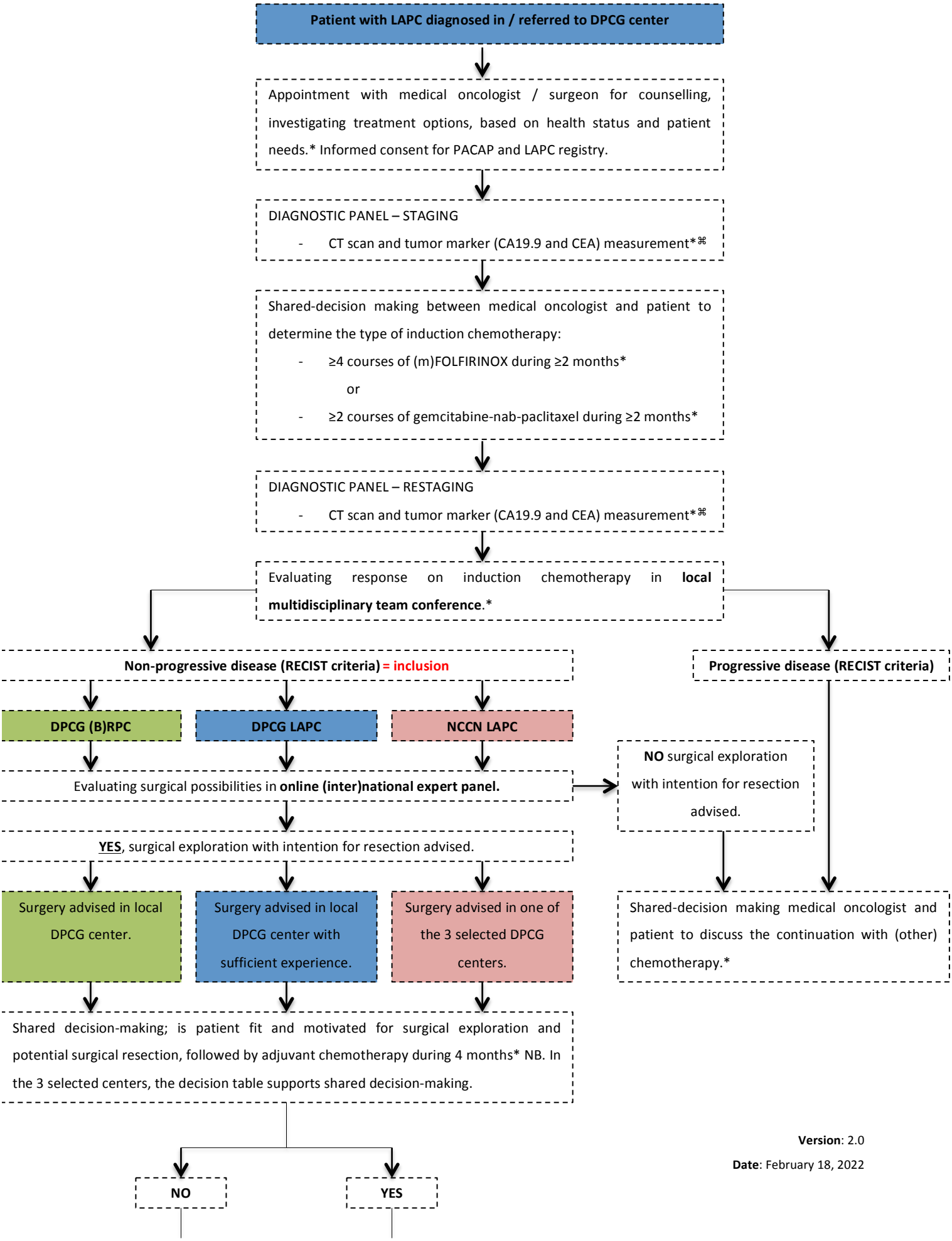
Exclusion criteria for second ^{18}F-FDG PET/CT scan:

- SUV_{max} <4.0 on the first ^{18}F-FDG PET/CT scan (i.e. prior to induction chemotherapy).

Clinical implementation:
The ^{18}F-FDG PET/CT scan after induction chemotherapy will be compared with the first ^{18}F-FDG PET/CT scan, comparing the ^{18}F-FDG uptakes from the pancreatic tumor by qualitative and/or quantitative methodology.

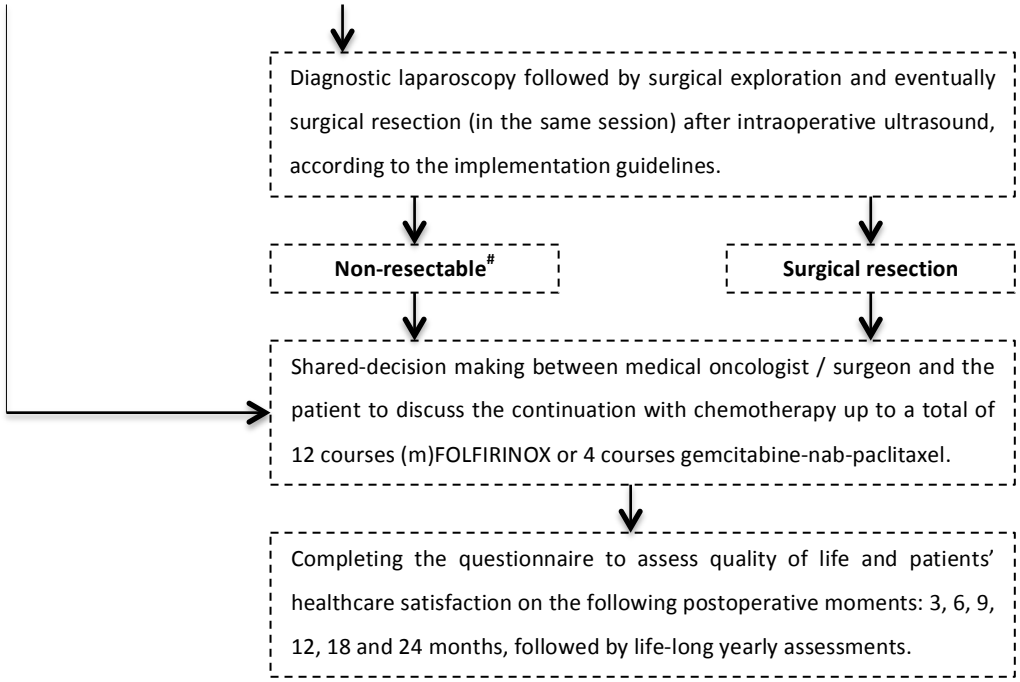
[1] Boellaard R, Delgado-Bolton R, Oyen WJ, et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. *Eur J Nucl Med Mol Imaging*. 2015; **42**(2): 328-54

APPENDIX 5. FLOW CHART OF NATIONWIDE LAPC CARE



Version: 2.0

Date: February 18, 2022



Legend

Intraoperative local ablation in case of a non-resectable tumor will be considered if patients are preoperatively included in the PELICAN study, including the confirmation by informed consent.

⌘ Eventually combined with MRI liver and PET/CT.

DPCG LAPC = locally advanced pancreatic cancer according to the Dutch guideline;

NCCN LAPC = locally advanced pancreatic cancer according to the international guideline.

APPENDIX 6. DEFINITION LOCALLY ADVANCED PANCREATIC CANCER

	SMA	Celiac axis	CHA	SMV-PV
Resectable (all four required)	no contact	no contact	no contact	≤ 90° contact
Borderline resectable (minimally one required)	≤ 90° contact	≤ 90° contact	≤ 90° contact	90°-270° contact, and no occlusion
Irresectable (minimally one required)	contact > 90°	contact > 90°	contact > 90°	contact > 270° or occlusion

APPENDIX 7. PATIENT ACCRUAL

7.1 Control groups

The outcomes of the PREOPANC-4 implementation project will be compared to the existing and complete datasets of the following four control groups:

(1) Survival and quality of life outcomes will be compared with a recent Dutch prospectively registered cohort (2015-2020) of patients with non-progressive LAPC after at least two months of induction chemotherapy (i.e. [m]FOLFIRINOX or gemcitabine-nab-paclitaxel) (see **Statistics** for further details).

a) For the survival analyses, the control group consists of 100 patients with LAPC who had RECIST non-progressive disease after at least two months of chemotherapy, but were not surgically explored.

b) For the analyses of quality of life, patients' mental and physical status, and adverse events (e.g. endocrine and exocrine insufficiency), the control group concerns a cohort of patients with non-progressive LAPC, regardless of any surgical exploration or resection. This comprises a cohort of 105 patients who completed the questionnaires, followed by 78 patients at 3 months, 66 patients after 6 months, 44 patients after 9 months and 33 patients after one year from time of diagnosis.

(2) Surgical outcomes in resected patients will be compared with a recent Dutch cohort of 200 patients with borderline resectable pancreatic cancer or LAPC, who underwent resection after induction/neoadjuvant therapy (2015-2020), registered in the nationwide Dutch Pancreatic Cancer Audit.

(3) Patients' healthcare satisfaction outcomes (assessed with the EORTC IN-PATSAT32 questionnaire), will be compared with a historical Dutch cohort of patients with non-metastatic periampullary or pancreatic cancer, including both resected and non-resected patients. This historical cohort comprises 71 patients, from 40 patients received treatment with curative intent and 31 patients received palliative treatment.

7.2 Patient accrual

To analyse the benefit of the implemented international best-practice for LAPC, 1-year survival of the included patients will be compared with a propensity score matched historical Dutch LAPC cohort (2015-2020) (see **Statistics** for further details).

To assess the impact of the implementation, patients with RECIST non-progressive LAPC after at least 2 months chemotherapy undergoing surgical resection [**implementation group**] will be compared with patients with RECIST non-progressive LAPC after at least 2 months chemotherapy from the Dutch LAPC registry (2015-2020) [**control group**]) who did not undergo surgical exploration.

We calculated the sample size to determine whether the number of patients to be included in PREOPANC-4 will also be sufficient to make a hypothesis generating comparison, using sealedenvelope.com with 5% significance level and 80% power, to compare the expected 1-year overall survival (OS) in both groups.

The estimated 1-year OS both groups are:

(1) Control group (RECIST non-progressive LAPC, following at least 2 months chemotherapy, no surgical exploration): 69% *

(2) Implementation group (surgical resection for RECIST non-progressive LAPC, following at least 2 months chemotherapy): 90%[7,8,10]

*This percentage is based on Dutch LAPC patients treated with at least 2 months of induction chemotherapy without surgical exploration in the period 2015-2020 (statistics from the Integraal Kankercentrum Nederland [IKNL]).

Based on these statistics, the required total sample size comprises 110 patients; 55 patients per group.

For the prospective inclusion during the PREOPANC-4 project, this means that the required number of resected patients is at least 55 during the three-year inclusion period. Striving for a 16% overall LAPC resection rate, we estimate that 344 patients will start with (m)FOLFIRINOX or gemcitabine-nab-paclitaxel from which approximately 65% (n = 223) has non-progressive disease after at least two months of induction chemotherapy and, therefore, included.

APPENDIX 8. DECISION TABLE

PREOPANC-4-keuzetabel: Operatie gevolgd door chemotherapie of alleen chemotherapie

Deze tabel is bedoeld voor patiënten met lokaal gevorderd alvleesklierkanker waarbij de tumor stabiel is na een behandeling van tenminste 2 maanden chemotherapie en de tumor niet is te verwijderen volgens de Nederlandse richtlijn. Als patiënt kunt u deze tabel gebruiken om samen met uw arts te overleggen over de behandelopties.

Veel gestelde vragen	**Operatie gevolgd door chemotherapie**	**Alleen chemotherapie**
Wat houdt mijn behandeling in?	U ondergaat een operatie waarbij de tumor kan worden verwijderd. De operatie start met een kijkoperatie. Via enkele kleine gaatjes wordt met een camera in uw buik gekeken. Als er geen uitzaaiingen zijn (20 van 100 patiënten heeft uitzaaiingen),[21] wordt de buik open gemaakt en wordt een echo gemaakt om de omvang van de tumor te bepalen. Als de tumor te verwijderen is, zal dit gebeuren volgens de internationale standaarden.[25] De tumor zal in **50 van 100** patiënten kunnen worden verwijderd. In enkele gevallen moet de hele alvleesklier worden verwijderd.[6, 7] Na de operatie wordt u behandeld met chemotherapie volgens het schema dat bij de andere behandeling wordt uitgelegd (zie hiernaast 'alleen chemotherapie').	U ondergaat geen operatie en u wordt doorbehandeld met chemotherapie De duur van de behandeling met chemotherapie is afhankelijk van de hoeveelheid chemotherapie die u tot nu toe heeft gekregen. In totaal wordt u 6 maanden behandeld met chemotherapie. Wanneer u voor dit beslismoment 2 maanden met chemotherapie bent behandeld, krijgt u vervolgens nog 4 maanden chemotherapie.
Wat zijn de gevolgen / complicaties van een operatie op de korte termijn?	Na de operatie krijgen 35-45 van 100 patiënten een complicatie waarvoor behandeling nodig is.[11, 16, 19, 20, 35] Tijdens de ziekenhuisopname overlijden 2-5 van 100 patiënten door een complicatie.[19, 20]	Niet van toepassing.
Wat zijn de gevolgen van een operatie op de lange termijn?	22 van 100 patiënten* ontwikkelen suikerziekte doordat de tumor en alvleesklierweefsel zijn verwijderd.[41] 74 van 100 patiënten* krijgen diarree of vettige ontlasting doordat de tumor en alvleesklierweefsel zijn verwijderd. Dit kan worden behandeld met tabletten voor de rest van uw leven.[42] *, wanneer de hele alvleesklier wordt verwijderd, krijgen alle patiënten (100 van 100 patiënten) deze bijwerkingen die moeilijk te behandelen zijn.[43]	Niet van toepassing.
Hoeveel tijd kost mijn herstel na een operatie?	Als er geen complicaties optreden, blijft u ongeveer 1 week in het ziekenhuis. Wanneer complicaties optreden (35-45 van 100 patiënten), duurt de ziekenhuisopname 2-4 weken. Het volledige herstel na de operatie duurt ongeveer 3 maanden.	Niet van toepassing.
Wat zijn de gevolgen / complicaties van de chemotherapie?	De chemotherapie geeft bij meer dan 60 van 100 patiënten tijdelijke bijwerkingen die eventueel moeten worden behandeld. Meest voorkomend zijn braken, diarree, zwakte en een daling van cellen in het bloed dat risico geeft op infecties.[7] Bij 6 van 100 patiënten moet de chemotherapie door bijwerkingen eerder worden gestopt.[7]	De chemotherapie geeft bij meer dan 60 van 100 patiënten tijdelijke bijwerkingen die eventueel moeten worden behandeld. Meest voorkomend zijn braken, diarree, zwakte en een daling van cellen in het bloed dat risico geeft op infecties.[7] Bij 6 van 100 patiënten moet de chemotherapie door bijwerkingen eerder worden gestopt.[7]
Wat is mijn risico op overlijden?	De gemiddelde overleving is 25 maanden als de tumor met de operatie kon worden verwijderd.[6, 13, 15] Na 1 jaar leven 90 van 100 patiënten[11, 15, 16] Na 3 jaar leven 50 van 100 patiënten[11, 15, 16] Na 5 jaar leven 20 van 100 patiënten[11, 15]	De gemiddelde overleving is 16 maanden als de tumor niet kon worden verwijderd en alleen met chemotherapie is behandeld.[8, 13, 14] Na 1 jaar leven 70 van 100 patiënten[13, 14] Na 3 jaar leven 10 van 100 patiënten[13] Na 5 jaar leven 0 van 100 patiënten[11, 14]

APPENDIX 9. STATISTICAL ANALYSIS

Next to the regular evaluations of the implementation results, the outcomes of the implementation will be evaluated and published after completing the one-year follow-up considering the challenging multimodal LAPC care. Outside the short-term scope of this project, patients' survival status will be evaluated and published after five-year follow-up as well. Below, the main surgical and oncological outcomes of interest for the overall and resection study population are described:

Overall population:

(1) Oncological outcome;
    a. Surgical resection rate;[44]
    b. 1- and 5-year survival from time of diagnosis.
(2) Patients' reported outcome;
    a. Patterns in quality of life, physical and mental status, and adverse events (e.g. endocrine and exocrine insufficiency);
    b. Healthcare satisfaction.

Surgically explored (and resected) population:

(1) Surgical outcome;
    a. 90-day major morbidity (Clavien-Dindo grade IIIa or higher[45]), including mortality;
    b. Pancreatic surgery-specific complications (i.e. delayed gastric emptying, postpancreatectomy hemorrhage, pancreatic fistula, and bile leakage).[46-49]
(2) Oncological outcome;
    a. Radicality status (R0) in case of resection (Royal College of Pathologists[50]);
    b. 1- and 5-year survival from time of diagnosis.
(3) Patients reported outcome;
    a. Patterns in quality of life, physical and mental status, and adverse events;
    b. Healthcare satisfaction.

<u>Oncological outcomes</u>

OS will be measured from date of diagnosis until death or last moment of follow-up. Patterns of OS within one- and five-year follow-up will be estimated by Kaplan-Meier method with a 95% confidence interval. Associations for OS will be investigated using cox regression analysis (e.g. baseline characteristics, types of chemotherapeutic regimens, imaging characteristics, tumor markers, type of resection).

The 1- and 5-year OS from time of diagnosis will be compared with a historical LAPC cohort group (see **Appendix 7** for further details). Propensity score matching will be performed to create comparability between both groups.[51] Propensity scores will be calculated based on patient characteristics (e.g. age, gender, World Health Organization Performance Status [WHO-PS], Charlson Comorbidity Index [CCI]), treatment characteristics (e.g. chemotherapy regimens, administered courses), and disease characteristics before and after induction chemotherapy (e.g. tumor markers, radiological vascular involvement). Statistical significance is considered as a two-tailed *P*-value <0.050.

<u>Surgical outcomes</u>

Complications and 90-day mortality will be analyzed by chi-square analysis between different groups, such as type of resection and its extent. Potential predictors (e.g. clinical, disease and intraoperative characteristics) will be studied using logistic regression analysis.

To carefully evaluate the surgical safety of this implementation surgery, the surgical outcomes will be compared with a large historical Dutch cohort of patients with borderline resectable pancreatic cancer or LAPC

(NCCN definition) (see **Appendix 7** for further details), using propensity score matching. Propensity score will be calculated based on baseline characteristics (e.g. age, gender, WHO-PS, CCI), disease characteristics (e.g. radiological and intraoperative vascular involvement), and surgical characteristics (e.g. type and extent of resection).[51] Statistical significance is considered as a two-tailed *P*-value <0.050.

Quality of life

Data on quality of life and mental and physical status will be analyzed in accordance with the recommended questionnaire manuals. Comparison analyses will be performed to investigate the differences in quality of life, functioning, and adverse events between resected and non-resected patients, the influences of various types of chemotherapy, and additionally resected structures among others. Also the course over time between subgroups will be explored. Data will be numerically and graphically represented across the follow-up and presented as domains and summary scores. Outcomes will be compared with linear mixed models and predictors will be investigated using logistic regression analysis.

Moreover, quality of life, mental and physical status, and adverse events will be compared with a historical Dutch cohort of LAPC patients. See **Appendix 7** for further details about the control groups.

These comparative analyses will be made by propensity score stratification[51] to create comparability between both groups. Propensity scores will be calculated based on patient characteristics (e.g. age, CCI], WHO-PS), treatment characteristics (e.g. chemotherapy regimens, administered courses), disease characteristics before and after induction chemotherapy (e.g. tumor markers, radiological vascular involvement), and surgical characteristics (e.g. [type and extent of] resection, complications). Statistical significance is considered as a two-tailed *P*-value <0.050.

APPENDIX 10. LIST OF VARIABLES

These data will be collected from patients who meet the PREOPANC-4 inclusion criteria. Variables who are labeled with * are related to the inclusion and exclusion criteria. Please check the methodology of this study protocol.

CATEGORIES	VARIABLES
Baseline characteristics (at time of diagnosis)	**Gender**
	Date of birth*
	Body mass index (BMI)
	Charlson Comorbidity Index (CCI)
	ECOG / WHO performance status
	Considered fit for induction therapy and surgery (yes/no)*
Staging at time of diagnosis (prior to start induction therapy)	**Date of diagnosis**
	Imaging modality (MRI, CT, PET-CT, EUS)
	_ CT according to pancreas protocol (yes/no)
	Localization (head/uncinatus, body/tail, no visible mass)
	Largest tumor size (in mm)
	cTNM tumor (8th edition)
	cTNM nodes (8th edition)
	cTNM metastasis (8th edition)
	AJCC TNM stage (8th edition)
	Vascular involvement (yes/no)
	_Portomesenteric venous involvement (yes/no)
	_ _ Degree of involvement (≤90, 91-180, 181-270, >270 degree)
	_ _ Stenosis (no, ≤50% reduction, >50% reduction, occlusion)
	_ _ Length (in mm)
	_ _ Thrombosis (yes/no)
	_Arterial involvement (yes/no)
	_ _ Involvement superior mesenteric artery (yes/no)
	_ _ _ Degree of involvement (≤90, 91-180, 181-270, >270 degree)
	_ _ Involvement celiac axis (yes/no)
	_ _ _Degree of involvement (≤90, 91-180, 181-270, >270 degree)
	_ _ _ Involvement aorta or gastroduodenal artery (yes/no)
	_ _ Involvement (common / proper) hepatic artery (yes/no)
	_ _ _Degree of involvement (≤90, 91-180, 181-270, >270 degree)
	Multivisceral ingrowth (yes/no)
	_ Peripancreatic tissue
	_ Stomach
	_ Colon transverse
	_ Small bowel
	_ Spleen
	_ Adrenal
	_ Kidney
	_ Common bile duct
	_ Liver
	Resectability DPCG criteria*
	Resectability NCCN criteria*
	CA19.9 (U/ml)
	CEA (ng/ml)
	Bilirubine
	Cytology / histology suspicious for malignancy (yes/no)*
Neoadjuvant therapy	**Neoadjuvant therapy (yes/no)**
	Starting date
	Chemotherapy (yes/no)
	_ Type of chemotherapy ([modified] FOLFIRINOX, gemcitabine-nab-paclitaxel)*
	_ Number of received courses*
	_Dose reduction (yes/no)
	_ _ Number of reduced cycles
	Radiotherapy (yes/no)
	_ Type of radiotherapy (SBRT, EBRT, IMRT, others)
	Adverse events (none, yes, grade I-II, grade III-IV according to CTCAE version 4.0)

Restaging (after induction therapy)	**Date of restaging on imaging** **Imaging modality (MRI, CT, PET-CT, EUS)** _ CT according to pancreas protocol (yes/no) **Largest tumor size (in mm)** **Vascular involvement (yes/no)** _Portomesenteric venous involvement (yes/no) _ _ Degree of involvement (≤90, 91-180, 181-270, >270 degree) _ _ Stenosis (no, ≤50% reduction, >50% reduction, occlusion) _ _ Length (in mm) _ _ Thrombosis (yes/no) _Arterial involvement (yes/no) _ _ Involvement superior mesenteric artery (yes/no) _ _ _Degree of involvement (≤90, 91-180, 181-270, >270 degree) _ _ Involvement celiac axis (yes/no) _ _ _Degree of involvement (≤90, 91-180, 181-270, >270 degree) _ _ _Involvement aorta or gastroduodenal artery (yes/no) _ _ Involvement (common / proper) hepatic artery (yes/no) _ _ _Degree of involvement (≤90, 91-180, 181-270, >270 degree) **Multivisceral ingrowth (yes/no)** _Peripancreatic tissue _Stomach _Colon transverse _Small bowel _Spleen _Adrenal _Kidney _Common bile duct _Liver **Lymphadenopathy (yes/no)** **Distant metastasis (yes/no)*** **Resectability DPCG criteria** **Resectability NCCN criteria** **CA19.9 (U/ml)*** **CEA (ng/ml)** **RECIST (complete response, partial response, stabile disease, progressive disease)***
Expert panel	**Discussed in national LAPC expert panel (yes/no)** _Advice (no exploration surgical / surgical exploration / consultation international expert panel) _ _ National LAPC expert panel advised exploration in local DPCG center versus high-volume LAPC center (i.e. Amsterdam UMC / RAKU / ErasmusMC) _ _ If national LAPC expert panel advised no exploration, reason of renouncement is based on clinical condition, risk of irradical surgery (by extent of vascular and/or multivisceral involvement technical reasons (by extent of vascular and/or multivisceral involvement) and/or tumor markers **Discussed in international expert panel (yes/no)** _Advice (no exploration surgical / surgical exploration) _ _ If international expert panel advised renouncement of exploration, reason of renouncement is based on clinical condition, risk of irradical surgery (by extent of vascular and/or multivisceral involvement technical reasons (by extent of vascular and/or multivisceral involvement) and/or tumor markers
Intervention radiology	**Preoperative CHA embolization in case of celiac axis involvement (yes/no)**
Surgery	**Date of surgery** **ASA-PS** **Diagnostic laparoscopy (yes/no)** **Surgical exploration (yes/no)** _ Reason of renouncement of surgical exploration (peritoneal metastasis / liver metastasis) _ IOUS (yes/no) _ _ Largest tumor size (in mm) _ _ Vascular involvement (yes/no) _ _ _ Portomesenteric venous involvement (yes/no) _ _ _ _ Degree of involvement (≤90, 91-180, 181-270, >270 degree) _ _ _ _ Stenosis (no, ≤50% reduction, >50% reduction, occlusion) _ _ _ _ Length (in mm)

	_ _ _ _ Thrombosis (yes/no) _ _ Arterial involvement (yes/no) _ _ _ Involvement superior mesenteric artery (yes/no) _ _ _ _ Degree of involvement (≤90, 91-180, 181-270, >270 degree) _ _ _ Involvement celiac axis (yes/no) _ _ _ _ Degree of involvement (≤90, 91-180, 181-270, >270 degree) _ _ _ _ Involvement aorta or gastroduodenal artery (yes/no) _ _ _ Involvement (common / proper) hepatic artery (yes/no) _ _ _ _ Degree of involvement (≤90, 91-180, 181-270, >270 degree) _ _ Multivisceral ingrowth (yes/no) _ _ Resectability DPCG criteria _ _ Resectability NCCN criteria **Surgical resection (yes/no)** _ Reason of renouncement of resection (vascular involvement / multivisceral involvement / positive distant lymph nodes / peritoneal or liver metastasis) _ Local ablative therapy (no / RFA / IRE) _ Type of surgical resection ([PP]PD / DP / TP / others) _ _ Extended surgery (yes/no) _ _ _ Multivisceral resection ([sub]total gastrectomy, right/left adrenal, right/left kidney and/or its vasculature, colectomy and/or its vasculature, small bowel beyond first jejunal segment, diaphragmatic crura and/or diaphragm, liver) _ _ _ Vascular resection (yes/no) _ _ _ _ SMV/PV/IMV/IVC resection (yes/no) _ _ _ _ _ Indication (iatrogenic / oncological) _ _ _ _ _ Wedge resection (yes/no) _ _ _ _ _ _ Primary closure alone / primary closure and patch reconstruction _ _ _ _ _ Segmental resection (yes/no) _ _ _ _ _ _ With end-to-end anastomosis (with[out] splenic vein ligation) / reconstruction with interposition graft (with[out] splenic vein ligation) _ _ _ _ _ Other reconstruction (yes/no) _ _ _ _ Superior mesenteric artery resection (yes/no) _ _ _ _ _ Indication (iatrogenic / oncological) _ _ _ _ _ Wedge resection (yes/no) _ _ _ _ _ _ Primary closure alone / primary closure and patch reconstruction _ _ _ _ _ Segmental resection (yes/no) _ _ _ _ _ _ With end-to-end anastomosis / reconstruction with interposition graft _ _ _ _ Superior mesenteric artery divestment (yes/no) _ _ _ _ Celiac axis resection (yes/no) _ _ _ _ _ Indication (iatrogenic / oncological) _ _ _ _ Celiac axis divestment (yes/no) _ _ _ _ Common / proper hepatic artery resection _ _ _ _ _ Indication (iatrogenic / oncological) _ _ _ _ _ Wedge resection (yes/no) _ _ _ _ _ Segmental resection (yes/no) _ _ _ _ Common / proper hepatic artery divestment (yes/no) _ _ _ _ Accessory right hepatic artery resection (yes/no) _ _ _ _ _ Wedge resection (yes/no) _ _ _ _ _ Segmental resection (yes/no) _ _ _ _ Accessory right hepatic artery divestment (yes/no) _ _ _ _ Aberrant right hepatic artery resection (yes/no) _ _ _ _ _ Wedge resection (yes/no) _ _ _ _ _ Segmental resection (yes/no) _ _ _ _ Aberrant right hepatic artery divestment (yes/no) _ _ _ _ Vascular resection/reconstruction performed by vascular surgeon / (HPB) transplant surgeon / HPB surgeon **Intraoperative outcomes** _ Intraoperative blood loss (in ml) _ Intraoperative blood transfusion (yes/no) _ Operation time (in min) _ Macroscopic irradical resection
Postoperative outcomes	**Any in-hospital complication (i.e. Clavien-Dindo grade ≥I) (yes/no)**

	In-hospital major morbidity (i.e. Clavien-Dindo grade ≥IIIa) (yes/no) _ Re-intervention _ _ Relaparotomy _ _ Endoscopic _ _ Radiological _ _ Medium care / intensive care admission _ Blood transfusion **In-hospital pancreatic surgery-specific complications** _ Postoperative pancreatic fistula (ISGPS, 2016) _ Delayed gastric emptying (ISGPS, 2007) _ Postpancreatectomy hemorrhage (ISGPS, 2007) _ Bile leakage (ISGLS, 2011) _ Chyle leakage (ISGPS, 2016) **Hospital stay** **Readmission** **30-day / in-hospital mortality**
Pathology (final histological diagnosis)	**Pancreatic adenocarcinoma (yes/no)** _ Originated from IPMN / MCN (yes/no) **Largest diameter (in mm)** **Radicality (Royal College of Pathologists)** **Tumor differentiation** **pT stadium (TNM 8th edition)** **Total number of resected lymph nodes** **Total number of positive resected lymph nodes** **Distant metastasis** **Pathological response (College of American Pathologist)**
Adjuvant treatment	**Adjuvant chemotherapy (yes/no)** _ Starting date _ Type of chemotherapy ([m]FOLFIRINOX, gemcitabine-nab-paclitaxel, gemcitabine, other multi-agent regimen, other single-agent regimen) _ Dose reduction (yes/no) _ _ Number of reduced cycles _ Number of administered courses **Adverse events (none, yes, grade I-II, grade III-IV according to CTCAE version 4.0)**
Follow-up	**Disease recurrence (yes/no)** _ Date of recurrence (confirmed on imaging) _ Locoregional vs. distant metastasis vs. locoregional + distant **Patient status (alive / dead due to cancer / another cause / unknown cause)** **Date of death / most recent moment of follow-up**